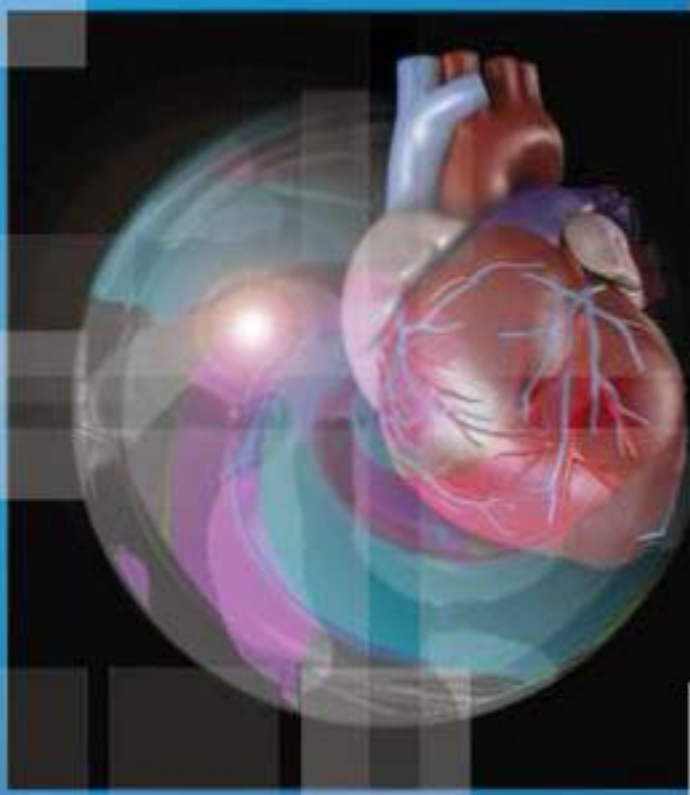
Clinical Cardiology

Current Practice Guidelines

UPDATED EDITION



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OXFORD

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Personal dedication by Demosthenes G. Katritsis
To Michael M. Webb-Peploe
Mentor, Teacher, Friend

Foreword

Over the years I have had the pleasure of writing forewords for a number of books that I considered to be timely and to fulfill important objectives. Without hesitation, I would say that *Clinical Cardiology: Current Practice Guidelines*, by D.G. Katritsis, B.J. Gersh, and A.J. Camm, is the most outstanding book for which I have had the pleasure to write a foreword. Further, this is probably the book that better serves the cardiovascular specialist in day-to-day practice than any other written in the last two decades. This is not just a textbook; it is an extraordinary "toolkit" in the context of an evidence-based cardiovascular practice in the midst of rapidly evolving scientific knowledge and guidelines.

Because of the need to integrate current knowledge on evidence-based cardiology, about three years ago, under the auspices of the American Heart Association, we published a book that included the most recent guidelines by both the ACC/AHA and the ESC. I believe that such integration was a step forward for the practicing cardiologist; indeed, in a "synopsis" fashion, this aspect is well served in *Clinical Cardiology: Current Practice Guidelines*. However, in the excellent compendium of my colleagues, three new components are incorporated, which we can describe as the "jewel" of the book: a very succinct definition, classification, pathophysiology, diagnosis, management, and need of specific clinical investigation (including genetics and molecular biology) of the various disease entities; a regularly updated online version on the most recent developments; and, most importantly a "user friendly, at a glance" presentation. These additional three components, that make *Clinical Cardiology: Current Practice Guidelines* so unique, deserve a brief description.

1) In regard to the various disease entities, general textbooks tend to employ, from definition to management, a rather long and descriptive format. In contrast, *Clinical Cardiology: Current Practice Guidelines* consolidates many of the topics, regardless of their complexity, from definition to management, in a clear, concise and instructive way, intermixed with the most recent guidelines. Thus, over 600 easily accessible tables dissect and summarize the key points of all the latest ACC/AHA and ESC guidelines.
2) Rapidly evolving scientific knowledge, including the value of new diagnostic and management approaches and their incorporation in practicing guidelines, makes it difficult for the cardiovascular specialist to be aware of the latest clinical evidence-base. Written by three leading authorities in the field, its annually updated online version provides the solution.
3) A novelty of this book is the "user-friendly, at a glance" way of presentation that makes it very useful to the practicing cardiovascular specialist. Useful because of its combination of succinctness and clarity, the book is up to date in every aspect of the cardiovascular science, and particularly on the most recent recommendations from both sides of the Atlantic. Thus, these recommendations are summarized in tables derived from the guideline documents and incorporated in the appropriate diagnostic or management sections of the 87 comprehensive chapters. For example, when confronted with complicated clinical issues that appear in everyday clinical practice (such as modern antiplatelet therapy of ACS, differential diagnosis of wide complex tachycardia, or management of stable CAD in view of COURAGE, FREEDOM or STICH) physicians consult general textbooks, or often several journal articles, in order to obtain this information in a rather loose form. In contrast, *Clinical Cardiology: Current Practice Guidelines* consolidates such topics in a summarized, succinct, and clear way.

This book is a tribute to the skill of the three editors who also served as the only authors. This limited, but unified and hardworking, internationally known authorship is, without doubt, a great part of the success. It is with great pleasure that I pen these words to relate my enthusiasm for their work as a remarkable addition to the cardiovascular field.

Valentin Fuster
Physician-in-Chief, Mount Sinai Medical Center
Director, Mount Sinai Heart

ΠΑΝΤΕΣ ΑΝΘΡΩΠΟΙ ΤΟΥ ΕΙΔΕΝΑΙ ΟΡΕΓΟΝΤΑΙ ΦΥΣΕΙ
All humans by nature desire to know

Aristotle
The Metaphysics

Prologue

The entire field of cardiovascular medicine has witnessed an era of rapid scientific progress, accompanied by continuous technological and applied innovation. This occurs against a backdrop of increasing emphasis on the importance of evidence-based practice, and rapid development of guidelines by major professional societies. The resultant expansion of our body of knowledge by evidence-based recommendations interjects a new set of challenges for the practicing clinician with ever-extensive clinical responsibilities.

In order to practice evidence-based medicine, information must be easily accessible and, more importantly, easily retrievable when the need arises; this may not always be easy with the current pace of dissemination of knowledge. The rationale for writing this book reflects exactly this need, both ours and that of our potential readers: to organize our continually evolving knowledge on often diverse cardiology issues, in our environment of networked and facilitated communication. In other words, to provide a clinical tool that can be used in everyday clinical practice as a concise guide to what we know and, more importantly, what we do not know, and what we think we know. To quote Mark Twain, "what gets us into trouble is not what we don't know, it is what we know for sure that just ain't so."

The prerequisites of informed clinical practice are: a satisfactory background of basic knowledge of disease entities, remaining up-to-date on important clinical trials and emerging scientific evidence that shape current diagnosis and therapy, and acquaintance with current practice guidelines from established professional societies such as the American College of Cardiology Foundation/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC), among many others.

Each chapter of this book has therefore been structured around the following parts:

1. **A clear definition and modern classification of disease entities, followed by updated, focused information on recent developments on the epidemiology and pathophysiology of each condition**. Recent original articles and reviews from leading journals were consulted and a summary of the most relevant information is included. Special care was taken not to omit the most recent information on medical genetics, an expanding and promising aspect.
2. **A description of the clinical presentation of the disease, with instructions on necessary clinical investigations**. Clinical investigations are presented in the context of recent evidence that dictates their current value or obsolescence. An effort has been made to include the very latest published knowledge on the clinical value of existing and evolving tests, based on recent randomized clinical trials and guidelines by both ACC/AHA and ESC.
3. **Recommendations on management as derived from the most recent evidence available to the authors**. Because of the comprehensive nature of guidelines offered by learned societies, it was also decided to provide the most recent recommendations in a summarized, tabulated format. These are not readily accessible since overlapping guidelines may appear on the same condition from different working groups, and updated documents are continually appearing. Thus, all guideline documents and their updates published in the US and Europe were scrutinized and classified according to year of publication. The most recent recommendations were defined, extracted and tabulated. The resulting tables provided in the book offer the most recent recommendations on each disease entity by both ACC/AHA and ESC. Where appropriate, new evidence that questions the validity of specific recommendations, as well as the opinions of established experts, and other data, such as FDA alerts are included.
4. **Practical advice on "what and why to do"**. Therapies, drug doses and selection of procedures are presented in a clear and user-friendly way.
5. **Carefully chosen references**. Major randomized clinical trials and seminal scientific studies that define evidence-based practice are included for further reference. In addition, recent, scholarly reviews are provided, which together with the contents of the book should allow in-depth study of specific entities that may interest the individual reader.
6. **Presentation of all recent guidelines**. Guidelines are referenced and presented separately in order to guide the reader to the most recent publications by ACC/AHA and ESC. Thus, the most recent recommendations on each particular issue, as they appear in new and updated guidelines, are presented.

An inherent disadvantage of a medical textbook is inability to keep up-to-date with recent developments. To overcome the problem, the online version of this book will be updated, initially on an annual basis. The updated edition of the book emphasizes our commitment to this task.

This book would have never been possible without the wholehearted support and commitment of Helen Liepman, our Senior Editor at Oxford University Press. We are grateful for her acceptance of our view of a "next generation textbook". We are grateful to Dr P. Kostaki of Athens Euroclinic for her scholarship and dedication in proof-reading and correcting our text. Finally, we also thank involved staff at Oxford University Press. Their professionalism and assistance throughout the revision and production process are much appreciated.

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List of abbreviations

<	less than
>	more than
≥	equal to or greater than
≤	equal to or less than
~	approximately
≈	approximately equal to
=	equal to
α	alpha
β	beta
δ	delta
γ	gamma
$	Dollar
€	Euro
ACC	American College of Cardiology
ACCP	American College of Chest Physicians
ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
ACHD	adult congenital heart disease
ACS	acute coronary syndrome
ACT	activated clotting time
ADP	adenosine diphosphate
AF	atrial fibrillation
AH	atrial-His
AHA	American Heart Association
AHF	acute heart failure
AIDS	acquired immunodeficiency syndrome
AMI	acute myocardial infarction
AMP	adenosine monophosphate
ANP	atrial natriuretic peptide
Ao	aorta
AoD	aortic dissection
AP	action potential
APB	atrial premature beat
aPTT	activated partial thromboplastin time
AR	aortic regurgitation
ARB	angiotensin receptor blocker
ARF	acute rheumatic fever
ARVC/D	arrhythmogenic right ventricular cardiomyopathy or dysplasia
AS	aortic stenosis
ASD	atrial septal defects
ASO	arterial switch operation
AT	atrial tachycardia
AT1	angiotensin II type 1
AV	atrioventricular; aortic valve
AVNRT	atrioventricular nodal reentrant tachycardia
AVR	aortic valve replacement
AVRT	atrioventricular reentrant tachycardia
BAV	bicuspid aortic valve
bd	twice daily
BLS	basic life support
bpm	beat per minute
BMS	bare metal stent
BMV	balloon mitral valvotomy
BNP	brain natriuretic peptide
BP	blood pressure
bpm	beats per minute
BrS	Brugada syndrome
BSA	body surface area
BUN	blood urea nitrogen
Ca^{++}	calcium
CABG	coronary artery bypass grafting
CAD	coronary artery disease
cAMP	cyclic adenosine monophosphate
CAVF	coronary arteriovenous fistula
CCB	calcium channel blocker
CCD	cardiac conduction disease
CCF	congestive heart failure
CCS	Canadian Cardiovascular Society
CCT	coronary artery computed tomography
CCTGA	congenitally corrected transposition of the great arteries
CCU	Coronary Care Unit
CDT	catheter-directed thrombolysis
cGMP	cyclic guanine monophosphate
CHB	congenital heart block
CHD	congenital heart disease
CHF	chronic heart failure
CIED	cardiovascular implantable electronic device
CKD	chronic kidney disease
CL	cycle length
cm	centimetre
CMR	cardiac magnetic resonance
CMV	cytomegalovirus
CO_2	carbon dioxide
CoA	coarctation of the aorta
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure

CPET	cardiopulmonary exercise testing
CPVT	catecholaminergic polymorphic ventricular tachycardia
CrCl	creatinine clearance
CRP	C-reactive protein
CRT	cardiac resynchronization therapy
CSNRT	corrected sinus nodal recovery time
CSM	carotid sinus massage
CSS	carotid sinus syndrome
CT	computed tomography
CTEPH	chronic thromboembolic pulmonary hypertension
CTI	cavotricuspid isthmus
CUS	compression ultrasonography
CVA	cerebrovascular accident
Cx	circumflex
d	day
2D	two-dimensional
3D	three-dimensional
4D	four-dimensional
Da	Dalton
DAD	delayed after-depolarization
DAPT	dual oral antiplatelet therapy
DC	direct current
DCC	direct current cardioversion
DCM	dilated cardiomyopathy
DES	drug-eluting stent
DFT	defibrillator threshold
dL	decilitre
DNA	deoxyribonucleic acid
DSE	dobutamine stress echocardiography
DTI	direct thrombin inhibitor
DVT	deep vein thrombosis
dyn	dyne
EAD	early after-depolarization
EBV	Epstein–Barr virus
ECG	electrocardiogram
ECS	elastic compression stocking
EHRA	European Heart Rhythm Association
ELISA	enzyme-linked immunosorbent assay
ELT	endless loop tachycardia
EMA	European Medicines Agency
EP	electrophysiology
EPS	electrophysiological study
ERA	endothelin receptor antagonist
ERO	effective regurgitant orifice (area)
ERS	early repolarization syndrome
ESC	European Society of Cardiology
ESR	erythrocyte sedimentation rate
FA	Friedreich's ataxia
FDA	Food and Drug Administration
FDC	familial dilated cardiomyopathy
FFR	fractional flow reserve
FMC	first medical contact
FIRM	focal impulse and rotor modulation
g	gram
GAS	group A Streptococcus
GDF	growth differentiation factor
GFR	glomerular filtration rate
GI	gastrointestinal
GP	glycoprotein
GRACE	Global Registry of Acute Coronary Event
h	hour
HA	His-atrial
HBV	hepatitis B virus
HCM	hypertrophic cardiomyopathy
Hct	haematocrit
HCV	hepatitis C virus
HDL	high density lipoprotein
HELLP	haemolysis, elevated liver enzymes, low platelet (count)
HF	heart failure
HIV	human immunodeficiency virus
HIT	heparin-induced thrombocytopenia
HLA	human leucocyte antigen
H_2O	water
HOCM	hypertrophic obstructive cardiomyopathy
HRS	Heart Rhythm Society
HRV	heart rate variability
Hz	hertz
IABP	intra-aortic balloon pump
IART	intra-atrial reentrant tachycardia
ICD	implantable cardioverter-defibrillator
IDC	idiopathic dilated cardiomyopathy
IE	infective endocarditis
IFDVT	iliofemoral deep vein thrombosis
IHD	ischaemic heart disease
ILR	implantable loop recorder
IM	intramuscular
IMH	intramural haematoma
IMT	intima-media thickness
INR	international normalized ratio
IOCM	iso-osmolar contrast media
IPAH	idiopathic pulmonary arterial hypertension
ISDN	isosorbide dinitrate
IU	international unit
IV	intravenous
IVC	inferior vena cava

J	Joule
JVP	jugular venous pressure
K	potassium
KCl	potassium chloride
kDa	kilodalton
kg	kilogram
km	kilometre
kPa	kilopascal
L	litre
LA	left atrium
LAA	left atrial appendage
LAH	left anterior hemiblock
lb	pound
LBBB	left bundle branch block
LDL	low density lipoprotein
LDL-C	low density cholesterol
LGE	late gadolinium enhancement
LIMA	left internal mammary artery
LMWH	low molecular weight heparin
LOCM	low osmolar contrast media
Lp(a)	lipoprotein (a)
LPH	left posterior hemiblock
LQTS	long QT syndrome
LVAD	left ventricular assist device
LVEDD	left ventricular end-diastolic diameter
LVEDP	left ventricular end-diastolic pressure
LVEF	left ventricular ejection fraction
LVESD	left ventricular end-systolic diameter
LVH	left ventricular hypertrophy
LVNC	left ventricular non-compaction
LVOT	left ventricular outflow tract
LVOTO	left ventricular outflow tract obstruction
m	metre
MAT	multifocal atrial tachycardia
MBC	mitral balloon commissurotomy
MBG	myocardial blush grade
MCT	multidetector computed tomography
MDCT	multidetector computed tomography
MEN	multiple endocrine neoplasia
mEq	milliequivalent
METS	metabolic equivalents
mg	milligram
mGy	milligray
MI	myocardial infarction
MIC	minimum inhibitory concentration
min	minute
µL	microlitre
mL	millilitre
µm	micron
mm	millimetre
mmHg	millimetre mercury
mmol	millimole
µmol	micromole
mo	month
mPAP	mean pulmonary artery pressure
MPI	myocardial perfusion imaging
MPS	myocardial perfusion stress
MRA	magnetic resonance angiography; mineralocorticoid receptor antagonist
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
ms	millisecond
MS	mitral stenosis
mSv	milliSievert
mV	millivolt
MVA	mitral valve area
MVP	mitral valve prolapse
MVR	mitral valve replacement
Na	sodium
NaCl	sodium chloride
ng	nanogram
NIPPV	non-invasive positive pressure ventilation
NIV	non-invasive ventilation
NO	nitric oxide
NSAID	non-steroidal anti-inflammatory drug
NSTEMI	non-ST elevation myocardial infarction
NSVT	non-sustained ventricular tachycardia
NSTEACS	non-ST elevation acute coronary syndrome
NTG	nitroglycerin
NYHA	New York Heart Association
O_2	oxygen
OAC	oral anticoagulant
od	once daily
OH	orthostatic hypotension
OPAT	outpatient parenteral antibiotic therapy
OPCAB	off-pump beating heart bypass surgery
oz	ounce
p	probability
PA	pulmonary artery
PAH	pulmonary artery hypertension
PaO_2	partial pressure of oxygen
PAPVC	partial anomalous pulmonary venous connection
PAU	penetrating atherosclerotic ulcer
PAWP	pulmonary artery wedge pressure
PBV	percutaneous balloon valvuloplasty
PCC	prothrombin complex concentrate

PCDT	pharmacomechanical catheter-directed thrombolysis
PCWP	pulmonary capillary wedge pressure
PCI	percutaneous coronary intervention
PCR	polymerase chain reaction
PDA	patent ductus arteriosus
PDE	phosphodiesterase
PDE-5I	phosphodiesterase-5 inhibitor
PE	pulmonary embolism
PEEP	positive end-expiratory pressure
PES	programmed electrical stimulation
PFO	patent foramen ovale
pg	pictogram
PH	pulmonary hypertension
PHV	prosthetic heart valve
PISA	proximal isovelocity surface area
PJRT	permanent junctional reciprocating tachycardia
PMBV	percutaneous mitral balloon valvotomy
PMC	percutaneous mitral commissurotomy
po	oral route
PO_2	partial pressure of oxygen
POTS	postural orthostatic tachycardia syndrome
PPCM	post-partum cardiomyopathy
PPM	permanent pacemaker
PMT	pacemaker-mediated tachycardia
PR	pulmonary regurgitation
PV	pulmonary vein
PVARP	post-ventricular pacing atrial refractory period
PVC	premature ventricular contraction
PVOD	pulmonary veno-occlusive disease
PVR	pulmonary vascular resistance; pulmonary valve replacement
Qp	pulmonary flow
Qs	systemic flow
RA	right atrium; rheumatoid arthritis
RADT	rapid antigen detection test
RAO	right anterior oblique
RAAS	renin-angiotensin-aldosterone system
RBBB	right bundle branch block
RBC	red blood cell
RCA	right coronary artery
RCM	restrictive cardiomyopathy
RCT	randomized controlled trial
RF	radiofrequency; rheumatic fever
RNA	ribonucleic acid
rPA	rateplase
RVSP	right ventricular systolic pressure
RV	right ventricle
RVEF	right ventricular ejection fraction
RVOT	right ventricular outflow tract
RVOTO	right ventricular outflow tract obstruction
RWPT	R wave peak time
s	second
SAECG	signal-averaged electrocardiogram
SAM	systolic anterior motion
SaO_2	oxygen saturation
SBP	systolic blood pressure
SC	subcutaneous route
SCD	sudden cardiac death
SIHD	stable ischaemic heart disease
SLE	systemic lupus erythematosus
SND	sinus node dysfunction
SNP	single-nucleotide polymorphism
SNRT	sinus nodal recovery time
SOBOE	shortness of breath on exertion
SPECT	single photon emission computed tomography
SPERRI	shortest pre-excited RR interval
sPESI	simplified pulmonary embolism severity index
SpO_2	saturation of peripheral oxygen
spp.	species
SQTS	short QT syndrome
SR	sinus rhythm
SSS	sick sinus syndrome
SSRI	selective serotonin reuptake inhibitor
STEMI	ST elevation myocardial elevation
SVC	superior vena cava
SVR	systemic vascular resistance
SVT	supraventricular tachycardia
TAPSE	tricuspid annular plane systolic excursion
TAPVC	total anomalous pulmonary venous connection
TAVI	transcatheter aortic valve implantation
TdP	torsade de pointe
tds	three times daily
TEVAR	thoracic endovascular aortic repair
TGA	transposition of great arteries
TIA	transient ischaemic attack
TIC	tachycardia-induced cardiomyopathy
TIMI	thrombolysis in myocardial infarction
TLR	target lesion revascularization
TnI	troponin I
TNK-tPA	tenecteplase
TnT	troponin T
TOE	transoesophageal echocardiogram
TOF	tetralogy of Fallot
tPA	tissue plasminogen activator

TR	tricuspid regurgitation
TS	tricuspid stenosis
TTE	transthoracic echocardiography
TV	tricuspid valve
TWA	T wave alternans
U	unit
UA	unstable angina
UFH	unfractionated heparin
ULN	upper limit of normal
URL	upper reference limit
V	volt
VA	ventricular arrhythmia
VD	valve disease
VEGF	vascular endothelial growth factor
VF	ventricular fibrillation
VHL	von Hippel–Lindau
VKA	vitamin K antagonist
VPB	ventricular premature beat
V/Q	ventilation perfusion
VSD	ventral septal defect
VT	ventricular tachycardia
VTE	venous thromboembolism
WBC	white blood cell
WPW	Wolff–Parkinson–White
WU	Woods unit
y	year

Part I

Adult congenital heart disease

Relevant guidelines

ACC/AHA 2008 Guidelines on ACHD

ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. *J Am Coll Cardiol*. 2008;**52**:e1–e121.

AHA 2015 Scientific Statement

American Heart Association Council on Clinical Cardiology. Congenital heart disease in the older adult: a scientific statement from the American Heart Association. *Circulation*. 2015;**131**:1884–931.

ESC 2010 Guidelines on ACHD

ESC Guidelines for the management of grown-up congenital heart disease. *Eur Heart J*. 2010;**31**:2915–57.

PACES/HRS 2014 Consensus Statement on Arrhythmias in ACHD

PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease. *Heart Rhythm*. 2014;**11**:e102–e165.

ACC/AHA 2010 Guidelines on aortic disease

2010 ACC/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease. *J Am Coll Cardiol*. 2010;**55**:e27–e129.

ESC 2014 Guidelines on aortic diseases

2014 ESC Guidelines on the diagnosis and treatment of aortic diseases. *Eur Heart J*. 2014;**35**:2873–926.

AHA/ACC 2014 Guidelines on valve disease

2014 AHA/ACC Guideline for the management of patients with valvular heart disease: *J Am Coll Cardiol*. 2014;**63**:e57–185.

AHA/ASA 2014 Guidelines on stroke and TIA

Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;**45**:2160–236.

ESC 2012 Guidelines on valve disease

Guidelines on the management of valvular heart disease. *Eur Heart J*. 2012;**33**:2451–2496.

ESC 2011 Guidelines on pregnancy

ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**:3147–97.

Chapter 1

Adult congenital heart disease: general principles

Definition

Congenital heart disease refers to a defect in the structure of the heart and great vessels, which is present at birth.

Epidemiology

Approximately 0.8% of the population is born with congenital heart disease. Up to 40% of them are cured spontaneously (mainly small VSDs) and, with current surgical and interventional techniques, 56–98% survive into adulthood (adult congenital heart disease-ACHD, or grown-up congenital heart disease-GUCH) (Table 1.1).[1–3] According to data from Europe, Canada, and the USA, the live birth prevalence of congenital heart disease is 7–12/1000 births.[2,3]

Adult congenital heart disease comprises a population that is currently estimated at one million in the USA and 1.2 million in Europe, and admission rates in hospital are twice higher than in the general population.[4–6] The majority of patients with congenital heart disease are now adults.[7] Congenital heart disease is the most common form of heart disease complicating pregnancy in the Western world (accounting for 74% of cases in the Canadian Cardiac Disease in Pregnancy [CARPREG] registry and 66% of cases in the European Registry on Pregnancy and Cardiac Disease [ROPAC] registry), whereas, in less developed countries, rheumatic heart disease plays a larger role.[8] There is also a growing number of elderly ACHD patients (>60 years) with high mortality rates and a higher utilization of healthcare resources, compared with younger patients.[9] In adults, VSD and ASD are the most common defects (each of them approximately 20% of all defects), followed by PDA and pulmonary valve stenosis.[4]

Congenital heart defects are more common in twins than in singletons, and the increased occurrence is not restricted to monochorionic twins. Thus, intrauterine surveillance and a post-natal comprehensive cardiac assessment for both twins may be considered, regardless of chorionicity and zygosity.[10] Survival after operation is better in patients without heterotaxy, i.e. randomized variation in the left-right asymmetry of visceral organs that differs from complete situs solitus and situs inversus, probably due to ciliary dysfunction that is associated with heterotaxy.[11]

Aetiology

The causes of congenital heart disease in humans remain undefined in the majority of cases and probably depend on the interplay of multiple genetic and environmental factors. There has been evidence that an intrinsically angiogenic impairment exists in congenital heart disease, that appears to be present in both the maternal and fetal circulation and fetal heart.[12]

Environmental factors are rare: congenital rubella, maternal diabetes or SLE, paternal exposure to phthalates, maternal smoking, alcohol and drug abuse, air pollutants, and pesticides.[13,14] Weight control, smoking cessation, and folic acid supplementation appear to decrease the risk of congenital heart disease in the offspring.[8]

Genetic factors Disruption at any point during cardiac primary morphogenesis (i.e. ornation of the heart tube, looping, septation, and resultant systemic and pulmonary circulations) results in the large spectrum of congenital heart defects. Genetic disorders responsible for these alterations can be classified into three types: chromosomal disorders, single-gene disorders, and polygenic disorders.

Chromosomal disorders (5–8% of congenital heart disease patients), caused by absent or duplicated chromosomes, include trisomy 21 (Down's syndrome), 22q11 deletion (DiGeorge syndrome), and 45X deletion (Turner's syndrome). Recurrence risk in an offspring is that of the chromosomal disorder.

Single-gene disorders (3% of congenital heart disease patients) are caused by gene deletions, duplications, or mutations. These disorders follow autosomal dominant, autosomal recessive, or X-linked inheritance patterns. Some examples are Holt–Oram syndrome, atrial septal defect with conduction abnormalities, and supravalvular aortic stenosis. Recurrence risk is high in first-degree relatives of patients with these disorders.

Polygenic disorders result from environmental and genetic factors.

The majority of cases (80%) occur as sporadic events but, in some, multiple family members are affected. In up to 31% of families in which multiple relatives are affected by CHD, a genetic basis can be identified, and rapid screening for disease-related genes can be facilitated using advanced sequencing technologies.[15]

Recurrence rate

The recurrence rate of congenital heart disease in offspring ranges from 3% to 50% and is higher when the mother, rather than the father, has congenital heart disease. Diseases with a single-gene disorder and/or chromosomal abnormalities are associated with a high recurrence rate. For isolated cases of congenital heart disease without a family history of CHD (e.g. sporadic defects), the recurrence risk of congenital heart disease in the offspring is 3-8%.[8] The risk is higher if the mother is the affected parent or if more than one sibling is affected. In autosomal dominant syndromes, such as Marfan's, Noonan's, and Holt–Oram, there is a 50% risk of recurrence. Genetic counselling should be offered to all patients with congenital heart disease, with referral for genetic testing in specific situations.

Table 1.1 Adult patients with congenital heart disease

Complex conditions
Eisenmenger syndrome
Double-outlet ventricle
Fontan procedure
Mitral atresia
Pulmonary atresia
Pulmonary vascular obstructive diseases
Single ventricle (double inlet or outlet, common or primitive)
Transposition of the great arteries
Tricuspid atresia
Truncus arteriosus/hemitruncus
Other rare complex conditions include abnormalities of atrioventricular or ventriculoarterial connection, such as criss-cross heart, isomerism, heterotaxy syndromes, and ventricular inversion.
Moderate conditions
Anomalous pulmonary venous drainage (partial or total)
Aortic valve disease (valvar, supravalvar, subvalvar)
Atrioventricular septal defects
Coarctation of the aorta
Coronary fistulae
Ebstein's anomaly
Mitral valve disease
Patent ductus arteriosus
Pulmonary valve disease (valvar, supravalvar, subvalvar)
Pulmonary arteriovenous malformations
Sinus of Valsalva fistula/aneurysm
Tetralogy of Fallot
Ventricular septal defects
Simple conditions
Isolated aortic valve disease
Isolated mitral valve disease (not parachute valve or cleft leaflet)
Small patent ductus arteriosus
Mild pulmonary stenosis
Small ASD
Small VSD

1. Conditions may start acyanotic and become cyanotic with time: Fallot's tetralogy, Ebstein's anomaly, and left-to-right shunts, resulting in Eisenmenger syndrome.
2. Cardiac dextroversion with situs solitus (i.e. normal position of viscera—gastric bubble on the left) is associated with congenital defects (TGA mainly, VSD, PS, tricuspid atresia) in 90% of cases. Dextrocardia with situs inversus (gastric bubble on the right) carries a low incidence of congenital heart disease, whereas situs inversus with levocardia is invariably associated with complex congenital abnormalities.

The changing profile of congenital heart disease in adult life. *J Am Coll Cardiol*. 2001;**37**:1170–5 with permission from Elsevier.

Clinical problems in ACHD

Patients with complex lesions and/or complications should be managed in experienced ACHD centres.[16–19]

Peripheral cyanosis may be due to peripheral vasoconstriction, polycythaemia, or poor cardiac output.

Central cyanosis (arterial saturation <85% or >5g reduced haemoglobin) may be due to right-to-left shunting or reduced pulmonary flow. Differential cyanosis may be seen with PDA and pulmonary hypertension or interrupted aortic arch. In cyanosis from pulmonary causes, there is an increase of PO_2 to, at least, >21 kPa (160 mmHg) after breathing 100% O_2 for 5 min.

In patients with ACHD, cyanosis and chronic hypoxaemia lead to marked erythrocytosis and, frequently, to low platelet counts (<100 000), which may predispose to bleeding. The absence of erythrocytosis (e.g. haemoglobin >17.0 g/dL) in such patients suggests a 'relative anaemia'. Phlebotomy should be undertaken with haemoglobin >20 g/dL and Hct >65%, associated with headache, increasing fatigue, or other symptoms of hyperviscosity in the absence of dehydration or anaemia (ACC/AHA 2008 GL on ACHD, Class I-C), under careful volume replacement with normal saline. Multiple phlebotomies result in iron deficiency that is associated with impaired small-vessel blood flow and an increase in the risk of reversible ischaemic neurological deficits and stroke. The use of anticoagulation and antiplatelet agents is controversial and should be reserved for well-defined indications.

Digital clubbing Apart from ACHD, it may be seen in pulmonary malignancy, chronic infection, and primary hypertrophic osteoarthropathy.

Renal function Sclerotic renal glomeruli leading to increased creatinine levels, proteinuria, and hyperuricaemia.

Gallstones Increased breakdown of red cells results in increased risk of calcium bilirubinate gallstones, especially in the cyanotic and Fontan populations.[1]

Hypertrophic osteoarthropathy with thickened periosteum and **scoliosis** that may compromise pulmonary function.

Cerebrovascular events (embolic or haemorrhagic), **brain abscess, cognitive and psychological problems** are also common.

Arrhythmias arise from the abnormal myocardial substrate due to variable pressure/volume loads and/or scars following cardiac surgery (see also Chapter 51 and Chapter 56).[20,21] Malignant arrhythmias typically become manifest the third decade of life.[21] *Atrial fibrillation* is usually a late finding, and restoration of sinus rhythm may be difficult. *Atrial tachycardia* (usually macroreentrant) is often seen in tetralogy of Fallot and following Fontan, Mustard, and Senning procedures. These arrhythmias can be treated with catheter ablation, usually assisted by electroanatomic mapping. *Atrioventricular reentrant tachycardia* (accessory pathways) in Ebstein's anomaly and corrected transposition. *Ventricular tachycardia* in conditions with the greatest known risk of late sudden cardiac death, such as tetralogy of Fallot, d- or l-transposition, aortic stenosis, and univentricular hearts.[16,22] *Sick sinus syndrome* in ASD, post-operative Fontan, Mustard, Senning. *AV block* in ASD, corrected transposition, VSD closure, AVR.

Imaging techniques and investigations

Two- or three-dimensional echocardiography with Doppler imaging and **cardiac magnetic resonance** have now replaced cardiac catheterization as a diagnostic tool in most patients with ACHD.[23]

MRI is considered superior to echocardiography for:

- Quantification of RV volume and function, and PR
- Evaluation of the RVOT, RV-PA conduits, and great vessels
- Tissue characterization (fibrosis, fat, iron, etc.).

CT is superior to MRI for:

- Collaterals, arteriovenous malformations, and coronary anomalies
- Evaluation of intra- and extra-cardiac masses.

Haemodynamic assessment

Haemodynamic measurements of cardiac output and systemic and pulmonary flow are derived by Doppler echocardiography that has replaced calculations by the Fick method. However, verification of pressures by direct measurement at cardiac catheterization is necessary for therapeutic decision making in the presence of pulmonary hypertension (>½ of systemic pressure) and for angiographic delineation of defects and selection of appropriate closure devices.

Pulmonary vascular (arterial) resistance (PVR) = (PA pressure–wedge pressure)/cardiac output (normal range: 0.25–1.5 Wood units (mmHg/L/min) or 20–120 dynes/cm^5)

Systemic vascular (arterial) resistance (SVR) = (Ao pressure–RA pressure)/cardiac output (normal range: 9–20 Wood units (mmHg/L/min) or 700–1600 dynes/cm^5)

If PVR is greater than two-thirds of SVR, vasodilating challenge, either acute in the catheter laboratory or chronic, with oxygen, nitric oxide, adenosine, epoprostenol, calcium channel blockers, endothelin antagonists, and phosphodiesterase inhibitors, is indicated to investigate the responsiveness of the pulmonary vascular bed. With fixed values, irreversible damage and Eisenmenger syndrome have developed.

Pulmonary flow/systemic flow (Qp/Qs)—usually derived by echocardiography.

According to the Fick method, Qp/Qs is calculated by oximetry as:

Qp/Qs = (Ao saturation–mixed venous saturation) / (PV–PA saturation), where
Mixed venous saturation = (3 × SVC saturation + IVC saturation)/4

If PV saturation is not available, the value of 98 is used instead.

Routine *saturation run* during catheterization for exclusion of shunt involves blood sampling from: high SVC, RA/SVC junction, high RA, mid-RA, low RA, IVC, RV inflow, RV body, RV outflow, main PA, PV and LA if possible, LV, and Ao.

A step-up of saturation >10% indicates shunt.

Coronary angiography

Coronary angiography, or computed coronary angiography in low or intermediate pretest probability,[1] is indicated preoperatively in patients >40 years, post-menopausal women, adults with multiple risk factors for coronary artery disease, and children with suspicion of congenital coronary anomalies.

Exercise testing

The presence of chronotropic incompetence on conventional exercise testing is a predictor of pregnancy outcome.[8] *Cardiopulmonary exercise testing* provides strong prognostic information in adult patients with congenital heart disease. Peak oxygen consumption (max VO_2) is one of the best predictors of morbidity and mortality.[24,25]

Spirometry

There is a high prevalence of markedly abnormal forced vital capacity (FVC) in patients with ACHD, and reduced FVC is associated with increased mortality.[26]

Assessment of arrhythmia

Surveillance for adults with moderate or severe CHD should include a *12-lead ECG* at least once per year, and periodic *Holter* monitoring in adults with transposition of the great arteries and atrial switch surgery, Fontan palliation, and in patients with tetralogy of Fallot >35 years of age.[18]

Electrophysiologic testing is indicated in patients with unexplained syncope and 'high-risk' substrates associated with primary ventricular arrhythmias or poorly tolerated atrial tachyarrhythmias, such as tetralogy of Fallot, transposition of the great arteries with atrial switch surgery, or significant systemic or single ventricular dysfunction. Programmed ventricular stimulation may also be useful in risk-stratifying adults with tetralogy of Fallot who have additional risk factors for sudden cardiac death (see Chapter 9).[20] Prior to cardiac surgery, EPS is indicated in the presence of history of syncope, VT, SVT (not AF), and ventricular pre-excitation. It may also be considered in patients with a history of palpitations or nonsustained atrial or ventricular arrhythmias, and in cases known to be at high risk for atrial arrhythmia development.[20] A detailed discussion is presented in Chapter 50 and Chapter 55.

Genetic screening

The AHA recommendations are provided in Table 1.2.

Table 1.2 AHA 2015 statement on congenital heart disease in the older adult

Recommendations for Genetic Screening and Counseling of the Older ACHD Patient	
A detailed family history for CHD and other birth defects that spans at least 3 generations to identify familial inheritance. Parental consanguinity should be documented, along with a history of miscarriages and stillbirths	I-C
Detailed history and physical examination for dysmorphic features, extracardiac malformations, and other organ system involvement,including neuromuscular abnormalities, mental retardation, psychiatric abnormalities, short stature, visual or hearing loss, immune deficiency, endocrine disorders, and other systemic disorders	I-C
Family member screening through history, physical examination, and/or echocardiographic screening, particularly in patients reporting a positive family history This may aid in the detection of clinically silent defects such as ASDs, small VSDs, BAV, and right aortic arch in asymptomatic family members.	IIa-C
Recommendations for Genetic Testing	
Patients with a history of parental consanguinity or a family history of CHD that includes frequent miscarriages or stillbirths	I-C
Patients with associated clinical features suggestive of an underlying genetic syndrome, such as facial dysmorphism, extracardiac malformations, cognitive impairment, neuropsychiatric disorders, or multisystem involvement (eg, hepatic, renal, hematologic, immunologic, endocrinologic, and sensorineural abnormalities)	IIa-C
Patients with certain types of isolated cardiac defects commonly associated with genetic syndromes even in the absence of syndromic features. Common examples are screening for 22q11.2 deletion syndrome in patients with interrupted aortic arch, truncus arteriosus, TOF, VSD with aortic arch anomaly, right aortic arch, or discontinuous branch PAs and screening for 7q11.23 deletion or Williams-Beuren syndrome in patients with supravalvar AS, coronary stenosis, and supravalvar and peripheral pulmonary stenosis.	IIa-C

American Heart Association Council on Clinical Cardiology. Congenital heart disease in the older adult: a scientific statement from the American Heart Association. *Circulation*. 2015;**131**:1884–931 with permission from Wolters Kluwer.

Principles of therapy

General measures are presented in Table 1.3. Specific management is discussed in relevant chapters. In neonates who undergo cardiac surgery, optimal early outcomes are associated with delivery at 39–40 weeks' gestation. Birth during the early term period of 37–38 weeks' gestation is associated with worse outcomes after neonatal cardiac surgery.[27] The IMPACT (Improving Pediatric and Adult Congenital Treatment) database that was launched by the National Cardiovascular Data Registry (NCDR) provides measures and predictors of procedural success that may be considered in evaluating patients with congenital heart disease for common interventional procedures. Procedures directed at PDA and ASD closure are among the safest and most successful procedures for congenital heart disease in the US compared with aortic valvuloplasty and coarctation angioplasty and/or stenting, which are generally less successful and are associated with greater risk.[28] Following major treatment advances during the past 50 years, surgical correction of nearly all congenital heart defects is now possible, and substantial improvements in short-term survival have been documented for most conditions.[29,30]

Arrhythmias

The most common indications for permanent pacemaker implantation in children, adolescents, and patients with congenital heart disease are symptomatic sinus bradycardia, the bradycardia–tachycardia syndromes, and advanced second- or third-degree AV block, either congenital or post-surgical.[22,31] Indications for pacing are presented in Chapter 56 and Chapter 66. Indications for CRT in patients with congenital heart disease are presented in Chapter 32. The management of tachyarrhythmias

Table 1.3 ESC 2010 GL on ACHD. Risk reduction strategies in patients with cyanotic congenital heart disease

Prophylactic measures are the mainstay of care to avoid complications. The following exposures/activities should be avoided:
• Pregnancy
• Iron deficiency and anaemia (no routine, inappropriate phlebotomies to maintain predetermined haemoglobin)
• Dehydration
• Infectious disease: annual influenza vaccination, Pneumovax (every 5 years)
• Cigarette smoking, recreational drug abuse, including alcohol
• Transvenous PM/ICD leads
• Strenuous exercise
• Acute exposure to heat (sauna, hot tub/shower)
Other risk reduction strategies include:
• Use of an air filter in an intravenous line to prevent air embolism
• Consultation of a ACHD cardiologist before administration of any agent and performance of any surgical/interventional procedure
• Prompt therapy of upper respiratory tract infections
• Cautious use or avoidance of agents that impair renal function
• Contraceptive advice

ESC Guidelines for the management of grown-up congenital heart disease. *Eur Heart J*. 2010;**31**:2915–57 with permission from Oxford University Press.

in ACHD is discussed in Chapter 51, Chapter 53, and Chapter 56. Recommendations for ICD are not, in general, different than that to other patients with cardiac disease. Indications for ICD are discussed in detail in Chapter 56. Patients with AF should receive anticoagulation regardless of other risk factors (AHA 2015 statement, I-C).[1] Recommendations for concomitant arrhythmia surgery are provided in Chapter 51 and Chapter 56.

Endocarditis prophylaxis

The risk of endocarditis in patients with ACHD is estimated to 4.1 first cases/10 000 person-years. The greatest risk is seen in children with cyanotic congenital heart disease, endocardial cushion defects, or left-sided lesions, and recent cardiac surgery and young age.[32]

Prophylaxis is now indicated only in high-risk patients and only before dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa, or before vaginal delivery.[16,17] Congenital conditions for which endocarditis prophylaxis is recommended before the aforementioned procedures are presented in Table 1.4. A detailed discussion and specific recommendations are provided in the chapter on infective endocarditis.

Table 1.4 ACC/AHA 2008 GL on ACHD

Recommendations for infective endocarditis (IE) prophylaxis in patients with adult congenital heart disease	
Patients must be informed of their potential risk for IE and should be provided with the AHA information card with instructions for prophylaxis.	I-B
When patients present with an unexplained febrile illness and potential IE, blood cultures should be drawn before antibiotic treatment is initiated to avoid delay in diagnosis due to 'culture-negative' IE.	I-B
Transthoracic echocardiography (TTE) when the diagnosis of native-valve IE is suspected.	I-B
Transoesophageal echocardiography if TTE windows are inadequate or equivocal, in the presence of a prosthetic valve or material or surgically constructed shunt, in the presence of complex congenital cardiovascular anatomy, or to define possible complications of endocarditis.	I-B
Patients with evidence of IE should have early consultation with a surgeon with experience in adult congenital heart disease (ACHD) because of the potential for rapid deterioration and concern about possible infection of prosthetic material.	I-C
Antibiotic prophylaxis before dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa, in patients with CHD with the highest risk for adverse outcome from IE: a. Prosthetic cardiac valve or prosthetic material used for cardiac valve repair. b. Previous IE. c. Unrepaired and palliated cyanotic CHD, including surgically constructed palliative shunts and conduits. d. Completely repaired CHD with prosthetic materials, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure. e. Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device that inhibits endothelialization.	IIa-B
Antibiotic prophylaxis against IE before vaginal delivery at the time of membrane rupture in select patients with the highest risk of adverse outcomes: a. Prosthetic cardiac valve or prosthetic material used for cardiac valve repair. b. Unrepaired and palliated cyanotic CHD, including surgically constructed palliative shunts and conduits.	IIa-C
Prophylaxis against IE is not recommended for non-dental procedures (such as oesophagogastroduodenoscopy or colonoscopy) in the absence of active infection.	III-C

ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. *J Am Coll Cardiol*. 2008;**52**:e1–e121 with permission from Elsevier.

Hypertension

In the treatment of the hypertensive patient with cyanotic CHD, ACE inhibitors, angiotensin receptor blockers, and diuretic agents should be used cautiously, and care should be coordinated at an ACHD center (AHA 2015 statement, I-C).[1]

Table 1.5 AHA 2015 statement on congenital heart disease in the older adult

Recommendations for Heart Failure (HF) in the Adult With CHD	
Patients with moderate to complex ACHD are at risk for development of HF, and early referral to an ACHD center with a HF service and electrophysiological service is indicated	I-C
The ACHD specialist should lead the direction of care, because these patients are not directly comparable to heart failure patients with acquired disease (ischemic and nonischemic)	I-C
Transplant evaluation, when considered, should include in the risk-benefit assessment not only the mortality or morbidity of transplantation but also the presence of antibodies secondary to multiple prior surgeries in some patients and the coexistence of multisystem dysfunction (ie, renal, hepatic, pulmonary hypertension)	I-C

American Heart Association Council on Clinical Cardiology. Congenital heart disease in the older adult: a scientific statement from the American Heart Association. *Circulation*. 2015;**131**:1884–931 with permission from Wolters Kluwer.

Heart failure

Recommendations by AHA are provided in Table 1.5.

Psychosocial issues and sexual dysfunction

Individual and family psychosocial screening should be part of the care of ACHD patients.[1] Phosphodiesterase 5 inhibitors are safe provided the patient is not taking nitrates (AHA 2015 statement, I-C). It is reasonable to treat dyspareunia in women with nonsystemic estrogen therapy, which has not been shown to increase cardiovascular risk (AHA 2015 statement, IIa-C).[1]

Non-cardiac surgery

Preoperative evaluation and surgery for patients with congenital heart disease should be performed in specializing centres with experienced surgeons and cardiac anaesthesiologists. The ACC/AHA recommendations are provided in Table 1.6.

Risk factors of non-cardiac perioperative risk are:

- Cyanosis and/or pulmonary hypertension
- LVEF <35% and/or NYHA III or IV
- Prior Fontan procedure
- Complex congenital heart disease with heart failure, severe left-sided obstructive lesions, malignant arrhythmias, or the need for anticoagulation.

Exercise

Adults with congenital heart disease have subnormal exercise tolerance. However, participation in regular exercise is beneficial for fitness and psychological well-being.[33] In a recent statement, AHA recognized the importance of physically active lifestyles to the health and well-being of children and adults with congenital heart defects.[34] There is no evidence regarding whether or not there is a need to restrict recreational physical activity among patients with congenital heart defects, apart from those with rhythm disorders. Counselling to encourage daily participation in appropriate physical activity should be a core component of every patient encounter. As a general recommendation, dynamic exercise is more suitable than static exercise. Conditions that are not compatible with competitive sports are:

- Eisenmenger syndrome
- Pulmonary hypertension
- Univentricular heart physiology
- Ebstein's anomaly
- Transposition of great arteries
- Coronary artery anomalies.

Maximal exercise testing is contraindicated in all patients with pulmonary hypertension.

Table 1.6 ACC/AHA 2008 GL on ACHD

Recommendations for non-cardiac surgery in patients with adult congenital heart disease (ACHD)	
Preoperative assessment with systemic arterial oximetry, ECG, chest X-ray, TTE, and blood tests for full blood count and coagulation screen.	I-C
When possible, the preoperative evaluation and surgery for ACHD patients should be performed in a regional centre specializing in congenital cardiology, with experienced surgeons and cardiac anaesthesiologists.	I-C
High-risk patient should be managed at centres for the care of ACHD under all circumstances, unless the operative intervention is an absolute emergency. High-risk categories:	
a. Prior Fontan procedure.	I-C
b. Severe pulmonary arterial hypertension.	I-C
c. Cyanotic CHD.	I-C
d. Complex CHD with residua, such as heart failure, valve disease, or the need for anticoagulation.	I-C
e. Patients with CHD and malignant arrhythmias.	I-C
Consultation with ACHD experts regarding the assessment of risk for patients with CHD who will undergo non-cardiac surgery.	I-C
Consultation with a cardiac anaesthesiologist for moderate- and high-risk patients.	I-C

ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. *J Am Coll Cardiol*. 2008;**52**:e1–e121 with permission from Elsevier.

Long-distance flights

Cyanotic patients should use only pressurized commercial airplanes and should drink non-alcoholic and non-caffeinated fluids frequently on long-distance flights

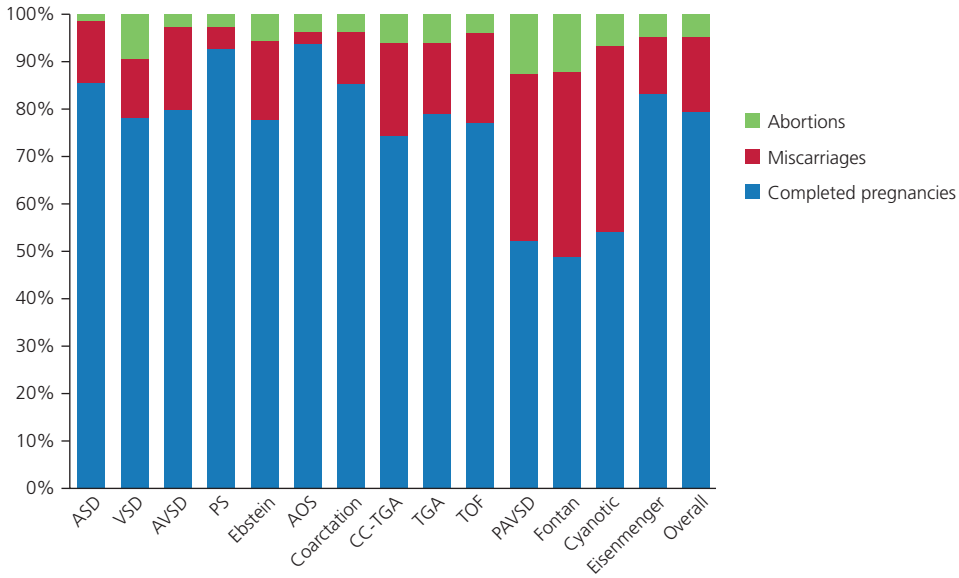

Figure 1.1 Distribution of miscarriages, completed pregnancies (>20 weeks pregnancy duration), and elective abortions for each congenital heart disease separately and the overall rates (from ESC 2011 guidelines on pregnancy).

ASD, atrial septal defect; AVSD, atrioventricular septal defect; AOS, aortic stenosis; CC-TGA, congenital corrected transposition of the great arteries; coarctation, aortic coarctation; Ebstein, Ebstein's anomaly; Eisenmenger, Eisenmenger syndrome; Fontan, patients after Fontan repair; PAVSD, pulmonary atresia with ventricular septal defects; PS, pulmonary valve stenosis; TGA, complete transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**: 3147–97 with permission from Oxford University Press.

to avoid dehydration. Oxygen therapy, although often unnecessary, may be suggested for prolonged travel in cyanotic patients. Similarly, residence at high altitude is detrimental for patients with cyanosis.

Pregnancy

Uteroplacental Doppler flow parameters are abnormal in pregnant women with CHD and are related to offspring outcome.[35] Generally, pregnancy is not recommended in Eisenmenger syndrome. In women with congenital defects not complicated by Eisenmenger syndrome, significant pulmonary hypertension or Marfan's syndrome (and Ehlers–Danlos or Loeys–Dietz syndromes) with aortic root >40 mm, pregnancy can be tolerated (Figure 1.1). The most prevalent cardiac complications during pregnancy are arrhythmias, heart failure, and hypertensive complications. Oestrogen-only contraceptives potentially increase the thrombotic risk and should be avoided. Risk factors are discussed in the chapter on pregnancy (miscellaneous topics).

The ACC/AHA recommendations, as well as the ESC guidelines on pregnancy,[36] are presented in Tables 1.7 and 1.8.

Table 1.7 ACC/AHA 2008 GL on ACHD

Recommendations for pregnancy and contraception	
Consultation with an expert in adult congenital heart disease (ACHD) before patients plan to become pregnant.	I-C
Patients with intracardiac right-to-left shunting should have fastidious care taken of intravenous lines to avoid paradoxical air embolus.	I-C
Pre-pregnancy counselling is recommended for women receiving chronic anticoagulation with warfarin.	I-B
Meticulous prophylaxis for deep venous thrombosis, including early ambulation and compression stockings, for all patients with an intracardiac right-to-left shunt. Subcutaneous heparin or LMWH for prolonged bed rest. Full anticoagulation for high-risk patients.	IIa-C
The oestrogen-containing oral contraceptive pill is not recommended in ACHD patients at risk of thromboembolism, such as those with cyanosis related to an intracardiac shunt, severe pulmonary arterial hypertension (PAH), or Fontan repair.	III-C

ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. *J Am Coll Cardiol*. 2008;**52**:e1–e121 with permission from Elsevier.

Table 1.8 ESC 2011 GL on pregnancy

Recommendations for the management of congenital heart disease	
Pre-pregnancy relief of stenosis (usually by balloon valvulotomy) in severe PV stenosis (peak Doppler gradient >64 mmHg).	I-B
Follow-up should range from twice during pregnancy to monthly.	I-C
Symptomatic patients with Ebstein's anomaly with cyanosis and/or heart failure should be treated before pregnancy or advised against pregnancy.	I-C
Pre-pregnancy pulmonary valve replacement (bioprosthesis) in symptomatic women with marked dilatation of the RV due to severe pulmonary regurgitation (PR).	I-C
Pre-pregnancy pulmonary valve replacement (bioprosthesis) in asymptomatic women with marked dilatation of the RV due to severe PR.	IIa-C
All women with a bicuspid aortic valve should undergo imaging of the ascending aorta before pregnancy, and surgery should be considered when the aortic diameter is >50 mm.	IIa-C
Anticoagulation during pregnancy in Fontan patients.	IIa-C
Anticoagulation in pulmonary arterial hypertension (PAH) with suspicion of pulmonary embolism as the cause (or partly the cause) of the pulmonary hypertension.	IIa-C
In patients who are already taking drug therapy for pulmonary arterial hypertension before becoming pregnant, continuation should be considered after information about the teratogenic effects.	IIa-C
Women with pulmonary hypertension should be advised against pregnancy.	III-C
Women with an oxygen saturation <85% at rest should be advised against pregnancy.	III-C
Patients with TGA and a systemic RV with more than moderate impairment of RV function and/or severe TR should be advised against pregnancy.	III-C
Fontan patients with depressed ventricular function and/or moderate to severe atrioventricular valvular regurgitation or with cyanosis or with protein-losing enteropathy should be advised against pregnancy.	III-C

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Chapter 2

Ventricular septal defects

Definition and classification

The ventricular septum can be divided into two morphological components, the membranous septum and the muscular septum. The **membranous septum** is small and located at the base of the heart between the inlet and outlet components of the muscular septum, behind the septal leaflet of the tricuspid valve and below the right and non-coronary cusps of the aortic valve. Defects that involve the membranous septum are the most common VSD (70–80%) and are called **perimembranous, paramembranous, or infracristal**. Perimembranous defects may extend into the adjacent muscular septum and, in this case, are called **perimembranous inlet, perimembranous muscular**, and **perimembranous outlet** (Figure 2.1).[1,2]

The **muscular septum** can be divided into inlet, trabecular, and infundibular components. Defects in the inlet muscular septum, i.e. inferoposterior to the membranous septum, are called **inlet VSD** (usually part of a complete

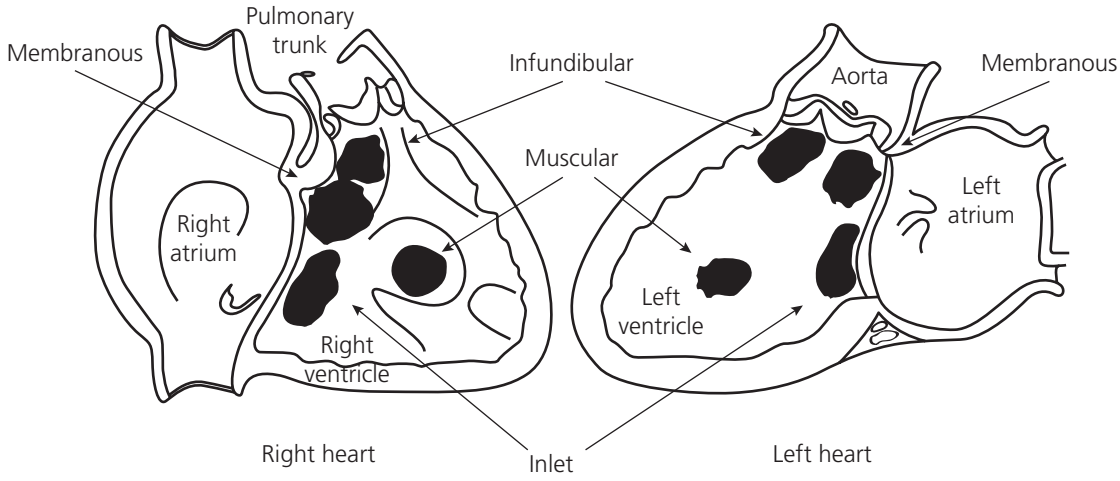

Figure 2.1 Location of VSDs.

Minette MS, Sahn DJ. Ventricular septal defects. *Circulation*. 2006;**114**:2190–7 with permission from Wolters Kluwer.

AV canal defect) (5%). A defect in the trabecular septum is called **muscular VSD** if the defect is completely rimmed by muscle (15–20%). Muscular VSDs may be multiple and can be acquired after a septal myocardial infarction. The infundibular septum separates the right and left ventricular outflow tracts. Defects in the infundibulum (5%) are called **infundibular, subarterial, or supracristal** (also referred to as **doubly committed** and **juxta-arterial**), **subpulmonary** or **subaortic**, **outlet, conal**, and **conoventricular**. Perimembranous or infundibular VSDs are often associated with progressive AR due to prolapse of an aortic cusp.

Epidemiology

VSD is the most common congenital heart defect after the bicuspid aortic valve, occurring in 40% of all children with congenital heart disease and with an estimated prevalence of 5% in newborn babies.[2] With paternal VSD, the recurrence risk in an offspring is 2%. Maternal VSD has a recurrence risk of 6–10%.

Aetiology

The origins of VSD are not known, and as in most cases of ACHD, they are most probably multifactorial (see Chapter 1). Initial reports about the teratogenic effects of selective serotonin uptake inhibitors in this respect have not been verified.[3] Recently a locus on chromosome 10p15 was associated with familial ventricular aneurysms and VSDs,[4] and mutations in the transcription factors TBX5 and GATA4 have been identified in familial cases of VSD.[2] No direct genetic testing at this time for VSD exists. **Associated disorders** are tetralogy of Fallot, AV canal, aortic coarctation, and, rarely, double-outlet right ventricle in which the VSD is subaortic, subpulmonary (Taussig-Bing anomaly), or noncommited (remote from the outlets).

Pathophysiology

The shunt volume in a VSD depends on the size of the defect and the pulmonary vascular resistance. Without pulmonary hypertension or obstruction to the right ventricle, the direction of shunt is left to right, with decreased LV output and compensatory intravascular volume overload. Thus, pulmonary artery, left atrial, and left ventricular volume overload develop. Moderate or large VSDs result in the transmission of LV pressure to pulmonary vascular bed with increased shear forces. This combination of high volume and pressure contributes to the development of irreversible pulmonary vascular disease.[5] VSD is the most common cause of pulmonary hypertension. Eventually, the elevated pulmonary vascular resistance becomes irreversible and leads to reversal of shunt and cyanosis, and Eisenmenger syndrome develops. In the setting of elevated pulmonary vascular resistance or right ventricular obstruction resulting from muscle bundles or pulmonary stenosis, the shunt volume is limited and may be right to left, depending on the difference in pressure.

Spontaneous closure Muscular or membranous VSDs can undergo spontaneous closure, usually in the first years of life. Up to 90% of such defects close spontaneously by one year of age.[6]

Presentation

Adults with small defects and normal pulmonary artery pressure are generally asymptomatic. Patients with large defects who survive to adulthood usually have left ventricular failure or pulmonary hypertension with associated RV failure.[7]

Physical examination

Physical signs depend on the size of VSD.

Holosystolic (pansystolic) murmur, with or without a **thrill**, with moderate or large defects. The grade of murmur depends on the velocity of flow. ***Very small or large defects*** with no shunt and defects with Eisenmenger physiology and right-to-left shunt may not have a VSD murmur. ***Muscular*** defects can be heard along the lower left sternal border and may vary in intensity, as the defect size changes with muscular contraction throughout systole. ***Infundibular*** defects close to the pulmonary valve can be heard best at the left upper sternal border.

Short, **mid-diastolic apical rumble** (increased mitral flow) may be heard.

Decrescendo murmur in the presence of AR.

Cyanosis with **clubbing** and **peripheral oedema** due to right-sided heart failure gradually appear.

Investigations

ECG is normal in small VSD. With large defects, there is LA and LV hypertrophy. When pulmonary hypertension develops, there is right axis deviation and RV hypertrophy.

Chest radiography is normal with small VSDs. With large defects, there is 'shunt vascularity', i.e. well-visualized small pulmonary arteries in the periphery of both lungs. When pulmonary hypertension develops, there is marked enlargement of the proximal pulmonary arteries, rapid tapering of the peripheral arteries (pruning), and oligaemic lung fields.

Transthoracic or **transoesophageal echocardiography** with colour flow mapping are used for quantification of the shunt, assessment of pulmonary artery pressure, distortion of the aortic valve, and obstruction of the right ventricular outflow tract (double-chamber RV). **Three-dimensional echocardiography** is useful for defects that are difficult to evaluate by two-dimensional imaging.

Cardiac magnetic resonance is very useful with complex associated lesions.

Cardiac catheterization is no longer necessary. However, it can be used to determine Qp/Qs by oximetry, and pulmonary artery pressure and resistance in case of anticipated closure (Table 2.1). It can also assess response to pulmonary vasodilators that can guide therapy and evaluate coexistent AR, dual-chamber RV, or multiple VSDs.

Table 2.1 ACC/AHA 2008 GL on ACHD

Recommendations for cardiac catheterization	
Cardiac catheterization to assess the operability of adults with VSD and PAH should be performed in an ACHD regional centre in collaboration with experts.	I-C
In adults with VSD in whom non-invasive data are inconclusive and further information is needed for management. Data to be obtained include the following:	
a. Quantification of shunting.	IIa-B
b. Assessment of pulmonary pressure and resistance in patients with suspected PAH. Reversibility of PAH should be tested with various vasodilators.	IIa-B
c. Evaluation of other lesions, such as AR and double-chambered right ventricle.	IIa-C
d. Determination of whether multiple VSDs are present before surgery.	IIa-C
e. Performance of coronary arteriography is indicated in patients at risk for coronary artery disease.	IIa-C
f. VSD anatomy, especially if device closure is contemplated.	IIa-C

ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. *J Am Coll Cardiol*. 2008;**52**:e1–e121 with permission from Elsevier.

Therapy

Medical

Adult patients with small VSD without evidence of left ventricular volume overload or AR do not require intervention.[8] These patients, as well as patients who had VSD repair, need surveillance for AR (perimembranous and infundibular VSDs) and endocarditis. Endocarditis is a lifelong risk in unoperated patients, being six times higher than in the normal population, but is primarily associated with the associated valve disease rather than the VSD itself.[9,10] Routine **endocarditis prophylaxis**, however, is not recommended any more for unrepaired VSDs. For closed VSDs, prophylaxis is recommended for 6 months after the procedure.[9,10] Patients with unrepaired VSDs are advised on dental hygiene and the physician should be alert of suspicious symptoms (see Chapter 1 and Chapter 79 on endocarditis). Survival up to 40 years after successful surgical VSD closure is slightly lower than in the general population, and follow-up for the identification of LV or RV dysfunction may be advisable. Aortic cross-clamp time and, most probably, post-operative arrhythmia are unfavourable prognostic signs.[11] In adults with inoperable VSDs with progressive/severe pulmonary vascular disease, pulmonary vasodilator therapy may be considered (ACC/AHA 2008 GL on ACHD, Class IIb-B).

Indications for closure

Indications are presented in Tables 2.2 and 2.3.[9,10] Main indications are:

- Qp/Qs >1.5
- History of endocarditis
- Progressive AR
- LV volume overload.

Contraindications for closure

Irreversible pulmonary arterial hypertension, i.e. PA pressure >2/3 systemic pressure or PVR >2/3 SVR at baseline or after oxygen or vasodilation.

Catheter closure

Currently, defect-specific devices are in the investigational stage and have been used both for congenital and post-MI VSD. They may interfere with AV or TV and carry a higher risk for AV block than surgical closure. Recent experience with closure of perimembranous VSDs indicates a <1% risk of complete AV block, which is comparable to that after surgical closure.[12,13]

Table 2.2 ACC/AHA 2008 GL on ACHD

Recommendations for Ventricular Septal Defect Closure	
Surgeons with training and expertise in CHD should perform VSD closure operations.	I-C
Closure of VSD when there is a Qp/Qs ≥2.0 and clinical evidence of LV volume overload.	I-B
Closure of VSD with a history of endocarditis.	I-C
Closure of VSD with net left-to-right shunting and PA pressure <2/3 systemic pressure and PVR <2/3 SVR.	IIa-B
Closure of VSD with net left-to-right shunting and Qp/Qs >1.5 and LV systolic or diastolic failure.	IIa-B
Device closure of a muscular VSD may be considered, especially if the VSD is remote from the tricuspid valve and the aorta, if the VSD is associated with severe left-sided heart chamber enlargement, or if there is PAH.	IIb-C
VSD closure in severe irreversible PAH.	III-B

ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. *J Am Coll Cardiol*. 2008;**52**:e1–e121 with permission from Elsevier.

Table 2.3 ESC 2010 GL on ACHD

Indications for intervention in VSD	
Surgical VSD closure in patients with symptoms that can be attributed to L–R shunting through the (residual) VSD and who have no severe pulmonary vascular disease.	I-C
Surgical VSD closure in asymptomatic patients with evidence of LV volume overload attributable to the VSD.	I-C
Surgical VSD closure in patients with a history of IE.	IIa-C
Surgery for patients with VSD-associated prolapse of an aortic valve cusp, causing progressive AR.	IIa-C
Surgery for patients with VSD and PAH when there is still net L–R shunt (Qp/Qs >1.5) present and PAP or PVR are <2/3 of systemic values (baseline or when challenged with vasodilators, preferably nitric oxide, or after targeted PAH therapy).	IIa-C
Surgery in Eisenmenger VSD and when exercise-induced.	III-C
Surgery if the VSD is small, not subarterial, does not lead to LV volume overload or pulmonary hypertension, and if there is no history of IE.	III-C

ESC Guidelines for the management of grown-up congenital heart disease. *Eur Heart J*. 2010;**31**:2915–57 with permission from Oxford University Press.

Pregnancy

Contraindicated in Eisenmerger syndrome.[8,9] Women with large shunts and pulmonary arterial hypertension may have arrhythmias, LV dysfunction, and progression of pulmonary hypertension. Combinations of epoprostenol and sildenafil may improve outcome in pregnant women with severe pulmonary hypertension who choose to continue pregnancy (see also General principles).[2] The estimated recurrence rate in the offspring is 6–10%.[9]

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Chapter 3

Atrioventricular septal defects

Definitions and classification of atrioventricular septal defects

The primordial single atrium divides into right and left sides by formation and fusion of the septum primum and septum secundum. The septum primum grows from the primordial atrial roof toward the endocardial cushions, and the septum secundum grows from the ventrocranial atrial wall on the right side of the septum primum.

Atrioventricular septal defects (**AV canal or endocardial cushion defects**) are **complete** (large VSD, common AV junction, and common AV valve with five leaflets) or **partial** (ostium primum ASD with a common AV junction, but two separate AV valves) (Figure 3.1).[1,2,3]

Ostium primum defect at the lower part of the atrial septum is a partial atrioventricular septal defect and may, or may not, have a VSD component (15% of ASDs).

Ostium secundum defect involves the region of the fossa ovalis (80%).

Sinus venosus defect at the junction of the right atrium and superior vena cava (5%).

Coronary sinus septal defect ('unroofed' coronary sinus) and **inferior sinus venosus defect** (at the junction of the right atrium and inferior vena cava): very rare (<1%).

Patent foramen ovale is the incomplete septal partition (usually an oval-shaped window) at the point where the septum secundum overlaps perforations of the septum primum (i.e. the foramen secundum).

Complete AV canals rarely reach adulthood without Eisenmenger syndrome. Partial AV canal defects (including ostium primum ASD) are not uncommon in adults.

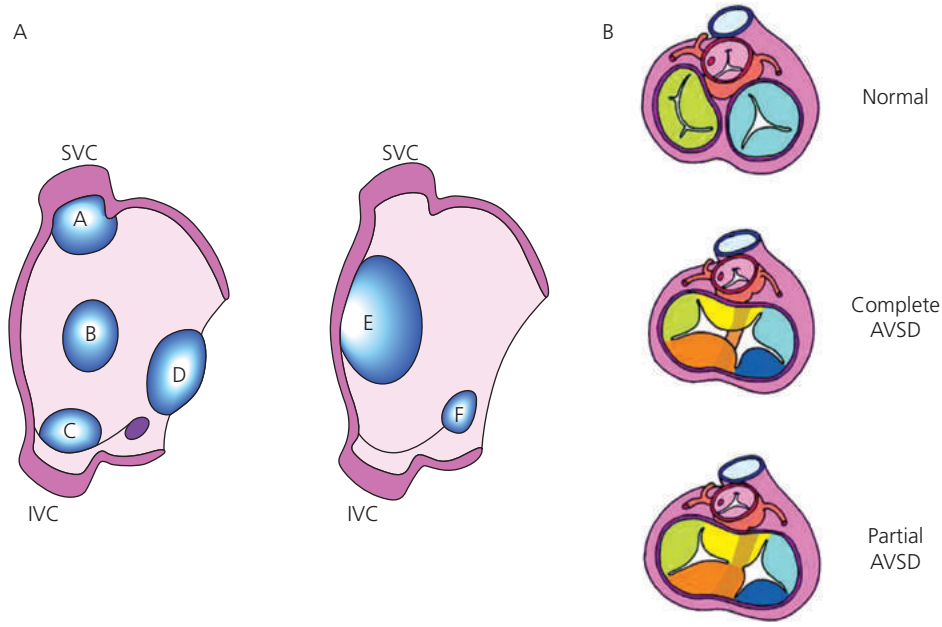

Figure 3.1 Anatomy of ASDs. A: superior sinus venosus ASD; B: secundum ASD; C: inferior sinus venosus ASD; D: ostium primum ASD or partial AV septal defect; E, secundum ASD without posterior septal rim; F: coronary sinus ASD.

Webb G, Gatzoulis MA. Atrial septal defects in the adult: recent progress and overview. *Circulation*. 2006;**114**:1645–53 with permission from Wolters Kluwer.

Ostium primum atrial septal defects

Epidemiology

All kinds of ASD, in general, represent one-third of the cases of congenital heart disease detected in adults, with an estimated incidence of 56/100 000 live births.[3,4]

Aetiology

Approximately 40% of patients with Down's syndrome have an AV septal defect, usually complete. Primum ASD may also be associated with DiGeorge, Ellis–Van Creveld, and Noonan's syndromes. Gender distribution is equal for ostium primum ASD. Adults with AV septal defects have an approximate 3–10% risk of recurrence in their offspring (excluding familial ASD and heart-hand syndromes with autosomal dominant inheritance).[5,6]

Abnormalities in genes essential to cardiac septation have been associated with atrial septal defects, including mutations in the cardiac transcription factor gene *NKX2-5* (associated with conduction abnormalities), *GATA4* and *TBX5, MYH6* located on chromosome 14q12,12.[3]

Pathophysiology

In ostium primum ASD, there is a cleft (trileaflet) mitral valve and results in variable degrees of regurgitation.[1,6] The shorter distance from the left AV valve annulus to the left ventricular apex, compared to that from the apex to the aortic annulus, combined with the cleft mitral valve, creates the characteristic 'gooseneck' deformity that used to be a major diagnostic feature on left ventriculography. The elongation of the left ventricular outflow tract as well as the chordal attachments of the left AV valve to the ventricular septum is the reason for the development of LV outflow tract obstruction which may occur even late after successful repair of the defect and require reoperation. The abnormal AV junction affects the AV conduction tissue, which, in turn, produces the characteristic left axis deviation and predisposes these patients to heart block. Most primum ASDs are relatively large and lead to right heart dilation. Right atrial dilation and stretching predisposes to the development of atrial flutter and fibrillation. The pathophysiology of isolated primum ASD is similar to that of a large secundum ASD (see Chapter 4).

Presentation

Depending on the severity of dysfunction of the left AV valve, adult patients with ostium primum ASD may become symptomatic at a much younger age than patients with other types of ASD.

Physical examination

Physical signs as in secundum ASD (see Chapter 4), but there is usually an additional **pansystolic murmur** due to MR (or TR). If there is also a ventricular defect, signs resemble those found in a large VSD with MR or TR. **Cyanosis** suggests pulmonary hypertension or pulmonary stenosis.

Investigations

Chest radiography in ostium primum ASD may be normal; otherwise resembles that of secundum ASD. Coexistent VSD usually is associated with cardiomegaly and pulmonary plethora.

ECG Long PR (unless if AF or flutter), left axis deviation, RBBB with RV hypertrophy. Development of right axis deviation in primum ASD suggests pulmonary hypertension. Patients should be monitored with an annual ECG and periodic monitoring for dysrhythmias (AHA 2015 statement, I-C).[7]

Echocardiography and **cardiac magnetic resonance** have replaced angiography as the main diagnostic tool for documentation of the type and size of the ASD, direction of the shunt and pulmonary venous return.

Maximal **exercise testing** can be useful to document exercise capacity in patients with symptoms that are discrepant with clinical findings or to document changes in oxygen saturation in patients with pulmonary hypertension (Class IIa-C, ACC/AHA guidelines on ACHD 2008).

Cardiac catheterization is used only to assess pulmonary hypertension and test vasoreactivity in patients with repaired or unrepaired ASD.[8]

Therapy

Primary surgical repair is recommended for partial AV canals, provided there is no irreversible pulmonary hypertension (Tables 3.1 and 3.2). In cases of residual interatrial or interventricular communications, endocardial pacing causes an elevated risk of paradoxical emboli, and epicardial pacing may be required.[9]

Endocarditis prophylaxis

It is recommended only in high-risk patients with repaired ASDs. Revised indications are discussed in Chapter 1 and Chapter 79 on endocarditis.

Pregnancy

It is well tolerated in the absence of severe pulmonary arterial hypertension, but with an increased risk of paradoxical embolus and stroke, arrhythmia, and heart failure (see Introduction). All women with a history of AVSD should be evaluated before conception to ensure that there are no significant residual haemodynamic lesions that might complicate the management of pregnancy. The issue of pregnancy risk and preventive measures should be discussed with women with Down's syndrome and their

Table 3.1 ACC/AHA 2008 GL on ACHD. Management of atrioventricular septal defect (AVSD)

Recommendations for surgical therapy	
Surgeons with training and expertise in CHD should perform operations for AVSD.	I-C
Surgical reoperation is recommended in adults with previously repaired AVSD, with the following indications: 1. Left AV valve repair or replacement for regurgitation or stenosis that causes symptoms, atrial or ventricular arrhythmias, a progressive increase in LV dimensions, or deterioration of LV function. 2. LVOT obstruction with a mean gradient >50 mmHg or peak instantaneous gradient >70 mmHg or a gradient <50 mmHg in association with significant mitral regurgitation or AR. 3. Residual/recurrent ASD or VSD with significant left-to-right shunting.	I-B

ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. *J Am Coll Cardiol*. 2008;**52**:e1–e121 with permission from Elsevier.

Table 3.2 ESC 2010 GL on ACHD. Indications for intervention in AVSD

Complete AVSD	
Cardiac surgery in patients with Eisenmenger physiology. In case of doubt, PVR testing is recommended.	III-C
Partial AVSD	
Surgical closure in case of significant volume overload of the RV.	I-C
AV valve regurgitation	
Symptomatic patients with moderate to severe AV valve regurgitation should undergo valve surgery, preferably AV valve repair.	I-C
Valve surgery for asymptomatic patients with moderate or severe left-sided valve regurgitation and LVESD >45 mm and/or impaired LV function (LVEF <60%) when other causes of LV dysfunction are excluded.	I-B
Surgical repair in asymptomatic patients with moderate or severe left-sided AV valve regurgitation who have signs of volume overload of the LV and a substrate of regurgitation that is very likely to be amenable for surgical repair.	IIa-C

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caregivers (Class I-C, ACC/AHA GL on ACHD 2008). The recurrence risk of congenital defects is up to 11%, and genetic counselling is necessary.[8]

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Chapter 4

Atrial septal defects

Ostium secundum atrial septum defect

Epidemiology

Secundum atrial septum defects (ASD) account for approximately 7% of all congenital malformations. Females predominate (70%). Secundum ASD is the most common cardiac manifestation of Holt–Oram syndrome (triphalangeal thumbs, ASD, or VSD) due to mutation of TBX5. Familial forms associated with gene mutations are rare and usually coexist with conduction disturbances.[1,2]

Pathophysiology

The pathophysiology of ASD is complex and multifactorial.[1] Conventionally, an ASD must be at least 10 mm in diameter for a significant left-to-right shunt (although most ASDs are not circular). A left-to-right atrial shunt is considered significant when the Qp/Qs ratio is greater than 1.5 or if it causes dilation of the right heart chambers. The RV is more compliant than the LV and, as a result, left atrial blood is shunted to the right atrium, causing increased pulmonary blood flow and dilatation of the pulmonary arteries. However, as opposed to VSD, pulmonary hypertension is uncommon, even with large defects, although, when it develops, it results in pulmonary pressures that approach systemic levels. It has been suggested that the ASD may be an associated marker of pulmonary hypertension, but not necessarily causative. Once a patient has reached adulthood with normal PA pressures he seldom develops pulmonary hypertension later. Left ventricular hypertrophy and mitral stenosis increase left-to-right shunting, whereas pulmonary stenosis, tricuspid stenosis, and pulmonary hypertension reduce a left-to-right shunt and may also cause a right-to-left shunt.

Presentation

Spontaneous closure of ASDs (<1 cm) may occur within the first year of life. Patients with small defects are asymptomatic. Patients with moderate/large ASDs often have no symptoms until the third of fifth decade of life despite substantial left-to-right shunting. The age at which symptoms appear is variable and not exclusively related to the size of the shunt. SOBOE is the most common initial presenting symptom. Atrial fibrillation (AF) or flutter due to atrial dilatation occurs at >40 years of age and is symptomatic. Eisenmenger syndrome occurs rarely only with large ASD in adults (<10%).[1] Occasionally, a paradoxical embolus or transient ischaemic attack may be the first clue to the presence of an ASD. Rarely, cyanosis may be seen, especially with inferior sinus venosus defects. Patients with unexplained RV volume overload should be investigated to rule out obscure ASD, partial anomalous venous connection, or coronary sinoseptal defect (ACC/AHA 2008 GL on ACHD, I-C). Morbidity and mortality are higher in men than in women.[3]

Physical examination

The absence of clinical signs does not necessarily exclude a haemodynamically important ASD.

Dilated pulmonary artery may be palpable in the second left interspace.

RV lift may be felt on held expiration or in the subxiphoid area on deep inspiration.

Soft systolic ejection murmur is heard at the upper left sternal border (pulmonary flow).

Wide and fixed split of S_2, the auscultatory hallmark of an ASD, is not always present.

Tricuspid diastolic rumble heard at the lower left sternal border reflects a large shunt.

Loud P_2 and **tricuspid regurgitation** may be heard with pulmonary hypertension.

Investigations

ECG SR, AF, or atrial flutter with right axis deviation and RV hypertrophy (incomplete RBBB). Inverted P waves in the inferior leads suggest an absent or deficient sinus node, as may be seen in a sinus venosus defect. First-degree heart block suggests a primum ASD, but may be seen in older patients with a secundum ASD.

Chest radiography May be normal, even with significant ASD. The central pulmonary arteries may also be characteristically enlarged, with pulmonary plethora and peripheral vascular pattern of shunt vascularity (well-visualized small pulmonary arteries in the periphery of both lungs).

Transthoracic echocardiography The functional importance of the defect can be estimated by the size of the right atrium and ventricle, the presence/absence of paradoxical septal motion (right ventricular volume overload),

ventricular septal orientation in diastole (volume overload) and systole (pressure overload), and an estimation of the shunt ratio. Pulmonary artery systolic pressures may be estimated from the Doppler velocity of tricuspid regurgitation.

Transoesophageal echocardiography may be needed to confirm the type of ASD, to delineate the pulmonary venous return, and to guide device closure.

Cardiac magnetic resonance is the gold standard for the assessment of right ventricular size and function and pulmonary venous return. It is also important for the diagnosis of sinus venosus defects.[1] In patients who cannot be subjected to MRI, computed tomographic scanning and angiography can offer similar information.

Cardiac catheterization is not necessary any more, unless to test vasoreactivity in pulmonary hypertension. Oximetry is now rarely used for shunt detection and Qp/Qs calculation. Coronary angiography is needed preoperatively in patients >40 years old.

Maximal exercise testing may be useful to document exercise capacity in patients with symptoms that are discrepant with clinical findings or to document changes in oxygen saturation in patients with mild or moderate PAH (ACC/AHA 2008 GL on ACHD, IIa-C).

Therapy

Small defects (<1 cm) may be left alone, but some patients develop right heart dilation later in life due to increased LVEDP and left-to-right shunting. Efforts should be made to maintain SR (Table 4.1).

Closure indications

Indications for ostium secundum ASDs are presented in Tables 4.1 and 4.2.[4–6] Main indications for closure are:

- Qp/Qs >1.5
- RA/RV enlargement
- Paradoxical embolism.

Device closure of significant secundum ASDs is beneficial regardless of age.[7]

Closure contraindications

- Irreversible pulmonary arterial hypertension more than 2/3 of SVR (see VSD). There have been case reports of such patients being managed with intravenous epoprostenol or oral bosentan in a way that ASD closure subsequently became possible.[2] A calculated PVR >8 Woods units generally precludes closure.[1]
- Severe left ventricular dysfunction.

Device closure is the treatment of choice for secundum ASDs.[4,5] Unsuitable anatomy includes inadequate atrial septal rims to allow stable device deployment (<5 mm), proximity of the defect to the AV valves, the coronary sinus, or the vena cavae, and very large secundum ASD (>35 mm). Complications are device embolization (<1%) and cardiac perforation (<0.1%). Small residual shunts seen on transoesophageal echocardiography after the end of the procedure are of no clinical significance. Late complications, such as mitral valve dysfunction, obstruction of the pulmonary veins, migraine, and erosion or perforation of the atrial wall or aorta, are very rare. However, arrhythmia and neurologic events remain long-term risks after ASD closure (device or surgical), especially if the patient had pre-existing arrhythmia.[8] After closure, aspirin and clopidogrel are prescribed for 6–12 months. Device erosion, which may present with chest pain or syncope, should warrant urgent evaluation (Table 4.1).

Surgical closure is required for patients with secundum ASD, whose anatomy is unsuitable for device closure. Perioperative mortality is <1%. Surgical repair, particularly before the age of 25 years, has been shown to result in normal long-term survival and reduce the incidence of arrhythmias, RV failure, and stroke.[9] Patients over the age of 40 remain at risk of atrial arrhythmias and systemic thromboembolism despite complete closure of the ASD, but surgery is preferable to medical treatment.[10,11] Age and pre-procedure arrhythmia are risk factors for late arrhythmia.[8]

Effect of closure on arrhythmias Surgical repair of ASD before 25 years of age has been shown to reduce the incidence of arrhythmias, such as atrial flutter and AF, but patients over the age of 40 years may remain at risk of atrial arrhythmias.[10,11] Up to 68% of patients who present with preoperative AF may remain in AF after successful ASD closure,[9] whereas, in patients over 40 years old, post-operative AF develops in 8–23% over the next 7–10 years.[10,11] New-onset AF occurs in 7% of patients after transcatheter patent foramen ovale (PFO) closure and in 12% of patients with an underlying ASD over the next 20 months.[7] A history of previous arrhythmia and age >40 years at closure are associated with an increased incidence of AF.[12–14] Usually, patients with pre-existing persistent AF remain in AF after device closure of their ASD,[7] whereas, in 45–67% of patients, resolution of paroxysmal atrial arrhythmias may be seen.[15] There has also been, however, some evidence that device closure might be proarrhythmic.[14] If ASD does not require closure on haemodynamic grounds, closure is unlikely to abolish flutter or AF. Recommendations on arrhythmia therapy in this setting are provided in Chapter 51.

Endocarditis prophylaxis

It is not recommended for unrepaired ASDs. Revised indications are discussed in Chapter 1 and Chapter 81 on endocarditis.

Table 4.1 Management of ASD

ACC/AHA 2008 GL on ACHD	
Recommendations for medical therapy	
Cardioversion after appropriate anticoagulation to attempt restoration of SR if AF occurs.	I-A
Rate control and anticoagulation if SR cannot be maintained by medical or interventional means.	I-A
Recommendations for interventional and surgical therapy	
Percutaneous or surgical ASD closure for right atrial and RV enlargement with or without symptoms.	I-B
A sinus venosus, coronary sinus, or primum ASD should be repaired surgically rather than by percutaneous closure	I-B
Surgeons with training and expertise in CHD should perform operations for various ASD closures.	I-C
Surgical closure of secundum ASD when concomitant surgical repair/replacement of a tricuspid valve is considered or when the anatomy of the defect precludes the use of a percutaneous device.	IIa-C
Percutaneous or surgical ASD closure for paradoxical embolism.	IIa-C
Percutaneous or surgical ASD closure for documented platypnoea orthodeoxia.	IIa-B
Percutaneous or surgical ASD closure with net left-to-right shunting and PA pressure <2/3 systemic levels, PVR <2/3 SVR, or when responsive to either pulmonary vasodilator therapy or test occlusion.	IIb-C
Concomitant Maze procedure may be considered for atrial tachyarrhythmias.	IIb-C
Irreversible PAH and no evidence of a left-to-right shunt.	III-B
Recommendations for post-intervention follow-up	
Early post-operative symptoms of undue fever, fatigue, vomiting, chest pain, or abdominal pain may represent post-pericardiotomy syndrome with tamponade and should prompt immediate evaluation with echocardiography.	I-C
Annual clinical follow-up is recommended for patients post-operatively if their ASD was repaired as an adult and the following conditions persist or develop: a. Pulmonary arterial hypertension. b. Atrial arrhythmias. c. RV or LV dysfunction. d. Coexisting valvular or other cardiac lesions.	I-C
Evaluation for possible device migration, erosion, or other complications is recommended for patients 3 months to 1 year after device closure and periodically thereafter.	I-C
Device erosion, which may present with chest pain or syncope, should warrant urgent evaluation.	I-C
AHA 2015 statement on congenital disease in the older adult	
Atrial level shunts with RV enlargement and without pulmonary hypertension should be closed to prevent the development of RV failure, improve exercise capacity and likely decrease future burden of atrial arrhythmia	I-B

ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. *J Am Coll Cardiol*. 2008;**52**:e1–e121 with permission from Elsevier.

American Heart Association Council on Clinical Cardiology. Congenital heart disease in the older adult: a scientific statement from the American Heart Association. *Circulation*. 2015;**131**:1884–931 with permission from Wolters Kluwer.

Table 4.2 ESC 2010 GL on ACHD

Indications for intervention in ASD	
ASD closure, regardless of symptoms in significant shunt (signs of RV volume overload) and PVR <5 WU.	I-B
Device closure for secundum ASD closure when applicable.	I-C
Intervention for all ASDs, regardless of size, in patients with suspicion of paradoxical embolism (exclusion of other causes).	IIa-C
Intervention for patients with PVR ≥5 WU, but <2/3 SVR or PAP <2/3 systemic pressure (baseline or when challenged with vasodilators, preferably nitric oxide, or after targeted PAH therapy), and evidence of net L–R shunt (Qp/Qs >1.5).	IIb-C
ASD closure in patients with Eisenmenger physiology.	III-C

ESC Guidelines for the management of grown-up congenital heart disease. *Eur Heart J*. 2010;**31**:2915–57 with permission from Oxford University Press.

Pregnancy

It is well tolerated in the absence of severe pulmonary arterial hypertension, with a small risk of paradoxical embolus and stroke, arrhythmia, and heart failure (see Chapter 1). Thus, in ASD diagnosed during pregnancy, closure can be deferred for 6 months after delivery. For a secundum defect, catheter device closure can be performed during pregnancy, if necessary, with transoesophageal or intracardiac echocardiographic guidance. The recurrence rate in offspring is estimated in 6–10%.[4]

Sinus venosus defect

Partial anomalous pulmonary venous return to the SVC or the right atrium is very common with **superior sinus venosus defect** (5–10% of all ASDs). Diagnosis is often more difficult than for other forms of ASD, and catheter closure is not possible. Unexplained RA or RV dilatation, especially in the presence of dyspnoea, should raise the possibility of the disease.[16] The **inferior sinus venosus defect** near the IVC is very rare. **Surgical closure** is required for patients with sinus venosus ASD. Indications for closure are presented in Table 4.1.[4,5]

Patent foramen ovale

The prevalence of a PFO ranges from 15% to 25% in autopsy studies to 20–40% with transoesophageal echocardiography in patients with a history of cerebral events. The average PFO size ranges from 1 to 19 mm, but increases with each decade of life; the mean diameter in the first decade is 3.4 mm and in the tenth decade 5.8 mm.[17] A common association is **atrial septal aneurysm** where part, or all, of the atrial septum shows aneurysmal dilatation, protruding into either atria (prevalence 1–5%) for, at least, 15 mm during the cardiorespiratory cycle. Under normal physiological conditions, the left atrial pressure is higher than the right

one and pushes the thin septum primum against the septum secundum and, except for very brief periods in each cardiac cycle, seals the potential opening of the PFO. Actions, such as the release of a Valsalva manoeuvre, can transiently reverse the normal left-to-right pressure gradient and cause an exaggerated transient leftward shift of the free edge of the septum primum, with apparent enlargement of the orifice of the PFO. Transoesophageal echocardiography can diagnose PFO by injecting saline contrast, preferably in the femoral vein than the upper extremities, and detect microbubbles in the left atrium immediately after arriving in the right atrium. If bubbles appear in the left atrium before or <5 beats after they appear in the right atrium, then the possibility of an anomalous venous connection to the left atrium or pulmonary arteriovenous malformations must be considered.[17] PFO is a potential risk factor for several clinical syndromes, including paradoxical systemic embolism, such as ischaemic stroke, myocardial infarction, decompression sickness in divers, and possibly migraine or Alzheimer's disease.[17]

PFO and cryptogenic stroke

Approximately 25–50% of strokes are cryptogenic, and there is evidence for association between a PFO and cryptogenic stroke.[17–19] The size of the PFO and interatrial shunt, the presence of an atrial septal aneurysm and Chiari strands (congenital remnants of the right valve of the sinus venosus), as well as the Eustachian valve that virtually extends the vena cava to the foramen ovale, may all contribute to the relative risk for stroke. Cryptogenic stroke due to tiny emboli (a few millimetres in size) can form anywhere in the venous system and occur with increasing frequency after 50 years of age. Paradoxical embolism does not necessarily require clinically apparent deep vein thrombosis since thrombi may emerge from the inferior vena cava. Still, however, a definitive causal relationship between PFO and cryptogenic stroke has not been convincingly established for the majority of affected patients, and concurrent aetiologies are identified for more than one-third of recurrent ischaemic events in patients with cryptogenic stroke.[20–22] Silent paroxysmal AF is an important cause of cryptogenic stroke and its presence should be ruled out in patients with cryptogenic stroke.[23,24] The annual risk of recurrent cryptogenic stroke, with or without PFO, is estimated to be 6–8% without any treatment. With either medical treatment or PFO closure, the annual risk decreases to approximately 2–4%.[17] Atrial septal aneurysm is found in 7–15% of stroke patients, and the association also remains debatable. In the PICCS trial, the presence of PFO in cryptogenic stroke patients, either on aspirin or warfarin, did not increase the chance of adverse events regardless of PFO size or the presence of atrial septal aneurysm. Warfarin was not superior to aspirin in this respect,[25] and the same results were produced by a recent meta-analysis of observational studies.[26] Pacemaker and ICD implantation increases the risk of stroke in patients with PFOs.[27]

PFO and migraine

There has been evidence that migraine headaches improve in selected patients who are subjected to PFO closure. However, the only randomized trial to test this hypothesis has failed to confirm it, and other studies have found no association between migraine headaches and the presence of PFO (MIST),[28] and new on-set migraine can be a complication of transcatheter ASD closure. Thus, closure of a PFO for migraine is not yet considered standard medical practice.

Indications for PFO closure

The optimal therapy for prevention of recurrent stroke or transient ischaemic attack in patients with cryptogenic stroke and patent foramen ovale remains controversial (Table 4.3). Treatment choices include medical therapy with antiplatelet agents or vitamin K antagonists or percutaneous device closure. Percutaneous device closure is now easy, and the simplest technique is with the Amplatzer occluder. Complications include cardiac perforation or air embolization during implantation, induced AF, non-specific malaise attributed to nickel allergy, and puncture site problems. However, existing data do not support a recommendation for PFO closure in patients with cryptogenic stroke or TIA and PFO. CLOSURE I, the first randomized trial, has failed to detect any benefit by PFO closure in these patients.[29] A recent observational study demonstrated a significant reduction of a composite outcome of TIA, stroke, and peripheral embolism,[30] and meta-analyses indicated potential benefits, especially in the elderly, patients with atrial septal aneurysm, and

Table 4.3 AHA/ASA 2014 GL for the prevention of stroke. Recommendations for patients with PFO

There are insufficient data to establish whether anticoagulation is equivalent or superior to aspirin for secondary stroke prevention in patients with PFO.	IIb-B
Antiplatelet therapy for patients with an ischaemic stroke or TIA and a PFO who are not undergoing anticoagulation therapy.	I-B
For ischaemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on stroke characteristics.	I-A
Inferior vena cava filter when anticoagulation is contraindicated.	IIa-C
For cryptogenic ischaemic stroke or TIA and a PFO without evidence for DVT, available data do not support a benefit for PFO closure.	III-A
In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT.	IIb-C

Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;**45**:2160–236 with permission from Wolters Kluwer.

patients with thrombophilia, following paradoxical embolism,[31] and with the use of Amplatzer occluder.[32] It is not known whether failures of the CLOSURE I and MIST trials can be attributed to failures of some of the devices used.[33] Recently, results of two RCTs were reported. In the RESPECT trial of 980 patients with prior cryptogenic stroke, the intent-to-treat analysis did not achieve statistical significance (risk reduction 51%, p = 0.08), but the per-protocol (risk reduction 63%, p = 0.03) and as-treated (risk reduction 73%, p = 0.007) analyses did reach significance.[34]

In the PC trial, closing the PFO did not significantly reduce the primary composite endpoint of death from any cause, non-fatal stroke, transient ischaemic attack (TIA), and peripheral embolism (risk reduction 37%, p = 0.34) in 414 patients with prior cryptogenic stroke compared with standard medical therapy.[35] In a recent meta-analysis of three trials (CLOSURE I, PC, and RESPECT), the combined outcome of death and vascular events showed a borderline statistically significant benefit for PFO closure when compared to medical treatment, and this was more prominent in patients with a substantial shunt.[36] The possibility of a device-specific beneficial effect that affected results of RCTs using various unfavourable devices has also been raised.[37]

Currently, PFO device closure is recommended by the ACCP (2C) in patients with recurrent events despite aspirin therapy or in the presence of DVT.[38] The AHA/ASA 2014 guidelines on stroke and TIA give a weak (IIb-C) recommendation for closure only in the setting of PFO and DVT.[39] Closure should also be considered in the platypnoea orthodeoxia syndrome [dyspnoea (platypnoea) and arterial desaturation in the upright position with improvement in the supine position (orthodeoxia)] and in scuba divers for prevention of decompression illness.[40] The potential role of PFO in fat embolism following long bone fracture is also investigated; the potential value of preoperative closure in these patients remains to be determined.[41]

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Chapter 5

Patent ductus arteriosus

Definition

The patent ductus arteriosus (PDA) connects the proximal descending aorta to the roof of the main pulmonary artery near the origin of the left pulmonary artery.[1] This fetal structure normally closes spontaneously within the first days after birth. It rarely closes after infancy.

Epidemiology

PDA accounts for approximately 10% of all congenital heart disease in the adult with a 2:1 female to male ratio.

Aetiology

PDA occurs in genetic syndromes with chromosomal aberrations (such as trisomy 21 and 4p syndrome), single-gene mutations (such as Carpenter's syndrome and Holt–Oram syndrome), and X-linked mutations (such as incontinentia pigmenti). Although most cases of PDA are seemingly sporadic, many may be due to multifactorial inheritance. In a family having one sibling with a PDA, there is a 3% chance of a PDA in a subsequent offspring. Rubella infection during the first trimester of pregnancy, children born in high altitude, and prematurity are associated with a high incidence of PDA.[1]

Pathophysiology and natural history

The shunt flow depends on the ductal resistance and the pressure gradient between the aorta and the pulmonary artery. Left-to-right shunting through the ductus arteriosus results in increased pulmonary fluid volume and left atrial and ventricular volume overload. If the ductus is large enough, the diastolic run-off may result in 'steal' phenomenon with

impaired coronary perfusion. When pulmonary vascular resistance approaches and exceeds systemic vascular resistance, ductal shunting reverses and becomes right-to-left, with eventual development of Eisenmenger syndrome.[2] Patients with Eisenmenger syndrome are cyanotic and typically have differential cyanosis (cyanosis and clubbing of the toes, but not the fingers, because the right-to-left ductal shunting is distal to the subclavian arteries). Cyanosis may be more profound when systemic vascular resistance is reduced, such as in hot weather or after exercise. Infective endarteritis and aneurysm of ductus arteriosus are the most common complications. Rarely, the ductus arteriosus aneurysm may rupture or present with symptoms of a thoracic mass, including hoarseness due to left vocal cord paralysis from recurrent left laryngeal nerve impingement and left bronchial obstruction. In previous series, one-third of patients with unrepaired PDA died of heart failure, pulmonary hypertension, or endarteritis by the age of 40 years, and two-thirds died by the age of 60 years.[3]

Presentation

The clinical significance of the PDA depends on its size. Patients may be completely asymptomatic with a heart murmur or present due to exercise intolerance, endovascular infection, or atrial fibrillation. Although most patients compensate well, even with a moderate left-to-right shunt, and remain asymptomatic during childhood, they may develop congestive heart failure or Eisenmenger syndrome in adulthood.

Physical examination

Patients with **very small** patent ductus have no abnormal physical findings. A continuous murmur may be heard.

In **moderate** or **large** ductus:

Machinery murmur Continuous murmur in upper left sternal border below the left clavicle. It is louder in systole and may radiate into the back, and a thrill may be present. S_2 may be inaudible.

LV apex prominent and collapsing **peripheral pulses**.

Pulmonary ejection click and **pulmonary regurgitation** appear as pulmonary hypertension (PAH) develops.

Investigations

Chest radiography may be normal or display cardiomegaly (LA and LV enlargement) with increased pulmonary vascular markings. The main pulmonary artery is enlarged, and, in older adults with pulmonary hypertension, calcification of the ductus may be evident.

ECG Normal or AF, LV hypertrophy, and LA enlargement in patients with moderate or large ductus shunts.

Echocardiography Colour Doppler is used for detecting the presence of a PDA and estimating the degree of ductal shunting. In patients with high pulmonary vascular resistance and PDA with low velocity or right-to-left flow, the ductus arteriosus may be very difficult to demonstrate. Findings, such as septal flattening, unexplained right ventricular hypertrophy, and high-velocity pulmonary regurgitation, should prompt a thorough investigation for a PDA. **Contrast echocardiography** may be helpful.

Cardiac magnetic resonance useful in patients with unusual PDA geometry and associated abnormalities of the aortic arch. **Computed tomography** can assess the degree of calcification which may be important if surgical therapy is considered.

Cardiac catheterization Diagnostic cardiac catheterization for uncomplicated PDA with adequate non-invasive imaging is not indicated (ACC/AHA 2008 GL on ACHD, III-B). Detailed assessment of the ductal anatomy by angiography is essential for the selection of the proper device size for transcatheter closure. In patients with elevated pulmonary artery pressure, assessment of pulmonary vascular resistance and its response to vasodilating agents may be helpful in determining the possibility of ductus closure.

Table 5.1 ACC/AHA 2008 GL on ACHD

Recommendations for medical therapy	
Routine follow-up is recommended for patients with a small PDA without evidence of left-sided heart volume overload. Follow-up is recommended every 3 to 5 years for patients with a small PDA without evidence of left-heart volume overload.	I-C
Endocarditis prophylaxis is not recommended for those with a repaired PDA without residual shunt.	III-C
Recommendations for closure of patent ductus arteriosus	
Closure of a PDA, either percutaneously or surgically, for:	
a. Left atrial and/or LV enlargement or if PAH is present, or in the presence of net left-to-right shunting.	I-C
b. Prior endarteritis.	I-C
Careful evaluation and consultation with ACHD interventional cardiologists is recommended before surgical closure is selected as the method of repair for patients with a calcified PDA.	I-C
Surgical repair, by a surgeon experienced in CHD surgery, is recommended when:	
a. The PDA is too large for device closure.	I-C
b. Distorted ductal anatomy precludes device closure (e.g. aneurysm or endarteritis).	I-B
Closure of asymptomatic small PDA by catheter device.	IIa-C
PDA closure in PAH with a net left-to-right shunt.	IIa-C
PDA closure in PAH and net right-to-left shunt.	III-C

ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. *J Am Coll Cardiol*. 2008;**52**:e1–e121 with permission from Elsevier.

Table 5.2 ESC 2010 GL on ACHD

Indications for intervention in PDA	
PDA closure in patients with signs of LV volume overload.	I-C
PDA closure in patients with pulmonary arterial hypertension (PAH) but PAP <2/3 of systemic pressure or PVR <2/3 of SVR.	I-C
Device closure is the method of choice where technically suitable.	I-C
PDA closure in patients with PAH and PAP >2/3 of systemic pressure or PVR >2/3 of SVR but still net L–R shunt (Qp/Qs >1.5) or when testing (preferably with nitric oxide) or treatment demonstrates pulmonary vascular reactivity.	IIa-C
Device closure of small PDAs with continuous murmur (normal LV and PA pressure).	IIa-C
PDA closure should be avoided in silent duct (very small, no murmur).	III-C
PDA closure in PDA Eisenmenger and patients with exercise-induced lower limb desaturation.	III-C

ESC Guidelines for the management of grown-up congenital heart disease. *Eur Heart J.* 2010;**31**:2915–57 with permission from Oxford University Press.

Therapy

PDA is associated with various complications of prematurity, and cyclo-oxygenase inhibitors, such as high-dose ibuprofen, are the first-line intervention for closure of the PDA.[4]

Indications for closure of PDA are presented in Tables 5.1 and 5.2. Routine closure of even small PDAs is now recommended by most experts. The rationale is that endarteritis of clinically silent PDA has been reported, and device closure is now effective and safe.[5,6] In patients with borderline pulmonary arterial hypertension, a post-trial occlusion systolic pulmonary:systemic pressure ratio >0.5 is a useful haemodynamic parameter for identifying patients who have a high risk of postprocedural pulmonary arterial hypertension after transcatheter patent ductus arteriosus closure.[7] Patients with PDA and pulmonary vascular disease, who are considered unacceptable candidates for definitive closure, may be managed with pulmonary vasodilating agents, such as chronic oxygen, PGI_2, calcium channel blockers, endothelin antagonists, and phosphodiesterase inhibitors. One strategy in such patients is to accomplish partial closure of the ductus by surgery or transcatheter techniques to make it 'restrictive', but not completely closed, followed by long-term therapy with pulmonary vasodilating agents. If, in follow-up, the pulmonary vascular resistance decreases, then complete closure may be considered.[1] Follow-up is recommended every 3 to 5 years for patients with a small PDA without evidence of left heart volume overload (ACC/AHA 2008 GL on ACHD, I-C).

Transcatheter closure has become the treatment of choice in children and adults, especially in cases of calcified ductus arteriosus with increased pulmonary vascular resistance. The most commonly used occluders are the Nit-Occlud coil occlusion system and the Amplatzer duct occluder. Complications of transcatheter closure, such as device embolization of the patent ductus, are rare. Other rare complications are flow disturbance in the proximal left pulmonary artery or descending aorta from a protruding device, haemolysis from high-velocity residual shunting, and infection.

Surgical repair remains the treatment of choice for the rare very large ductus.

Infective endocarditis prophylaxis is not recommended any more for unrepaired PDAs. For closed PDAs, prophylaxis is recommended for 6 months after the procedure (see also Chapter 1).[8,9]

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Chapter 6

Right ventricular outflow tract obstruction

Definitions and classification of RVOT obstruction

Obstruction to the right ventricular outflow tract (RVOT) in the adult patient can be either congenital or acquired. Congenital obstruction can be at the pulmonary valve, below the pulmonary valve, or above the valve. Below the pulmonary valve, obstruction can be either at the infundibular (as happens in Fallot) or the subinfundibular level. Congenital pulmonary stenosis constitutes 10% of the cases of congenital heart disease in adults.[1]

Valvular pulmonary stenosis

Obstruction of the RV outflow tract is valvular in 90% of patients. Valvular pulmonary stenosis may be an isolated abnormality or in association with a VSD or Noonan's syndrome (dysplastic pulmonary valve, facial dysmorphism, cardiac defects, and variable cognitive deficits). The leaflets are thin and pliant. In 10–15% of patients, the valve is dysplastic and the leaflets thickened and immobile, composed of myxomatous tissue.[1,2]

Presentation

Adults may be asymptomatic. With severe stenosis, exercise intolerance, shortness of breath on exertion, anginal pain, and syncope may occur. Gradients >30 mmHg may deteriorate with ageing and result in RV hypertrophy and eventually right heart failure (elevated JVP, hepatic congestion, ascites, and peripheral oedema).

Physical examination

RV heave and thrill may be present in moderate/severe PS

S_2 widely split but moves normally with respiration

Pulmonary ejection click

Crescendo-decrescendo murmur increased by inspiration.

Investigations

ECG may show right axis deviation and RV hypertrophy.

Table 6.1 Severity of PS

PV	Area	Peak gradient	RVSP
Mild	>1 cm^2	<50 mmHg	<75 mmHg
Moderate	0.5–2 cm^2	50–80 mmHg	75–100 mmHg
Severe	<0.5 cm^2	>80 mmHg	>100 mmHg

Brickner ME, *et al*. Congenital heart disease in adults. *N Engl J Med*. 2000;**342**:256–63 with permission from Massachusetts Medical Society.

Chest radiography may show post-stenotic dilatation of the main PA and diminished vascular markings.

Echocardiography reveals RV hypertrophy and paradoxical septal motion. Doppler mean gradients are considered (Table 6.1).[3]

Stress testing with pulse oximetry may reveal a right-to-left shunt in the setting of severe pulmonary stenosis and an associated patent foramen ovale.

Cardiac catheterization is not necessary for diagnosis. It may be used for accurate gradient assessment in patients with echo peak gradients >30 mmHg for consideration of balloon valvotomy.

Therapy

Asymptomatic patients with mild stenosis do not need intervention (Tables 6.2 and 6.3) (see also Chapter 22).[4,5] Balloon valvotomy is the treatment of choice for symptomatic patients with less than moderate PR and peak gradient >50 mmHg (mean >30 mmHg) or asymptomatic patients with peak gradient >60 mmHg (mean >40 mmHg). Surgical valvotomy or replacement with a bioprosthetic valve is reserved for patients with significant pulmonary regurgitation (PR) (an ominous prognostic sign for subsequent RV dilation and failure) or dysplastic valves unsuitable for balloon valvuloplasty. Rare complications of balloon valvotomy are PR, pulmonary oedema, cardiac perforation, AV block, and transient reactive RVOT obstruction.

Subvalvular pulmonary stenosis

Usually occurs in association with tetralogy of Fallot (before or after surgery) or double-chambered RV.[2] In

Table 6.2 ACC/AHA 2008 GL on ACHD

Recommendations for intervention in patients with valvular pulmonary stenosis	
Balloon valvotomy for asymptomatic patients with a domed pulmonary valve and a peak instantaneous Doppler gradient >60 mmHg or a mean Doppler gradient >40 mmHg (in association with less than moderate PR).	I-B
Balloon valvotomy for symptomatic patients with a domed pulmonary valve and a peak instantaneous Doppler gradient >50 mmHg or a mean Doppler gradient >30 mmHg (in association with less than moderate PR).	I-C
Surgical therapy in severe PS and an associated hypoplastic pulmonary annulus, severe pulmonary regurgitation, subvalvular PS, or supravalvular PS. Surgery is also preferred for most dysplastic pulmonary valves and when there is associated severe TR or the need for a surgical Maze procedure.	I-C
Surgeons with training and expertise in CHD should perform operations for the RVOT and pulmonary valve.	I-B
Balloon valvotomy in asymptomatic patients with a dysplastic pulmonary valve and a peak instantaneous gradient by Doppler >60 mmHg or a mean Doppler gradient >40 mmHg.	IIb-C
Balloon valvotomy in selected symptomatic patients with a dysplastic pulmonary valve and peak instantaneous gradient by Doppler >50 mmHg or a mean Doppler gradient >30 mmHg.	IIb-C
Balloon valvotomy for asymptomatic patients with a peak instantaneous gradient by Doppler <30 mmHg or <50 mmHg and normal cardiac output.	III-C
Balloon valvotomy is not recommended for symptomatic patients with PS and severe PR.	III-C

ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. *J Am Coll Cardiol*. 2008;**52**:e1–e121 with permission from Elsevier.

Table 6.3 ESC 2010 GL on ACHD

Indications for intervention in RVOT obstruction	
Repair of RVOTO at any level, regardless of symptoms, when Doppler peak gradient is >64 mmHg (peak velocity >4 m/s), provided that RV function is normal and no valve substitute is required.	I-C
In valvular PS, balloon valvotomy should be the intervention of choice.	I-C
In asymptomatic patients in whom balloon valvotomy is ineffective and surgical valve replacement is the only option, surgery should be performed in the presence of a systolic RVP >80 mmHg (TR velocity >4.3 m/s).	I-C
Intervention in patients with gradient <64 mmHg in the presence of: – Symptoms related to PS, or – Decreased RV function, or – Double-chambered RV (which is usually progressive), or – Important arrhythmias, or – Right-to-left shunting via an ASD or VSD.	IIa-C
Repair in peripheral PS, regardless of symptoms, if >50% diameter narrowing and RV systolic pressure >50 mmHg and/or lung perfusion abnormalities are present.	IIa-C

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double-chambered RV, a muscular band divides the RV into a high-pressure proximal inflow portion and a low-pressure distal outflow chamber. VSD or membranous subaortic stenosis may also be present. When the obstruction is mild, these patients may present with exercise intolerance and a harsh systolic murmur as young adults. With more severe obstruction and hypertrophy, ventricular arrhythmia, syncope, and sudden cardiac death may be the first presenting sign. Surgical muscle resection, with or without patching of the outflow tract, is indicated in symptomatic patients with peak Doppler gradient >60 mmHg (mean 40 mmHg).[5]

Supravalvular pulmonary stenosis

Supravalvular pulmonary stenosis can occur as an isolated abnormality or in association with complex cardiac

malformations, such as Williams syndrome (infantile hypercalcaemia, elfin facies, and mental retardation), tetralogy of Fallot, Noonan's syndrome, and rubella or toxoplasmosis infection during the first trimester of pregnancy.[1] It may also be the result of surgical scarring from operations, such as pulmonary artery banding or arterial switch. Patients with exercise intolerance or significant gradients are referred for surgery. Stent-based valve implants are experimental.

Branch pulmonary artery stenosis

They may be isolated or multiple, as happens in Williams and Noonan's syndromes, congenital rubella, and Alagille (intrahepatic cholestasis) and Keutel (cartilage calcification and brachytelephalangia) syndromes.[1] Although uncommon, the diagnosis of branch PA stenosis should always be considered in patients with a history of congenital heart disease who present with symptoms of pulmonary embolism, such as dyspnoea, fatigue, and segmental lung ventilation-perfusion mismatches. Balloon and stent angioplasty are used in isolated stenoses with >50% diameter stenosis and RVSP >50 mmHg (Table 6.4).[5]

Double-chambered RV and **RV to PA conduits** may also result in RVOT obstruction (Tables 6.5 to Table 6.7).

Table 6.4 ACC/AHA 2008 GL on ACHD

Recommendations for interventional therapy in the management of branch and peripheral pulmonary stenosis	
Percutaneous interventional therapy for the management of appropriate focal branch and/or peripheral pulmonary artery stenosis with >50% diameter narrowing, elevated RV systolic pressure >50 mmHg, and/or symptoms.	I-B
Surgeons with training and expertise in CHD should perform operations for management of branch pulmonary artery stenosis not anatomically amenable to percutaneous interventional therapy.	I-B

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Table 6.5 ACC/AHA 2008 GL on ACHD

Recommendations for reintervention in patients with right ventricular-pulmonary artery conduit or bioprosthetic pulmonary valve stenosis	
Surgeons with training and expertise in CHD should perform operations for patients with severe pulmonary prosthetic valve stenosis (peak gradient >50 mmHg) or conduit regurgitation and any of the following: a. Decreased exercise capacity. b. Depressed RV function. c. At least moderately enlarged RV end-diastolic size. d. At least moderate TR.	I-C
Surgical or percutaneous therapy in symptomatic patients with discrete RV-pulmonary artery conduit obstructive lesions with >50% diameter narrowing or when a bioprosthetic pulmonary valve has a peak gradient by Doppler >50 mmHg or a mean gradient >30 mmHg.	IIa-C
Surgical or percutaneous therapy in asymptomatic patients when a pulmonary bioprosthetic valve has a peak Doppler gradient >50 mmHg.	IIa-C
Surgical intervention preferable to percutaneous catheter intervention when an associated Maze procedure is being considered.	IIb-C

ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. *J Am Coll Cardiol*. 2008;**52**:e1–e121 with permission from Elsevier.

Table 6.6 ACC/AHA 2008 GL on ACHD

Recommendations for intervention in patients with double-chambered right ventricle	
Surgery for patients with a peak mid-ventricular gradient by Doppler >60 mmHg or a mean Doppler gradient >40 mmHg, regardless of symptoms.	I-B
Symptomatic patients with a peak mid-ventricular gradient by Doppler >50 mmHg or a mean Doppler gradient >30 mmHg may be considered for surgical resection if no other cause of symptoms can be discerned.	IIb-C

ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. *J Am Coll Cardiol*. 2008;**52**:e1–e121 with permission from Elsevier.

Table 6.7 ESC 2010 GL on ACHD

Indications for intervention in patients with right ventricular to pulmonary artery conduits	
Surgery for symptomatic patients with RV systolic pressure >60 mmHg (TR velocity >3.5 m/s; may be lower in case of reduced flow) and/or moderate/severe PR	I-C
Surgery for asymptomatic patients with severe RVOTO and/or severe when at least one of the following criteria is present: – Decrease in exercise capacity (cardiopulmonary exercise testing). – Progressive RV dilation. – Progressive RV systolic dysfunction. – Progressive TR (at least moderate). – RV systolic pressure >80 mmHg (TR velocity >4.3 m/s). – Sustained atrial/ventricular arrhythmias.	IIa-C

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Chapter 7

Left ventricular outflow tract obstruction

Definitions and classification of LVOT obstruction

Left ventricular outflow tract (LVOT) obstruction syndromes include subvalvar AS, valvular AS, and supravalvular AS.[1] Aortic coarctation is also considered a form of LVOT obstruction.[2] Obstruction can occur singly or at multiple levels, as an isolated lesion, or in combination with septal defects or conotruncal anomalies. LVOTOs are congenital in the vast majority of individuals younger than 50 years, although some variants of subaortic obstruction do exist. For recommendations on the evaluation and management of these patients, see also Chapter 15 on valve disease.

Valvular aortic stenosis (bicuspid aortic valve)

Epidemiology

Bicuspid aortic valve (BAV) is the most common congenital heart defect, with a prevalence estimated between 0.5% and 2%.[3] There is a male predominance of approximately 3:1. In patients with symptomatic AS, younger than 65 years of age, a bicuspid valve is the most common pathological finding. Although BAV is more likely due to mutations in different genes with dissimilar patterns of inheritance,[4] clinical studies have reported a 9% prevalence of BAV in first-degree relatives of patients and echocardiographic screening in first-degree relatives is recommended.[5,6] Associated abnormalities (20% of patients with bicuspid valves) are coarctation and PDA. Aortic root and/or ascending aorta dilatation (bicuspid aortopathy) is present in 50% of patients.[7] In addition, BAV is found in several genetic syndromes involving left-sided obstructive lesions, such as Shone's syndrome (multiple left-sided lesions of inflow and outflow obstruction, and parachute mitral valve), Williams syndrome with supravalvular stenosis, and Turner's syndrome with coarctation of the aorta.

Pathophysiology

The morphologic patterns of the bileaflet valve vary according to which commissures have fused, with the

most common pattern involving fusion of the right and left cusps. Dilatation of the thoracic aorta is associated with a bicuspid valve and is attributed to structural abnormalities of the medial layer of the aortic (and the pulmonary) wall, such as decreased fibrillin, elastin fragmentation, and apoptosis, as well as valve-related haemodynamics and increased shear stress.[8] The bicuspid valve is not stenotic at birth, but it is subjected to haemodynamic stress that leads to thickening and calcification of the leaflets.

Presentation and natural history

Symptoms usually develop in adulthood due to haemodynamically induced calcification of the valve. By the age of 50 years, 25–49% of patients will require surgery or suffer a major cardiac event.[9,10] AS, AR, aortic aneurysm or dissection, and endocarditis may occur.

Physical examination

Ejection click followed by **murmur of AS** and possibly **AR**.

Investigations

Echocardiography The main task is to establish the diagnosis and exclude a tricuspid valve. The valve must be visualized in systole in the short-axis view since, during diastole, the raphe can make the valve appear trileaflet. In diastole, the orifice has a characteristic 'fish-mouthed' appearance. Evidence of aortic dilation should be always looked for in patients with a bicuspid valve. In asymptomatic adolescents and young adults with a mean Doppler gradient >30 mmHg or peak instantaneous gradient >50 mmHg, yearly echocardiographic assessment is recommended (ACC/AHA 2008 GL on ACHD, I-B). All patients with a bicuspid aortic valve should have both the aortic root and ascending thoracic aorta evaluated for evidence of aortic dilatation (ACC/AHA 2010 GL on Aortic Disease, I-B).[5]

Transoesophageal echocardiography or cardiac magnetic resonance may be needed in case of uncertainty.

Exercise stress testing is useful in patients with a mean Doppler gradient >30 mmHg or peak Doppler gradient >50 mmHg if the patient is interested in athletic participation or if clinical findings differ from non-invasive measurements (ACC/AHA 2008 GL on ACHD, IIa-C).

Dobutamine stress testing may be used in the evaluation of a mild aortic valve gradient in the face of low LV ejection fraction and reduced cardiac output.

First-degree relatives of patients with a bicuspid aortic valve should be evaluated for the presence of a bicuspid aortic valve and asymptomatic thoracic aortic disease (ACC/AHA 2008 GL on ACHD, II-B).

Therapy

Beta blockers in aortic root dilatation and ACE/ARB in hypertension are useful. Statins may also be used to slow the degenerative process (Table 7.1). Patients with moderate AS (mean gradient at least 25 mmHg or peak at least 40 mmHg) should be restricted from competitive sports.[11] Intervention is usually recommended in asymptomatic patients with peak-to-peak gradients >60 mmHg at catheterization or symptomatic patients with peak-to-peak

Table 7.1 ACC/AHA 2008 GL on ACHD. Medical therapy and intervention in LVOT obstruction and associated lesions

Recommendations for medical therapy	
Treat systemic hypertension in patients with AS while monitoring diastolic blood pressure to avoid reducing coronary perfusion.	IIa-C
Beta blockers in patients with BAV and aortic root dilatation.	IIa-C
Long-term vasodilator therapy in patients with AR and systemic hypertension while carefully monitoring diastolic blood pressure to avoid reducing coronary perfusion.	IIa-C
Statins in patients with risk factors for atherosclerosis for slowing down degenerative changes in the aortic valve and preventing atherosclerosis.	IIb-C
Vasodilator therapy is not indicated for long-term therapy in AR for the following:	
a. The asymptomatic patient with only mild to moderate AR and normal LV function.	III-B
b. The asymptomatic patient with LV systolic dysfunction who is a candidate for AVR.	III-B
c. The asymptomatic patient with either LV systolic function or mild to moderate LV diastolic dysfunction who is a candidate for AVR.	III-C
Recommendations for catheter interventions for adults with valvular aortic stenosis	
Aortic balloon valvotomy in young adults without calcified aortic valves and no AR in: a. Angina, syncope, dyspnoea on exertion, and peak-to-peak gradients at catheterization >50 mmHg. b. ST or T wave abnormalities in the left precordial leads on ECG at rest or with exercise and a peak-to-peak catheter gradient >60 mmHg.	I-C
Aortic balloon valvotomy in asymptomatic adolescents or young adults with a peak-to-peak gradient on catheterization >50 mmHg when the patient is interested in playing competitive sports or becoming pregnant.	IIa-C
Aortic balloon valvotomy as a bridge to surgery in haemodynamically unstable adults or at high risk for AVR, or when AVR cannot be performed due to co-morbidities.	IIb-C

(*Continued*)

Table 7.1 Continued

In older adults, aortic balloon valvotomy is not recommended as an alternative to AVR (younger patients may be an exception).	III-B
Aortic balloon valvotomy in adolescents and young adults with a peak-to-peak gradient <40 mmHg without symptoms or ECG changes.	III-B
Recommendations for aortic valve repair/replacement and aortic root replacement (see also Chapter 19 on AR and Chapters 70 and 71 on aortic diseases)	
Aortic valvuloplasty, AVR, or Ross repair in patients with severe AS or chronic severe AR while they undergo cardiac surgery.	I-C
AVR for patients with severe AS and LV dysfunction (LVEF <50%).	I-C
AVR in adolescents or young adults with severe AR and:	
a. Development of symptoms.	I-C
b. Development of persistent LV dysfunction (LVEF <50%) or progressive LV dilatation (LV end-diastolic diameter—4 standard deviations above normal).	I-C
Surgery to repair or replace the ascending aorta in a patient with a bicuspid aortic valve when the ascending aorta diameter is ≥5.0 cm or when there is progressive dilation at a rate ≥5 mm per year.	I-B
AVR for asymptomatic patients with severe AR and normal systolic function (LVEF >50%) but with severe LV dilatation (LV end-diastolic diameter >75 mm or end-systolic dimension >55 mm*).	IIa-B
Surgical aortic valve repair or replacement in patients with moderate AS undergoing other cardiac or aortic root surgery.	IIa-B
AVR for asymptomatic patients with any of the following indications: a. Severe AS and abnormal response to exercise. b. Evidence of rapid progression of AS or AR. c. Mild AS while undergoing other cardiac surgery and evidence of a calcific aortic valve. d. Extremely severe AS (aortic valve area <0.6 cm and/or mean Doppler systolic AV gradient >60 mmHg). e. Moderate AR undergoing other cardiac surgery. f. Severe AR with rapidly progressive LV dilation, end-diastolic dimension 70 mm or end-systolic dimension 50 mm, with declining exercise tolerance or with abnormal haemodynamic response to exercise.	IIb-C
Surgical repair in adults with AS or AR and concomitant ascending aortic dilatation (ascending aorta diameter >4.5 cm) coexisting with AS or AR.	IIb-B
Early surgical repair in adults with the following indications: a. AS and a progressive increase in ascending aortic size. b. Mild AR if valve-sparing aortic root replacement is being considered.	IIb-C
AVR for prevention of sudden death in asymptomatic adults with AS and without Class IIa/IIb indications for intervention.	III-B
AVR in asymptomatic patients with AR and normal LV size and function.	III-B

* Consider lower threshold values for patients of small stature of either gender.
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Table 7.2 ESC 2010 GL on ACHD

Indications for intervention in AS	
Valve replacement in severe AS and any valve-related symptoms (angina, dyspnoea, syncope).	I-B
Surgery for asymptomatic patients with severe AS when they develop symptoms during exercise testing	I-C
Surgery, regardless of symptoms, when systolic LV dysfunction is present in severe AS (LVEF <50%), unless it is due to other causes	I-C
Surgery, regardless of symptoms, when patients with severe AS undergo surgery of the ascending aorta or of another valve, or CABG	I-C
Surgery, regardless of symptoms, if the ascending aorta is >50 mm (27.5 mm/m^2 BSA) and no other indications for cardiac surgery are present	IIa-C
Surgery in asymptomatic patients with severe AS when they present with a fall in blood pressure below baseline during exercise testing	IIa-C
Surgery in asymptomatic patients with severe AS and moderate-to-severe calcification and a rate of peak velocity progression of ≥0.3 m/year	IIa-C
Additional valve replacement in patients with moderate AS undergoing CABG or surgery of the ascending aorta or another valve.	IIa-C
Surgery for severe AS with low gradient (<40 mmHg) and LV dysfunction with contractile reserve	IIa-C
Surgery for severe AS with low gradient (<40 mmHg) and LV dysfunction without contractile reserve	IIb-C
Surgery in asymptomatic patients with severe AS and excessive LV hypertrophy (≥15 mm), unless this is due to hypertension	IIb-C

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catheter gradients >50 mmHg. Valvuloplasty is the treatment of choice in children and perhaps young adults with BAV. Following successful valvuloplasty, sudden death is extremely rare and exercise restriction is not recommended.[12] The aortic root size should be taken into account (see Chapter 72). Aortic root size >5.5 cm, or >4.5 cm when valve surgery is contemplated, indicates AVR and root replacement,[13] and changes in root size >0.5 cm/year is probably also an indication for root replacement.[7] The ACC/AHA and ESC recommendations for management are presented in Tables 7.1 and 7.2.[1,6] For recommendations on bicuspid aortic valve, see also Chapter 19 and Chapter 20.

Pregnancy

Patients with bicuspid aortic valves may have an associated aortopathy making them prone to dilation and potentially dissection of the aortic root or ascending aorta. In women with bicuspid aortic valves, the aortic root and ascending aorta should be evaluated before pregnancy. Although data are limited, it is usually recommended that patients with aortic root dilatation associated with congenital bicuspid aortic valves should be advised to avoid pregnancy if their aortic root dimensions are ≥4.5 cm.[14]

Subvalvular aortic stenosis

Subvalvular aortic stenosis comprises a spectrum of obstructive processes in the LV outflow tract that ranges from a discrete subaortic membranous obstruction to a fibromuscular tunnel-type obstruction to hypertrophic cardiomyopathy.[15] In patients with **membranous obstruction**, a thin fibrous membrane of variable thickness and with a central lumen stretches across the LV outflow tract from the septal surface to the anterior leaflet of the mitral valve. In adults, as opposed to children, progression of the obstruction and development of AR is slow over time. With the **tunnel-type obstruction**, a thick fibromuscular tubular narrowing diffusely reduces the diameter of the outflow tract. This condition has to be differentiated from hypertrophic cardiomyopathy. Aortic regurgitation is present in 30–80% of patients and thought to develop secondary to aortic valve damage caused by the high-velocity subvalvular jet.[16] Surgery is offered when symptoms, in the context of a peak gradient >50 mmHg or LV hypertrophy with reduced systolic function, develop (Tables 7.3 and 7.4). Survival is excellent after surgery for discrete subaortic stenosis, but over time the LVOT gradient slowly increases, mild AR is common, and reoperation for recurrent discrete subaortic stenosis may be needed.[17] Myectomy does not show additional advantages, and because it is associated with an increased risk of complete heart block, it should not be performed routinely.[17] Stress testing to determine exercise capability, symptoms, ECG changes or arrhythmias, or increase in LVOT gradient is reasonable in the presence of otherwise equivocal indications for intervention (Class IIa-C, ACC/AHA 2008 GL on ACHD). Lifelong cardiology follow-up is recommended in all patients with subaortic stenosis. Patients without

Table 7.3 ACC/AHA 2008 GL on ACHD

Recommendations for surgical intervention in subaortic stenosis	
Surgical intervention in subAS and a peak instantaneous gradient of 50 mmHg or a mean gradient of 30 mmHg on echocardiography-Doppler.	I-C
Surgical intervention in subAS with <50 mmHg peak or <30 mmHg mean gradient and progressive AR and an LV end-systolic diameter of 50 mm or LVEF <55%.	I-C
Surgical resection in patients with a mean gradient of 30 mmHg, but careful follow-up is required to detect progression of stenosis or AR.	IIb-C
Surgical resection may be considered for patients with <50 mmHg peak gradient or <30 mmHg mean gradient in the following situations: a. When LV hypertrophy is present. b. When pregnancy is being planned. c. When the patient plans to engage in strenuous/competitive sports.	IIb-C
Surgical intervention to prevent AR for patients with subAS and trivial LVOT obstruction or trivial to mild AR.	III-C

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Table 7.4 ESC 2010 GL on ACHD

Indications for intervention in subaortic stenosis	
Surgery for symptomatic patients (spontaneous or on exercise test) with a mean Doppler gradient ≥50 mmHg or severe AR.	I-C
Surgery in asymptomatic patients when:	
LVEF is <50% (gradient may be <50 mmHg due to low flow).	IIa-C
AR is severe and LVESD >50 mm (or 25 mm/m^2 BSA) and/or EF <50%.	IIa-C
Mean Doppler gradient is ≥50 mmHg and LVH marked.	IIa-C
Mean Doppler gradient is ≥50 mmHg* and blood pressure response is abnormal on exercise testing.	IIb-C
Mean Doppler gradient is ≥50 mmHg, LV normal, exercise testing normal, and surgical risk low.	IIb-C
Progression of AR is documented, and AR becomes more than mild (to prevent further progression).	IIb-C

* Doppler-derived gradients may overestimate the obstruction and may need confirmation by cardiac catheterization.
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operation should be subjected to yearly echocardiograms. Discrete subaortic stenosis progresses very slowly in adulthood, but patients with associated congenital lesions, particularly a VSD, are at risk for faster disease progression and should be monitored cautiously.[16] In patients with isolated thin discrete subaortic stenosis, transluminal balloon tearing of the membrane is another option with good long-term results.[18]

Pregnancy is contraindicated in symptomatic patients with significant LV outflow obstruction or coronary artery abnormalities[14] (see also Chapter 18).

Supravalvular aortic stenosis

Rare condition usually associated with the Williams–Beuren syndrome (neurodevelopmental disorder characterized by connective tissue and central nervous system abnormalities).[15,19] Isolated Supravalvular aortic stenosis occurs at the level of the sinotubular junction in 70% of patients with cardiovascular manifestations. The Supravalvular lesion may involve the entire aortic root, the coronary arteries, and/or the aortic valve. In children, it is felt to be a progressive disease, perhaps related to an inadequate growth of the supravalvar aortic root and the sinotubular junction. However, progression of subvalvular AS in adulthood is rare.[20] Diffuse hypoplasia and PA stenosis, coarctation of the aorta, and septal defects are other associated conditions. TTE and/or TOE and either MRI or CT should be performed to assess the anatomy of the LVOT, aortic and mitral valve, the ascending aorta, and main and branch pulmonary artery anatomy. Adults with a history or presence of supraAS should be screened periodically for myocardial ischaemia (Class I-C, ACC/AHA 2008 GL on ACHD). Due to the potential of regression, surgery is recommended in the case of symptoms in the context of a peak gradient >70 mmHg or LV dysfunction (Tables 7.5 and 7.6).

Supravalvular AS, whether associated with Williams syndrome or non-syndromic, has a strong likelihood of being an inherited disorder. Undetected family members may be at risk for hypertension, coronary disease, or stroke; therefore, all available relatives should be screened (Class I-C, ACC/AHA 2008 GL on ACHD). Patients with significant obstruction, coronary involvement, or aortic disease should be counselled against pregnancy (Class I-C, ACC/AHA 2008 GL on ACHD).

Pregnancy is contraindicated in symptomatic patients with significant LV outflow obstruction or coronary artery abnormalities[14] (see also Chapter 18).

Table 7.5 ACC/AHA 2008 GL on ACHD

Recommendations for interventional and surgical therapy in supravalvar aortic stenosis	
Operative intervention in supravalvular LVOT obstruction (discrete or diffuse) with symptoms (i.e. angina, dyspnoea, or syncope) and/or mean gradient >50 mmHg or peak instantaneous gradient by Doppler echocardiography >70 mmHg.	I-B
Surgical repair in lesser degrees of supravalvular LVOT obstruction and the following indications:	
a. Symptoms (i.e. angina, dyspnoea, or syncope).	I-B
b. LV hypertrophy.	I-C
c. Desire for greater degrees of exercise or a planned pregnancy.	I-C
d. LV systolic dysfunction.	I-C
Interventions for coronary artery obstruction in patients with supraAS should be performed in ACHD centres with demonstrated expertise.	I-C

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Table 7.6 ESC 2010 GL on ACHD

Indications for intervention in supravalvar aortic stenosis	
Surgery for patients with symptoms (spontaneous or on exercise test) and mean Doppler gradient ≥50 mmHg.	I-C
Surgery for patients with mean Doppler gradient <50 mmHg when they have:	
Symptoms attributable to obstruction (exertional dyspnoea, angina, syncope), and/or	I-C
LV systolic dysfunction (without other explanation),	I-C
Severe LVH, attributable to obstruction (not related to hypertension),	I-C
When surgery for significant coronary artery disease is required.	I-C
Repair in patients with mean Doppler gradient ≥50 mmHg* but without symptoms, LV systolic dysfunction, LVH, or abnormal exercise test when the surgical risk is low.	IIb-C

* Doppler-derived gradients may overestimate the obstruction and may need confirmation by cardiac catheterization.
ESC Guidelines for the management of grown-up congenital heart disease. *Eur Heart J*. 2010;**31**:2915–57 with permission from Oxford University Press.

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Chapter 8

Coarctation of the aorta

Definitions

Aortic arch obstruction may be due to:

Coarctation of the aorta (CoA), i.e. a discrete obstructive lesion located just distal to the origin of the left subclavian artery where the fetal ductus arteriosus is inserted into the aorta

Tubular hypoplasia of some part of the aorta

Aortic arch interruption.

Epidemiology

CoA is found in about 5–8% of patients with congenital heart disease and is 2–5 times more common in males. Although most cases of CoA are sporadic, there is clearly a genetic component with congenital heart disease, occurring in, at least, 4% of offspring of women with CoA. Linkage analysis studies suggest a genetic susceptibility locus on chromosomes 2p23, 10q21, and 16p12. CoA is also present in 12–17% of patients with Turner's syndrome who are at high risk of aortic dissection.[1]

Pathophysiology and natural history

Obstruction of the aorta reduces flow to the juxtaglomerular apparatus in the kidneys, with resultant increase in vascular tone and intravascular volume. Thus, significant hypertension in the upper body occurs, and collateral circulation develops in the form of **intracranial** (circle of Willis) and **intercostal artery aneurysms**. In adults, a **bicuspid aortic valve** has been reported in 25–75% of patients with CoA.

In children, **VSD**, **PDA**, and **mitral valve abnormalities** are also common. The average survival of the adult with unrepaired coarctation is 35 years of age, with a 25% survival rate beyond 50 years of age.[2] Although the main cause of death in patients with corrected coarctation is coronary artery disease, coarctation itself does not predict for the development of coronary artery disease after adjustment for other risk factors, such as ageing, associated hypertension, hypercholesterolaemia, and diabetes mellitus.[3]

Presentation

In early age, CoA may lead to heart failure, but the adult is usually asymptomatic. Rarely, headache, epistaxis, dizziness, palpitations, and claudication are reported. Diagnosis is suspected when hypertension is associated with diminished or absent femoral pulses.

Physical examination

Patients with systemic arterial hypertension should have the brachial and femoral pulses palpated simultaneously to assess timing and amplitude evaluation to search for the 'brachial-femoral delay' of significant aortic coarctation. Supine bilateral arm (brachial artery) blood pressures and prone right or left supine leg (popliteal artery) blood pressures should be measured to search for **differential pressure**. There is differential systolic blood pressure (brachial-popliteal >10 mmHg) and radial-femoral pulse delay, unless significant AR coexists. The **diastolic** pressure is similar in arms and legs and, therefore, a widened pulse is felt in the arms.

Auscultation may reveal:

Interscapular systolic murmur

Widespread crescendo-decrescendo systolic murmur due to intercostal collaterals.

There may be also '**corkscrew**' **tortuosity** of retinal arteries.

Investigations

Chest radiography may be normal. Rib notching (unilateral or bilateral) in 50% of cases. The typical 'figure 3' configuration of the aorta may also be seen in the PA projection.

ECG may show LVH.

Echocardiography is useful, but **MRA** is the modality of choice, particularly for post-intervention surveillance. Every patient with coarctation (repaired or not) should have cardiovascular MRI or CT scan for complete evaluation of the thoracic aorta and intracranial vessels (ACC/AHA 2008 GL on ACHD, I-B).

Therapy

The natural history of unrepaired CoA includes the development of systemic hypertension. Most untreated patients will die before 50 years of age, and the condition should be diagnosed at a young age before hypertension develops.[4] Early detection and treatment of CoA is associated with the best outcomes,[5] although some patients will develop hypertension despite repair.

Surgical or endovascular repair indications

Indications for repair are presented in Tables 8.1 and 8.2. Main indications are:

- CoA gradient >20 mmHg
- Non-invasive pressure difference >20 mmHg between upper and lower limb, with upper limb hypertension (>140/90 mmHg)
- Anatomic imaging evidence of significant coarctation with collaterals.

Surgical repair

The surgical risk in simple CoA is <1%, but it increases significantly beyond the age of 30–40 years and carries the risk of spinal cord injury. **Recoarctation, aneurysms, or pseudoaneurysms** may occur in 10% of cases. When repair of CoA is performed between the ages of 20 and 40 years, the 25-year survival is 75%; in patients over 40 years old, the 15-year survival is only 50%.[1]

Table 8.1 Therapy of coarctation

ACC/AHA 2008 GL on ACHD. Recommendations for interventional and surgical treatment of coarctation of the aorta in adults	
Intervention for coarctation in: a. Peak-to-peak coarctation gradient ≥20 mmHg. b. Peak-to-peak coarctation gradient <20 mmHg in the presence of anatomic imaging evidence of significant coarctation with radiological evidence of significant collateral flow.	I-C
Choice of percutaneous catheter intervention versus surgical repair of native discrete coarctation should be determined by consultation with a team of ACHD cardiologists, interventionalists, and surgeons at an ACHD centre.	I-C
Percutaneous catheter intervention is indicated for recurrent, discrete coarctation and a peak-to-peak gradient ≥20 mmHg.	I-B
Surgeons with training and expertise in CHD should perform operations for previously repaired coarctation and the following indications: a. Long recoarctation segment. b. Concomitant hypoplasia of the aortic arch.	I-B
Stent placement for long-segment coarctation (usefulness not well established, and long-term efficacy and safety unknown).	IIb-C
AHA 2015 statement on congenital disease in the older adult	
Intervention for coarctation of the aorta with obstruction for palliation of hypertension and possibly heart failure.	I-C

ACC/AHA2008 guidelines for the management of adults with congenital heart disease. *J Am Coll Cardiol*. 2008;**52**:e1–e121 with permission from Elsevier.
American Heart Association Council on Clinical Cardiology. Congenital heart disease in the older adult: a scientific statement from the American Heart Association. *Circulation*. 2015;**131**:1884–931 with permission from Wolters Kluwer.

Table 8.2 ESC 2010 GL on ACHD*

Indications for intervention in coarctation of the aorta	
Intervention in all patients with a non-invasive pressure difference >20 mmHg between upper and lower limbs, regardless of symptoms, but with upper limb hypertension (>140/90 mmHg in adults), pathological blood pressure response during exercise, or significant LVH.	I-C
Intervention independent of the pressure gradient, in hypertensive patients with ≥50% aortic narrowing relative to the aortic diameter at the diaphragm level (on CMR, CT, or invasive angiography).	IIa-C
Intervention independent of the pressure gradient and presence of hypertension, in patients with ≥50% aortic narrowing relative to the aortic diameter at the diaphragm level (on CMR, CT, or invasive angiography).	IIb-C

*Similar recommendations were provided by the ESC 2014 GL on aortic diseases.

ESC Guidelines for the management of grown-up congenital heart disease. *Eur Heart J*. 2010;**31**:2915–57 with permission from Oxford University Press.

Endovascular repair

Covered stent deployment is increasingly the treatment of choice for adults with comparable results with surgery,[6] but long-term results are missing. Stenting appears to offer lower acute complications compared with surgery patients or balloon angioplasty, but is more likely to require a planned reintervention.[7] Percutaneous intervention (balloon or stent) is particularly recommended for recoarctation.[8] Systemic hypertension can occur after both surgical and endovascular repair and may be due to residual or recurrent coarctation, but even patients with a successful repair may develop hypertension. Risk factors for subsequent hypertension include an older age at the time of repair and higher blood pressure before the time of repair. The pathophysiology of hypertension that occurs after repair of coarctation of the aorta is not fully known. Anatomical and functional changes in the arterial tree, such as impaired elasticity and compliance and aortic stiffness, may be involved. Post-repair surveillance for **hypertension**, **endocarditis or arteritis**, **and rupture of berry or thoracic aneurysms** is necessary. Even if the coarctation repair appears to be satisfactory, late postoperative thoracic aortic imaging should be performed to assess for aortic dilatation or aneurysm formation. Thus, lifelong follow-up is recommended for all patients with aortic coarctation (repaired or not). Recently, an uncovered stent was found safe and associated with persistent relief of aortic obstruction. Stent fracture and progression of fracture occurred, but did not result in clinically important sequelae. Re-intervention was needed in 20% of patients within 4 years, and related to early and late aortic wall injury and need for re-expansion of small-diameter stents.[9]

Pregnancy

It is allowed after repair. In unrepaired coarctation, residual significant hypertension, or aortic aneurysms, there is an increased risk of aortic rupture.[10]

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Chapter 9

Tetralogy of Fallot

Definition

Tetralogy of Fallot (TOF) denotes a group of conditions characterized by ventricular septal defect, overriding of the aorta, right ventricular outflow obstruction, and right ventricular hypertrophy.[1,2] It is the most common form of cyanotic congenital heart disease. Despite the basically similar anatomy, these conditions are variable in terms of pulmonary artery anatomy and associated abnormalities.

Epidemiology

About 3.5% of all infants born with a congenital heart disease have tetralogy of Fallot, with males and females being affected equally. The risk of recurrence in siblings is about 3% if there are no other affected first-degree relatives.[2]

Aetiology

The aetiology of Fallot is multifactorial, but approximately 25% of patients have chromosomal abnormalities, with trisomy 21 and 22q11.2 microdeletions being most frequent.[2] Trisomies 18 and 13, as well as other less common chromosomal abnormalities and mutations, have been reported. Chromosome 22q11.2 microdeletions occur in approximately 20% of TOF patients with pulmonary stenosis and in 40% with pulmonary atresia. DiGeorge syndrome, the most severe type of 22q11.2 microdeletion, also includes palatal abnormalities, dysmorphic facies, learning disabilities, immune deficiencies, and/or hypocalcemia. Screening for 22q11 deletion should be offered to all patients with Fallot since this mutation raises the risk of recurrence in offspring to 50%. Right aortic arch, as well as ASD and coronary artery anomalies, may be associated abnormalities.

Pathophysiology

The ventricular septal defect is almost always large, ensuring that the pressure is equal in the two ventricles. Since the resistance to flow across the RV outflow tract is relatively fixed, changes in systemic vascular resistance affect the magnitude of right-to-left shunting. Most patients develop increasing cyanosis during the first few weeks and months of life. Severe cyanosis, recurrent hypercyanotic spells, and squatting for reduction of cyanosis, through increase in pulmonary flow and reduction of the shunt, are nowadays rare because usually infants undergo surgery at the age of 3–6 months. Due to recent advances in the diagnosis and surgical treatment, almost all those born with tetralogy of Fallot are now expected to survive to adulthood.

Presentation

Survival to adult life is rare without palliation or correction, and it is unusual for a patient to survive longer than 30 years.[1] These patients are cyanotic with marked clubbing. Usually, patients with repaired tetralogy are seen. Approximately 85% of patients with a previous repair remain asymptomatic but with reduced exercise ability and life expectancy (85% vs 92% 35-year survival, respectively).

Physical examination

Unoperated patients

- RV heave and palpable thrill
- RVOT systolic ejection murmur (intensity and duration inversely related to obstruction severity)
- Single A2 and diastolic murmur due to AR

Patients with palliative surgery with systemic-to-pulmonary arterial shunts

- Cyanosis with worsening of RVOT obstruction and/or aortopulmonary shunt stenosis. Progressive dilation of the aortic root may also occur.

Patients with anatomic repair

- PR or RVOT systolic ejection murmur
- Progressive dilation of the aortic root with aortic ejection click and AR.

Investigations

Chest radiography Normal-sized boot-shaped heart (coeur en sabot) with prominence of the right heart and the apex lifted off the hemidiaphragm. Lung fields are oligaemic, and the aortic arch may be on the right side.

ECG Right axis deviation with RV and RA hypertophy and RBBB, especially after anatomic repair. QRS width (to >180 ms) reflects RV dilatation and is a risk factor for VT.

BNP levels correlate with end-diastolic RV dimensions and PR severity.[3]

Echocardiography is adequate for diagnosis before or after operation, but the ideal method for assessing PR is cardiac **MRI**.

Cardiac catheterization may be useful in cases of **pulmonary atresia**, with **major aortopulmonary collaterals**

to delineate arterial supply to lungs or to delineate **coronary artery anatomy** before reoperation (Class I-B, ACC/AHA 2008 GL on ACHD).

Programmed ventricular stimulation is indicated in patients with unexplained syncope (PACES/HRS 2014 statement, I-C) and in risk-stratifying adults with tetralogy of Fallot who have additional risk factors for sudden cardiac death such as left ventricular systolic or diastolic dysfunction, NSVT, QRS duration >180 ms, and extensive RV scarring (PACES/HRS 2014 statement, IIa-B).[4]

Annual surveillance of patients with repaired TOF, including taking a history, ECG, assessment of RV function, periodic monitoring for dysrhythmias, and periodic exercise testing, is recommended for asymptomatic patients (AHA 2015 statement, I-C).[5]

Therapy

Anatomical repair is traditionally aimed at VSD closure and relief of RVOT obstruction (with resection of the infundibulum and pulmonary valvotomy and, if needed, RVOT or transannular patches). A modern approach is preservation of the pulmonary valve and avoidance of ventriculotomy at the expense of an accepted degree of RVOT obstruction.[1] Patients undergoing repair have good long-term survival, but after 40 years 36% of survivors have undergone PV replacement.[6] Prior shunt, low temperature during surgery, and early post-operative arrhythmias predict late mortality.[7]

Palliative systemic-to-pulmonary arterial shunts, such as **Blalock–Taussig** (either subclavian to respective PA), **Waterston** (back of ascending aorta to PA), or **Potts** (descending aorta to left PA), are associated with long-term complications such as LV volume overload and pulmonary hypertension and distortion of pulmonary artery branches. They may still be offered today in the context of a staged procedure.

Clinical problems of adults with repaired tetralogy

Ventricular tachycardia, atrial macro re-entrant tachycardia, and atrial fibrillation are frequent and appear to be influenced more by left- than right-sided ventricular function.[8] Atrial re-entrant tachycardia will develop in >30% of patients, and high-grade ventricular arrhythmias will be seen in about 10% of patients.[2] Approximately 10% of patients develop incisional or CTI-dependent atrial flutter within the next 35 years after repair.[9] There is usually RBBB in the resting ECG of the majority of patients, and SVT is conducted with RBBB aberration, but this pattern also occurs in 25% of VT in this setting. The development of atrial flutter can be an indication of worsening ventricular function and tricuspid regurgitation, and reassessment for surgical revision may be indicated. Ventricular arrhythmias can be detected with Holter monitoring in up to 50% of patients with repaired tetralogy of Fallot, and there is a 4-14% prevalence of sustained VT.[8–10] The incidence of sudden death in the adult population with Fallot is approximately 2.5% per decade of follow-up.[11] Programmed ventricular stimulation is useful in risk-stratifying adults with tetralogy of Fallot who have additional risk factors for sudden cardiac death, such as LV dysfunction, NSVT, QRS duration >180 ms, and extensive RV scarring (PACES/HRS 2014 Statement, IIa-B).[4] Patients with tetralogy of Fallot are the largest subgroup of implantable cardioverter defibrillator recipients with congenital heart disease. Significant PR (main predictor), QRS >180 ms, NSVT on Holter and inducible VT at EPS, and older age repair have been identified as risk markers for sudden death.[9–12] Patients with repaired tetralogy of Fallot undergoing PVR with a history of ventricular tachycardia or left ventricular dysfunction appear to be associated with a higher risk of arrhythmic events after operation, and in selected high-risk patients, surgical cryoablation may be protective.[13] Currently, ICDs are indicated for secondary prevention (previous cardiac arrest or sustained VT). Both RV and biventricular pacing might improve the intraventricular dyssynchrony of RV contraction. Recommendations on arrhythmia therapy in this setting are provided in Chapters 51 and 56.

Pulmonary regurgitation The degree of residual PR has been related to the most severe adverse outcomes of progressive exercise intolerance, right heart failure, ventricular arrhythmia, and sudden death. Indications for surgery are not established but usually consist of exercise intolerance, RVEF worsening, right heart failure, and new-onset symptomatic sustained VT. Pulmonary valve replacement in adults with palliated Fallot carries a procedural mortality of <1% and offers a 98% 5-year survival.[14,15] Although its impact on mortality remains unproven, PVR after repair of Fallot has a low and improving mortality, especially when performed early, with a peak oxygen consumption (VO_2) of ≥20 mL/(kg.min).[16]

Indications for PV replacement, in general, are also presented in Table 22.2.5.

Percutaneous pulmonary valve implantation is now possible with no periprocedural mortality and low late mortality.[17] Care must be taken during deployment to avoid compression of coronary arteries, which might be adjacent to the RVOT. The Melody valve, with or without pre-stenting of the RVOT, has been approved by the FDA.[18] The Sapien valve is also available. Valve failure occurs but usually can be treated by implantation of a second valve. The major limitation of the technique is that it is unsuitable for most patients with patch reconstruction of the RVOT and those with a grossly dilated native outflow tract. Other potential, but rare, complications are compression of the left main stem and endocarditis.[18]

Residual RVOT obstruction may require surgery, and **branch pulmonary stenosis**, especially in the setting of free pulmonary regurgitation, is treated by balloon dilation with or without stent.

Aortic root dilation is an increasingly recognized feature of late post-operative tetralogy of Fallot and can lead to significant AR. Progressive AR and aortic root dilation >55 mm are indications for surgery. However, although nearly one-third of adults with repaired TOF have an aortic root diameter ≥40 mm, the prevalence of a dilated aortic root, when defined by an indexed ratio of observed to expected values, is low, and moderate or severe AR is uncommon.[19]

Indications for intervention after repair

They are presented in Tables 9.1 and 9.2. Main indications are:

- Severe symptomatic PR or PS
- Residual RVOT obstruction with gradient >50 mmHg or RV/LV pressure ratio >0.7
- AR with LV dysfunction.

Table 9.1 ACC/AHA 2008 GL on ACHD. Tetralogy of Fallot

Recommendations for surgery for adults with previous repair of tetralogy of Fallot	
Surgeons with training and expertise in CHD should perform operations in adults with previous repair of tetralogy of Fallot.	I-C
Pulmonary valve replacement is indicated for severe PR and symptoms of decreased exercise tolerance.	I-B
The possibility of an anomalous LAD across the RVOT should be ascertained before operative intervention.	I-C
Pulmonary valve replacement in adults with previous tetralogy of Fallot, severe PR, and any of the following:	
a. Moderate to severe RV dysfunction.	IIa-B
b. Moderate to severe RV enlargement.	IIa-B
c. Development of symptomatic or sustained atrial and/or ventricular arrhythmias.	IIa-C
d. Moderate to severe TR.	IIa-C
Collaboration between ACHD surgeons and ACHD interventional cardiologists to determine the most feasible treatment for pulmonary artery stenosis.	IIa-C
Surgery in adults with prior repair of tetralogy of Fallot and residual RVOT obstruction (valvular or subvalvular) and any of the following indications:	
a. Residual RVOT obstruction (valvular or subvalvular) with peak instantaneous echocardiography gradient >50 mmHg.	IIa-C
b. Residual RVOT obstruction (valvular or subvalvular) with RV/LV pressure ratio >0.7.	IIa-C
c. Residual RVOT obstruction (valvular or subvalvular) with progressive and/or severe dilatation of the right ventricle with dysfunction.	IIa-C
d. Residual VSD with a left-to-right shunt >1.5:1.	IIa-B
e. Severe AR with associated symptoms or more than mild LV dysfunction.	IIa-C
f. A combination of multiple residual lesions (e.g. VSD and RVOT obstruction), leading to RV enlargement or reduced RV function.	IIa-C

ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. *J Am Coll Cardiol*. 2008;**52**:e1–e121 with permission from Elsevier.

Table 9.2 ESC 2010 GL on ACHD

Indications for intervention after repair of tetralogy of Fallot	
Aortic valve replacement in patients with severe AR with symptoms or signs of LV dysfunction.	I-C
PV replacement in symptomatic patients with severe PR and/or stenosis (RV systolic pressure >60 mmHg, TR velocity >3.5 m/s).	I-C
PV replacement in asymptomatic patients with severe PR and/or PS when at least one of the following criteria is present:	IIa-C
– Decrease in objective exercise capacity.	
– Progressive RV dilation.	
– Progressive RV systolic dysfunction.	
– Progressive TR (at least moderate).	
– RVOTO with RV systolic pressure >80 mmHg (TR velocity >4.3 m/s).	
– Sustained atrial/ventricular arrhythmias.	
VSD closure in patients with residual VSD and significant LV volume overload or if the patient is undergoing pulmonary valve surgery	IIa-C

ESC Guidelines for the management of grown-up congenital heart disease. *Eur Heart J*. 2010;**31**:2915–57 with permission from Oxford University Press.

Participation in exercise

Full exercise activity should be encouraged for patients with only minimal residual abnormalities. Sports should be avoided by individuals with exercise-induced life-threatening arrhythmias. In patients with high right ventricular pressure (>50% of systemic values), severe pulmonary regurgitation with right ventricular dilatation, or rhythm disturbances, restriction to low dynamic and low static sport activities is advised.

Pregnancy

Before pregnancy, consultation with a geneticist is advisable. The risk is low in patients without substantial residual obstruction across the RVOT, severe pulmonary regurgitation, tricuspid regurgitation, and right and left ventricular dysfunction.[1,20] The RV is already compromised from previous surgery, and pregnancy in these patients is associated with persisting midterm dilatation of the subpulmonary ventricle. Thus, patients with repaired tetralogy of Fallot and severe pulmonary regurgitation should be considered for pulmonary valve replacement before becoming pregnant. Vaginal delivery is the recommended mode of delivery for most women with tetralogy of Fallot. If right ventricular failure occurs during pregnancy, delivery should be considered before term. The estimated recurrence rate in the offspring is 3%,[12] but this depends on the genetic background of particular patients (see Aetiology).

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Chapter 10

Transposition of great arteries

Definitions and classification of transposition

Morphological right and left ventricles refer to the anatomic characteristics of the chambers and not their positions.[1]

Atrioventricular discordance Inappropriate connections of the morphological right atrium to the morphological left ventricle and morphological left atrium to right ventricle.

Ventriculoarterial discordance The pulmonary artery arises from a morphological left ventricle, and the aorta arises from a morphological right ventricle.

Complete or d-transposition of great arteries (TGA) denotes that the aorta arises from the morphological right ventricle, and the pulmonary artery arises from the morphological left ventricle (i.e. there is ventriculoarterial discordance).

In **congenitally 'corrected' or l-TGA**, there are inappropriate connections of the morphological right atrium to the morphological left ventricle and morphological left atrium to right ventricle (atrioventricular discordance and ventriculoarterial discordance) (Figure 10.1).

Complete transposition (d-TGA)

Anatomy and pathophysiology

d-TGA refers to the normal rightward (dextro) bend of the embryonic heart tube and indicates that the inflow portion of the right ventricle is to the right of the morphological left ventricle. The aorta arises from the morphological right

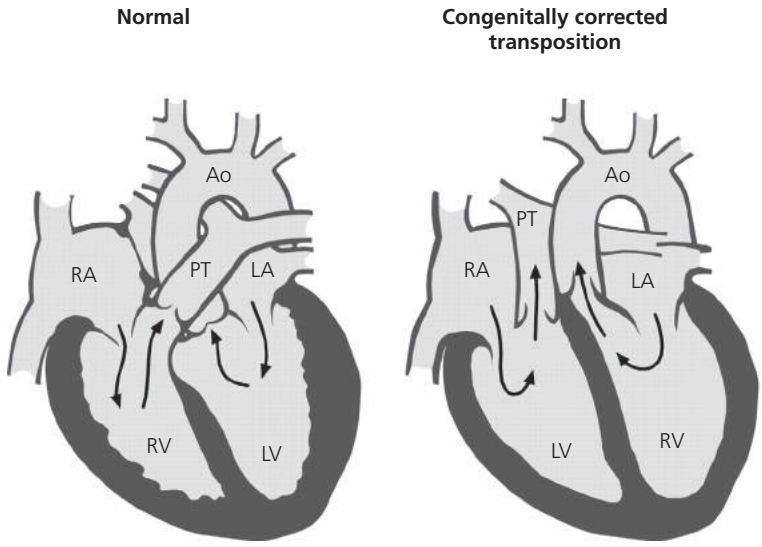

Figure 10.1 Anatomy of l-TGA.

Warnes CA. Transposition of the great arteries. *Circulation*. 2006;**114**:2699–709 with permission from Wolters Kluwer.

ventricle, and the pulmonary artery arises from the morphological left ventricle. The aorta also tends to be on the right and anterior, and the great arteries are parallel, rather than crossing as they do in the normal heart. Because the systemic and pulmonary circulations run in parallel, there has to be a communication between them, such as VSD, ASD, or PDA. Without intervention, the mortality rate is 90% by 6 months of age.[1]

Epidemiology

d-TGA accounts for 5% of all forms of congenital heart disease and is one of the most common cyanotic defects.[2]

Clinical problems and therapy in adults

Adult patients with TGA have survived due to previous repair. Their condition depends on the mode of operation performed.

Atrial switch (Senning and Mustard operations)

Atrial switch or atrial baffle procedures are the Senning (creation of an atrial baffle from autologous tissue to direct the venous return to the contralateral atrioventricular (AV) valve and ventricle) or Mustard (excision of the atrial septum and creation of the baffle with synthetic material) operations. These operations leave the morphological RV to support the systemic circulation, and **RV failure** and **TR** are common. Perioperative mortality is 20%, and 60% of patients are alive after 30 years of follow-up.[3] Patients should be monitored with annual ECG and periodic monitoring for dysrhythmias (AHA 2015 statement, I-C).[4]

Atrial arrhythmias (a marker of sudden death), **sinus nodal dysfunction**, **pulmonary hypertension**, and **atrial baffle obstruction** are problems encountered in adulthood.

Rastelli operation

When d-TGA coexists with a large subaortic VSD and PS, the Rastelli procedure may be used. A patch is placed to direct flow from the LV to the aorta through the VSD; the PV is oversewn, and continuity between RV and PV is established through a valve conduit. This operation has the advantage that the LV supports systemic circulation, but **conduit degeneration** and **atrial arrhythmias** are common and **sudden death** may occur.

Arterial switch

The modern surgical approach is arterial switch that restores normal anatomy of circulation. The arterial switch operation has replaced atrial switch procedures for d-TGA, and 90% of patients now reach adulthood.[3] Arterial switch involves transection of the great arteries above the sinuses and restoration of their anatomic sites (i.e. the aorta to LV outflow tract if normal, and the pulmonary artery anterior to the aorta to the morphological right ventricle). This operation is performed in the first weeks of life or later as a two-stage procedure with PA banding, in the absence of PV stenosis, to 'train' the LV in higher pressures. Early operation (3 days of life) is probably beneficial.[5] Late arterial switch after 'training' of the LV with a PV band can also be performed in young patients with previous atrial switch operations and failing RV. This strategy has the theoretical advantage of relieving the haemodynamic burden on

the RV and tricuspid valve, potentially improving surgical results and longevity. Long-term and arrhythmia-free survival is excellent after arterial switch operation, and most patients maintain normal systolic function and exercise capacity.[6] Complications include **chronotropic incompetence**, and **dilatation of the neoaortic root with AR**, **branch pulmonary stenosis**, **PR**, and **coronary stenoses**. Obstructed coronary arteries are seen in 5–7% of survivors and should be suspected in the presence of post-operative arrhythmias and ventricular dysfunction.[6] The effect of ACE inhibitors on RV function is debated, but they may be indicated in symptomatic patients with RV dysfunction.[7] The patient after arterial switch operation represents a potentially higher long-term coronary risk, so it is reasonable to optimize CAD risk factors from young adulthood (AHA 2015 statement, IIa-C).[4]

The ACC/AHA and ESC recommendations are presented in Tables 10.1 to Table 10.3.

Table 10.1 ACC/AHA 2008 GL on ACHD. Dextro-transposition

Recommendations for interventional catheterization for adults with dextro-transposition of the great arteries	
Interventional catheterization of the adult with d-TGA can be performed in centres with expertise.	I-C
For adults with d-TGA after atrial baffle procedure (Mustard or Senning), interventional catheterization to assist in: a. Occlusion of baffle leak. b. Dilation or stenting of superior vena cava or inferior vena cava pathway obstruction. c. Dilation or stenting of pulmonary venous pathway obstruction.	IIa-B
For adults with d-TGA after arterial switch operation (ASO), interventional catheterization to assist in dilation or stenting of supravalvular and branch pulmonary artery stenosis.	IIa-B
For adults with d-TGA, VSD, and PS, after Rastelli type repair, interventional catheterization to assist in: a.Dilation with or without stent implantation of conduit obstruction (RV pressure >50% of systemic levels or peak-to-peak gradient >30 mmHg) (these indications may be lessened in the setting of RV dysfunction). b. Device closure of residual VSD.	IIa-C
Recommendations for surgical interventions after atrial baffle procedure (Mustard, Senning)	
Surgeons with training and expertise in CHD should perform operations in patients with d-TGA and: a. Moderate to severe systemic (morphological tricuspid) AV valve regurgitation without significant ventricular dysfunction. b. Baffle leak with left-to-right shunt >1.5:1, right-to-left shunt with arterial desaturation at rest or with exercise, symptoms, and progressive ventricular enlargement that is not amenable to device intervention. c. Superior vena cava or inferior vena cava obstruction not amenable to percutaneous treatment. d. Pulmonary venous pathway obstruction not amenable to percutaneous intervention. e. Symptomatic severe subpulmonary stenosis.	I-B
Recommendations for surgical interventions after arterial switch operation	
Surgery in patients after ASO with the following indications: a. RVOT obstruction peak-to-peak gradient >50 mmHg or right ventricle/left ventricle pressure ratio >0.7, not amenable or responsive to percutaneous treatment; lesser degrees of obstruction if pregnancy is planned, greater degrees of exercise are desired, or concomitant severe pulmonary regurgitation is present. b. Coronary artery abnormality with myocardial ischaemia not amenable to percutaneous intervention. c. Severe neoaortic valve regurgitation. d. Severe neoaortic root dilatation (>55 mm) after ASO.	I-C
Recommendations for surgical interventions after Rastelli procedure	
Reoperation for conduit and/or valve replacement after Rastelli repair of d-TGA with: a. Conduit obstruction peak-to-peak gradient >50 mmHg. b. RV/LV pressure ratio >0.7. c. Lesser degrees of conduit obstruction if pregnancy is being planned or greater degrees of exercise are desired. d. Subaortic (baffle) obstruction (mean gradient >50 mmHg). e. Lesser degrees of subaortic baffle obstruction if LV hypertrophy is present, pregnancy is being planned, or greater degrees of exercise are desired. f. Presence of concomitant severe AR.	I-C

(*Continued*)

Table 10.1 Continued

Reoperation for conduit regurgitation after Rastelli repair of d-TGA in patients with severe conduit regurgitation and:	I-C
a. Symptoms or declining exercise tolerance.	
b. Severely depressed RV function.	
c. Severe RV enlargement.	
d. Development/progression of atrial or ventricular arrhythmias.	
e. More than moderate TR.	
Collaboration between surgeons and interventional cardiologists, which may include preoperative stenting, intraoperative stenting, or intraoperative patch angioplasty, with or without conduit replacements, to determine the most feasible treatment for pulmonary artery stenosis.	I-C
Surgical closure of residual VSD in adults after Rastelli repair of d-TGA with:	
a. Qp/Qs>1.5:1.	I-B
b. Systolic pulmonary artery pressure >50 mmHg.	I-B
c. Increasing LV size from volume overload.	I-C
d. Decreasing RV function from pressure overload.	I-C
e. RVOT obstruction (peak instantaneous gradient >50 mmHg).	I-B
Pulmonary artery pressure <2/3 of systemic pressure or PVR <2/3 of systemic vascular resistance, with a net left-to-right shunt of 1.5:1, or a decrease in pulmonary artery pressure with pulmonary vasodilators (oxygen, nitric oxide, or prostaglandins).	I-B
Surgery after Rastelli repair of d-TGA in adults with branch pulmonary artery stenosis not amenable to percutaneous treatment.	I-C
In the presence of a residual intracardiac shunt or significant systemic venous obstruction, permanent pacing, if indicated, should be performed with epicardial leads.	I-B
Concomitant Maze procedure for atrial tachyarrhythmias in adults with d-TGA requiring reoperation for any reason.	IIa-C

ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. J Am Coll Cardiol. 2008;52:e1–e121 with permission from Elsevier.

Table 10.2 ESC 2010 GL on ACHD. Indications for intervention in transposition of the great arteries after atrial switch

Indications for surgical intervention	
Valve repair or replacement in patients with severe symptomatic systemic (tricuspid) AV valve regurgitation without significant ventricular dysfunction (RVEF ≥45%).	I-C
Significant systemic ventricular dysfunction, with or without TR, should be treated conservatively or, eventually, with cardiac transplantation.	I-C
Surgery for LVOTO if symptomatic or if LV function deteriorates.	I-C
Surgical repair in symptomatic pulmonary venous obstruction (catheter intervention rarely possible).	I-C
Surgery for symptomatic patients with baffle stenosis not amenable to catheter intervention.	I-C
Surgery for symptomatic patients with baffle leaks not amenable to stenting.	I-C
Valve repair or replacement for severe asymptomatic systemic (tricuspid) AV valve regurgitation without significant ventricular dysfunction (RVEF ≥45%).	IIa-C
Pulmonary artery banding in adult patients to create septal shift, or as left ventricular training with subsequent arterial switch, is currently experimental and should be avoided.	III-C
Indications for catheter intervention	
Stenting in symptomatic patients with baffle stenosis.	I-C
Stenting (covered) or device closure in symptomatic patients with baffle leaks and substantial cyanosis at rest or during exercise.	I-C
Stenting (covered) or device closure in patients with baffle leaks and symptoms due to L–R shunt.	I-C
Stenting (covered) or device closure in asymptomatic patients with baffle leaks with substantial ventricular volume overload due to L–R shunt.	IIa-C
Stenting in asymptomatic patients with baffle stenosis who require a pacemaker.	IIa-C
Stenting in other asymptomatic patients with baffle stenosis.	IIb-C

ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J.* 2010;**31**:2915–57 with permission from Oxford University Press.

Table 10.3 ESC 2010 GL on ACHD

Indications for intervention in transposition of the great arteries after arterial switch	
Stenting or surgery (depending on substrate) for coronary artery stenosis causing ischaemia.	I-C
Surgical repair of RVOTO in symptomatic patients with RV systolic pressure >60 mmHg (TR velocity >3.5 m/s).	I-C
Surgical repair of RVOTO, regardless of symptoms, when RV dysfunction develops (RVP may then be lower).	I-C
Surgical repair in asymptomatic patients with RVOTO and systolic RVP >80 mmHg (TR velocity >4.3 m/s).	IIa-C
Aortic root surgery when the (neo-) aortic root is >55 mm, providing average adult stature.	IIa-C
Stenting or surgery (depending on substrate) for peripheral PS, regardless of symptoms, if >50% diameter narrowing and RV systolic pressure >50 mmHg and/or lung perfusion abnormalities are present.	IIa-C

ESC Guidelines for the management of grown-up congenital heart disease. *Eur Heart J*. 2010;**31**:2915–57 with permission from Oxford University Press.

Pregnancy

Pregnancy can be tolerated by successfully operated patients in the presence of reasonable RV function, but it carries a risk of heart failure. The risk of congenital heart defect in the offspring is <5%. Most patients need endocarditis prophylaxis, unless they have had an arterial switch procedure and have no residual valve dysfunction or outflow tract disturbance.[2,8]

Congenitally corrected transposition (l-TGA)

Anatomy and pathophysiology

There are inappropriate connections of the morphological right atrium to the morphological left ventricle and morphological left atrium to right ventricle. The right atrium enters the left ventricle, which gives rise to the pulmonary artery, and the left atrium enters the right ventricle, which gives rise to the aorta. The aorta is usually anterior and to the left, and the tricuspid valve always enters a morphological RV. Thus, the circulation continues in the appropriate direction but flows through the wrong ventricles. It is also called l-TGA since the morphological right ventricle is on the left of the morphological left ventricle.[1]

Associated anomalies

A **VSD** occurs in 70% of patients, usually in the perimembranous location.

Pulmonary stenosis occurs in 40% of patients and is commonly subvalvular, either due to an aneurysm of the membranous septum or due to fibrous tissue or ring in the subvalvular area. Associated valvar pulmonary stenosis also occurs.

Abnormalities of the TV, especially inferior displacement resembling Ebstein's anomaly, occur in up to 70% of patients.

Due to the displacement of the AV node and His bundle, **complete AV block** occurs at 2% per year. Tricuspid valve or VSD surgery may also precipitate heart block.

Epidemiology

l-TGA is a rare anomaly and comprises <1% of all forms of congenital heart disease.

Presentation

Patients may present for the first time in adulthood, and the diagnosis is often overlooked. Some patients may be relatively normal from a functional standpoint, and survival to the eighth decade has been reported in the absence of associated anomalies. Failure of the systemic ventricle is much more common earlier in life, usually with concomitant tricuspid regurgitation.

Physical findings

Physical signs are those of:

Systemic ventricular (RV) failure
Left AV valve regurgitation
Complete AV block and **SVT** or **AF**.

The cause of systemic ventricular failure is not established. Perfusion of the systemic ventricle by a single coronary artery (RCA) as well as systemic AV valve regurgitation are probably responsible.

Investigations

Chest radiography With mesocardia or levocardia, the diagnosis may be suspected from the chest radiography

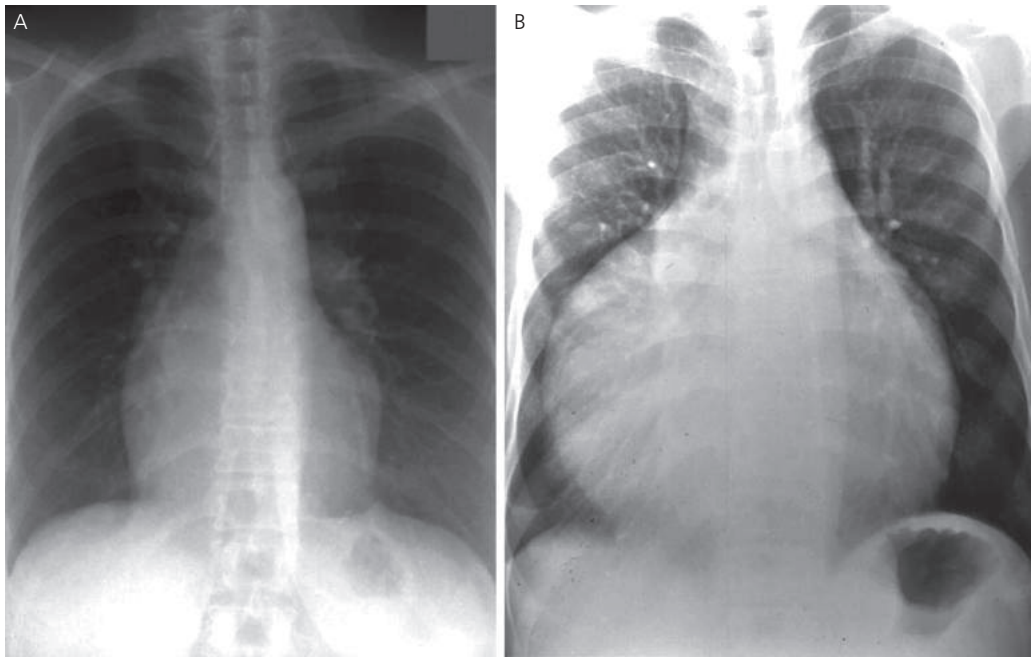

Figure 10.2 Chest X-rays in l-TGA.

Warnes CA. Transposition of the great arteries. *Circulation*. 2006;**114**:2699–709 with permission from Wolters Kluwer.

(Figure 10.2). The vascular pedicle appears abnormally straight because the normal arterial relationships are lost. The ascending aorta is not visible on the right side, and the convexities from the descending aortic knob and pulmonary artery are absent on the left side. l-TGA is one of the most common anomalies associated with dextrocardia and should be suspected when there is abdominal situs solitus (gastric bubble on the left) and dextrocardia (Figure 10.2).

ECG The ECG may resemble inferior myocardial infarction, with Q waves in the right precordial leads and absent Q waves in the left precordial leads. Various degrees of AV block may be present. Patients should be monitored with annual ECG and periodic monitoring for dysrhythmias (AHA 2015 statement, I-C).[4]

Echocardiography can be difficult, particularly with mesocardia or dextrocardia. Subcostal imaging facilitates detection of atrial situs and position of the cardiac apex and thus determines the presence or absence of dextrocardia or mesocardia. The morphological RV is on the patient's left (l-loop) and has prominent trabeculations. A high parasternal short-axis view may show the abnormal arterial relationships, with the aorta usually anterior and to the left of the pulmonary artery.

Electrophysiologic testing is indicated in patients with unexplained syncope and transposition of the great arteries with atrial switch surgery (PACES/HRS 2014 statement, I-C).[9]

Medical therapy

ACE inhibitors may be beneficial in symptomatic only patients with RV dysfunction.[7]

Surgical repair

Various procedures have been used in adult patients but with rather disappointing results (up to 67% 10-year survival).[10] The current approach is a double switch, i.e. a two-stage procedure with PA banding, in the absence of PV stenosis, to 'train' the LV in higher pressures. Early operation (3 days of life) is probably beneficial. A venous switch (either Mustard or Senning) and, in those with normal LVOT, an arterial switch can be performed later. If a large VSD is present, the Rastelli procedure may be used. Concomitant tricuspid valve surgery can also be performed, if necessary. LV failure, AR, and atrial arrhythmias are common problems with this approach, the long-term results of which are unknown. Patients

with corrected transposition should be scrutinized for the presence of systemic atrioventricular valve regurgitation. Valve replacement should be considered before systemic ventricular EF falls below 40% or the subpulmonary ventricular systolic pressure exceeds 50 mmHg (Tables 10.4 and 10.5).[2,11,12] In patients with a permanent pacemaker, regular echocardiographic monitoring is recommended because of the risk of worsening of systemic AV valve regurgitation with ventricular pacing (AHA 2015 statement, I-C).[4]

Table 10.4 ACC/AHA 2008 GL on ACHD

Patients with congenitally corrected transposition of the great arteries: recommendations for surgical intervention	
Surgeons with training and expertise in CHD should perform operations for patients with CCTGA for: a. Unrepaired CCTGA and severe AV valve regurgitation. b. Anatomic repair with atrial and arterial level switch/Rastelli repair in cases in which the left ventricle is functioning at systemic pressures. c. Simple VSD closure when the VSD is not favourable for left ventricle-to-aorta baffling or is restrictive. d. LV-to-pulmonary artery conduit in rare cases with LV dysfunction and severe LV outflow obstruction. e. Evidence of moderate or progressive systemic AV valve regurgitation. f. Conduit obstruction with systemic or nearly systemic RV pressures and/or RV dysfunction after anatomic repair. g. Conduit obstruction and systemic or suprasystemic LV pressures in a patient with non-anatomic correction. h. Moderate or severe AR/neo-AR and onset of ventricular dysfunction or progressive ventricular dilatation.	I-B

ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. *J Am Coll Cardiol*. 2008;**52**:e1–e121 with permission from Elsevier.

Table 10.5 ESC 2010 GL on ACHD

Indications for intervention in congenitally corrected transposition of the great arteries	
Systemic AV valve (tricuspid valve) surgery for severe regurgitation before systemic (subaortic) ventricular function deteriorates (before RVEF <45%).	IIa-C
Anatomic repair (atrial switch + arterial switch or Rastelli when feasible in case of non-restrictive VSD) may be considered when LV is functioning at systemic pressure.	IIb-C

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Pregnancy

Systemic ventricular ejection fraction <40% or significant systemic AV valve regurgitation are contraindications for pregnancy. Otherwise, pregnancy can be tolerated in most women with l-TGA, but careful evaluation is mandatory. Most patients require endocarditis prophylaxis, unless they have no valvular dysfunction, outflow obstruction, or VSD.[2,8]

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Chapter 11

Ebstein's anomaly

Definition

Ebstein's anomaly is a malformation of the tricuspid valve, with apical displacement of the septal and posterior leaflets from the atrioventricular ring, resulting in a reduction in size of the right ventricle.[1,2] There are no cords to suspend the leaflets, so they arise from the cavity of the ventricle and are attached to its wall. The anomaly results in right ventricular dysplasia, with dilatation and dyskinesis of the atrialized right ventricle. Thus, the disease is characterized by:[2]

- Adherence of the septal and posterior leaflets to the underlying myocardium
- Downward (apical) displacement of the functional annulus
- Dilation of the 'atrialized' portion of the right ventricle, with various degrees of hypertrophy and thinning of the wall
- Redundancy, fenestrations, and tethering of the anterior leaflet
- Dilation of the right atrioventricular junction (true tricuspid annulus).

Epidemiology

It represents 1% of all congenital heart disease. Associated cardiac malformations are ASD (80%), left ventricular fibrosis, and ventricular non-compaction.

Presentation

Ebstein's anomaly has an extremely variable natural history and prognosis. Adults usually present with exercise intolerance and varying degrees of dyspnoea and cyanosis and/or supraventricular tachycardia. Paradoxical embolization, brain abscess, and sudden death may occur. Patients with Ebstein's anomaly who reach late adolescence and adulthood often have a good outcome.[3] Accessory AV and atriofascicular pathways occur in up to 25% of patients and are more often right-sided and multiple than in patients without the disorder.[4,5] AF, atrial flutter, and AT may also occur. RBBB is usually present and, in the presence of a right-sided accessory pathway, ventricular pre-excitation can mask the ECG evidence of RBBB. LBBB tachycardias can be due to antidromic AVRT or conduction over a bystander accessory pathway. Depending on the severity of the malformation and the arrhythmia, SVT can produce cyanosis and severe symptoms or sudden death due to rapid conduction to the ventricles during AF or atrial flutter when an accessory pathway is present.

Physical examination

S_1 and **S_2** are widely split
S_3 or **S_4** usually present
Systolic murmur of TR
Hepatomegaly due to right heart failure may be present.

Investigations

The **ECG** shows enlarged P waves, prolonged PR interval, and complete or incomplete RBBB. The QRS duration is a marker of RV enlargement and dysfunction. QRS fractionation is associated with a greater atrialized RV volume. A preserved surface ECG identifies a subset of patients with Ebstein's anomaly with mild morphological and functional abnormalities and better clinical profile.[6] Arrhythmias are very common and represent AVRT (6–30% of patients have right lateral or posteroseptal accessory pathways), intra-atrial reentry, atrial flutter, or AVNRT.[7] Wolff–Parkinson–White syndrome with overt ventricular pre-excitation is seen in 60% of patients presenting with arrhythmias. In patients without pre-excitation, the absence of RBBB is a strong predictor of accessory pathways.

Chest radiography reveals cardiomegaly in severe cases. A cardiothoracic ratio >0.65 carries a poor prognosis.[2]

Two-dimensional echocardiography is essential to establish the diagnosis and guide management (Figure 11.1).

Three-dimensional echocardiography and **magnetic resonance imaging** also provide precise anatomical and functional assessment of the tricuspid valves and the right ventricle.

Therapy

Anticoagulation with warfarin is recommended for patients with Ebstein's anomaly with a history of paradoxical embolus or AF (Class I-C, ACC/AHA 2008 GL on ACHD). Surgery is recommended in symptomatic patients or in the presence of cyanosis (O_2 saturation <90%), progressive RV dilatation, severe TR, or paradoxical embolism (Tables 11.1 and 11.2).[8,9] Surgical treatment is now feasible

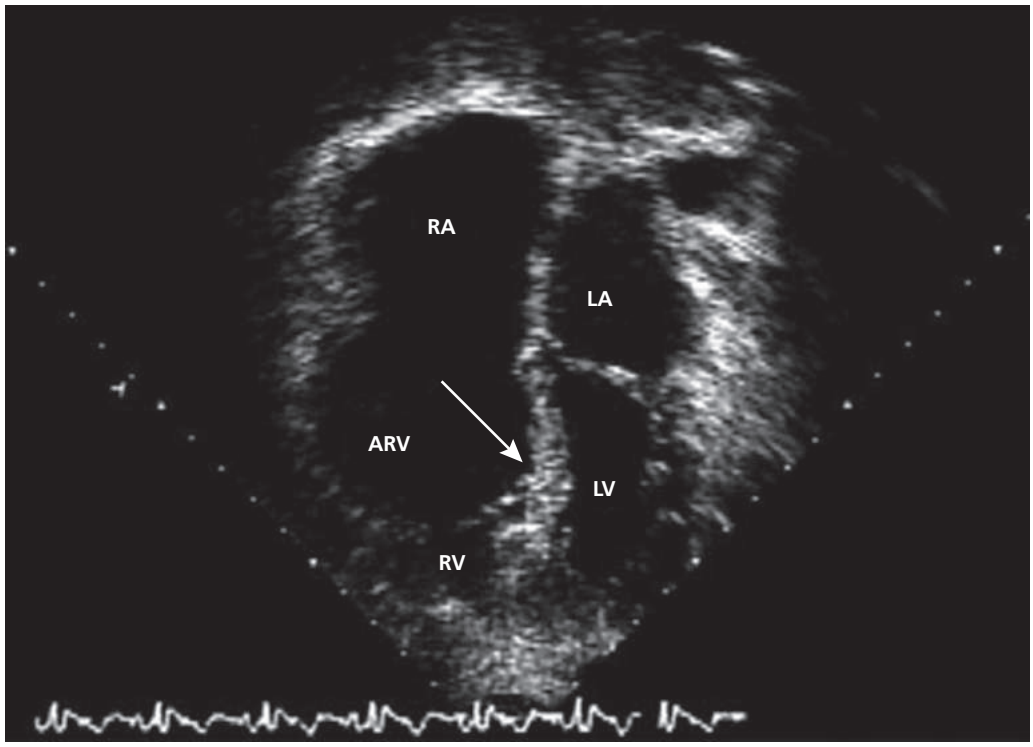

Figure 11.1 Ebstein's anomaly. Example of an echocardiogram (4-chamber view, apex down) of a patient with severe Ebstein's anomaly, showing a grossly displaced septal leaflet (arrow). The anterior leaflet is severely tethered and nearly immobile. The functional right ventricle (RV) is small.

ARV indicates atrialized right ventricle; LA, left atrium; LV, left ventricle; and RA, right atrium.
Attenhofer Jost CH, **et al**. Ebstein's anomaly. *Circulation*. 2007;**115**:277–85 with permission from Wolters Kluwer.

Table 11.1 ACC/AHA 2008 GL on ACHD. Ebstein's anomaly

Recommendations for surgical interventions	
Surgeons with training and expertise in CHD should perform tricuspid valve repair or replacement with concomitant closure of an ASD, when present, for patients with Ebstein's anomaly and: a. Symptoms or deteriorating exercise capacity. b. Cyanosis (oxygen saturation <90%). c. Paradoxical embolism. d. Progressive cardiomegaly on chest X-ray. e. Progressive RV dilation or reduction of RV systolic function.	I-B
Surgeons with training and expertise in CHD should perform concomitant arrhythmia surgery in patients with Ebstein's anomaly and: a. Appearance/progression of atrial and/or ventricular arrhythmias not amenable to percutaneous treatment. b. Ventricular pre-excitation not successfully treated in the electrophysiology laboratory.	I-B
Surgical repair or replacement of the tricuspid valve in adults with Ebstein's anomaly with: a. Symptoms, deteriorating exercise capacity, or NYHA III or IV. b. Severe TR after repair with progressive RV dilation, reduction of RV systolic function, or appearance/progression of atrial and/or ventricular arrhythmias. c. Bioprosthetic tricuspid valve dysfunction with significant mixed regurgitation and stenosis. d. Predominant bioprosthetic valve stenosis (mean gradient >12–15 mmHg). e. Operation can be considered earlier with lesser degrees of bioprosthetic stenosis, with symptoms or decreased exercise tolerance.	I-B

ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. *J Am Coll Cardiol*. 2008;**52**:e1–e121 with permission from Elsevier.

Table 11.2 ESC 2010 GL on ACHD

Indications for interventions in Ebstein's anomaly	
Surgical repair in patients with more than moderate TR and symptoms (NYHA class >II or arrhythmias) or deteriorating exercise capacity measured by cardiopulmonary exercise testing.	I-C
Surgical ASD/PFO closure at the time of valve repair if tricuspid valve surgery is indicated.	I-C
Surgical repair, regardless of symptoms, in patients with progressive right heart dilation or reduction of RV systolic function and/or progressive cardiomegaly on chest X-ray.	IIa-C
Patients with relevant arrhythmias should undergo electrophysiologic testing, followed by ablation therapy, if feasible, or surgical treatment of the arrhythmias in the case of planned heart surgery.	I-C
Isolated device closure of ASD/PFO in the case of documented systemic embolism, probably caused by paradoxical embolism.	IIa-C
If cyanosis (oxygen saturation at rest <90%) is the leading problem, isolated device closure of ASD/PFO may be considered but requires careful evaluation before intervention.	IIb-C

ESC Guidelines for the management of grown-up congenital heart disease. *Eur Heart J*. 2010;**31**:2915–57 with permission from Oxford University Press.

at specializing centres, with biventricular or univentricular tricuspid repair or tricuspid valve replacement with a bioprosthesis. Mortality is now <2.5%, with late death rate over 7 years of 7.6%.[2,10] Catheter ablation of accessory pathways is difficult, with 80% success rate and up to 40% recurrence rate,[7,11] and surgical ablation may be needed. Pulmonary vasodilation may also have a role in inoperable patients, but no clinical data exist.[12]

Pregnancy

Acyanotic patients with good RV and without cyanosis tolerate pregnancy well, although there is an increased risk of RV failure, arrhythmia and paradoxical embolism, premature birth, and fetal loss.[13]

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Chapter 12

Anomalous PV connections, AV malformations, coronary and LV abnormalities

Total anomalous pulmonary venous connection

In TAPVC, all four pulmonary veins drain into systemic veins or the right atrium, with or without pulmonary venous obstruction. Systemic and pulmonary venous blood mix in the right atrium. A VSD or an ASD allows flow to the left atrium, and a PDA may be present. Diagnosis of most patients occurs in early infancy.

Connections have been classified into **supracardiac** (the four pulmonary veins drain via a common vein into the right superior vena cava, left superior vena cava, or their tributaries), **cardiac** (the pulmonary veins connect directly to the right heart, e.g. coronary sinus or directly to the right atrium), **infradiaphragmatic** (the common pulmonary vein is anterior to the oesophagus through the diaphragm to connect to the portal venous system), and **mixed** (the right and left pulmonary veins drain to different sites, e.g. left pulmonary veins into the left vertical vein to the left innominate, right pulmonary veins directly into the right atrium or coronary sinus). The degree of cyanosis in the neonate depends on the degree of venous obstruction and the size of the ASD.

Without surgery, up to 90% of patients die within the first year of life. Surgical mortality in experienced centres is <10%, and 3-year survival exceeds 85%.[1] Most patients survive surgery without late cardiovascular problem manifestations. An increased incidence of neurodevelopmental difficulties has been reported, and there is a risk for recurrent pulmonary vein stenosis or anastomosis at the anastomosis site between the common pulmonary vein and the left atrium. Post-operative pulmonary vein obstruction may occur in patients with hypoplastic/stenotic pulmonary veins.[1]

Partial anomalous pulmonary venous connection

Part, or all, of one lung drains into systemic veins or the right atrium. Sinus venosus defects have PAPVC from the right upper and middle lobe pulmonary veins to the SVC. PAPVC to the IVC (**scimitar syndrome**) may be associated with a hypoplastic right lung, pulmonary sequestration, and ASD. Signs and symptoms resemble those of a secundum ASD. Surgical correction is indicated in the presence of RV overload.[2]

Pulmonary arteriovenous malformations

They are abnormal connections between branches of the pulmonary arterial and pulmonary venous system. They are usually part of the hereditary haemorrhagic telangiectasia syndrome, an autosomal dominant disorder, but may also occur as isolated or multiple defects secondary to trauma or infection.[3] They may create a pulmonary right-to-left shunt because the desaturated blood bypasses the oxygenation mechanisms at the alveolar level. In the presence of clinical cyanosis, transcatheter embolization is the treatment of choice. Surgical lung resections are rarely required.

Aneurysms of the pulmonary artery

The upper limit of the main PA in adults is 29 mm, and the upper interlobar PA is 17 mm. Diameters exceeding those are accepted as indicating aneurysms, although a number of 40 mm has also been used.[4] They are rare abnormalities usually seen in congenital heart disease and left-to-right shunts such as PDA, VSD, and ASD. Infectious causes such as syphilis and tuberculosis, vasculitis, pulmonary hypertension and chronic embolism, and neoplasms are other causes, whereas idiopathic formation is rare. Aneurysms are usually asymptomatic. Dyspnoea, chest pain, hoarseness, cough, and haemoptysis may be seen with aneurysms exceeding 70 mm. A systolic murmur is usually heard and chest X-ray reveals a hilar enlargement or pulmonary mass. Diagnosis is established by contrast-enhanced CT. Surgery is indicated with a diameter ≥55 mm or an increase in the diameter ≥5 mm in 6 months.[4]

Congenital coronary anomalies

Congenital anomalous origin of the coronary arteries may occur in 1–5% of all coronary angiograms performed, with 0.15% of them having the highest-risk lesions of the left coronary artery arising from the right sinus of Valsalva.[3] Anomalous origin of the left coronary artery from the right sinus is consistently related to sudden death (59% of cases), which follows exercise in 81% of events. Coronary anomalies account for approximately 15% of sudden cardiac deaths in athletes (potentially due to torsion or compression of the proximal coronary artery,

Table 12.1 ACC/AHA 2008 on ACHD

Recommendations for congenital coronary anomalies of ectopic arterial origin	
The evaluation of unexplained aborted sudden cardiac death or unexplained life-threatening arrhythmia, coronary ischaemic symptoms, or LV dysfunction should include assessment of coronary artery origins and course.	I-B
CT or magnetic resonance angiography as the initial screening method.	I-B
Surgical coronary revascularization with: a. Anomalous left main coronary artery coursing between the aorta and pulmonary artery.* b. Documented coronary ischaemia due to coronary compression (when coursing between the great arteries or in intramural fashion). c. Anomalous origin of the right coronary artery between aorta and pulmonary artery with evidence of ischaemia.*	I-B
Surgical coronary revascularization in documented vascular wall hypoplasia, coronary compression, or documented obstruction to coronary flow, regardless of inability to document coronary ischaemia.	IIa-C
Delineation of potential mechanisms of flow restriction via intravascular ultrasound in patients with documented anomalous coronary artery origin from the opposite sinus.	IIa-C
Surgical coronary revascularization in anomalous LAD coursing between the aorta and pulmonary artery.*	IIb-C
Recommendations for anomalous left coronary artery from the pulmonary artery	
Reconstruction of a dual coronary artery supply should be performed by surgeons with training and expertise in CHD.	I-C
For adult survivors of ALCAPA repair, clinical evaluation with echocardiography and non-invasive stress testing is indicated every 3 to 5 years.	I-C

* These recommendations for surgery in adults have also been adopted by the ACC/AHA/SCAI 2011 Guidelines on CABG.
ESC Guidelines for the management of grown-up congenital heart disease. *Eur Heart J*. 2010;**31**:2915–57 with permission from Oxford University Press.

Table 12.2 ACC/AHA 2008 on ACHD

Recommendations for coronary arteriovenous fistula	
The origin of a continuous murmur should be defined by echocardiography, MRI, CT angiography, or cardiac catheterization.	I-C
A large coronary arteriovenous fistula (CAVF), regardless of symptomatology, should be closed via either a transcatheter or surgical route after delineation of its course and its potential to fully obliterate the fistula.	I-C
A small to moderate CAVF, in the presence of documented myocardial ischaemia, arrhythmia, otherwise unexplained ventricular systolic or diastolic dysfunction or enlargement, or endarteritis, should be closed via either a transcatheter or surgical approach after delineation of its course and its potential to fully obliterate the fistula.	I-C
Clinical follow-up with echocardiography every 3 to 5 years for patients with small, asymptomatic CAVF to exclude development of symptoms or arrhythmias or progression of size or chamber enlargement.	IIa-C
Patients with small, asymptomatic CAVF should not undergo closure of CAVF.	III-C
Recommendations for management strategies of coronary arteriovenous fistula	
Surgeons with training and expertise in CHD should perform operations for management of patients with CAVF.	I-C
Transcatheter closure of CAVF should be performed only in centres with expertise in such procedures.	I-C
Transcatheter delineation of CAVF course and access to distal drainage should be performed in all patients with audible continuous murmur and recognition of CAVF.	I-C

ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. *J Am Coll Cardiol*. 2008;**52**:e1–e121 with permission from Elsevier.

exercise-induced compression, vasospasm, or ischaemic or scar-induced ventricular arrhythmia).[5] In 80% of autopsies in athletes with sudden cardiac death and anomalous coronary artery origins, the affected coronary artery coursed between the aorta and the pulmonary artery.[3,5] Treatment is necessary in these high-risk cases as described in Table 12.1. **Myocardial bridges** (intramyocardial course of the coronary) with systolic compression occurs in 1% of coronary angiograms and requires treatment when causing ischaemia.[3] CABG is the treatment of choice, although stents have also been successfully tried.

Coronary fistulas

Communications between the coronary arteries and the cardiac chambers (**coronary-cameral fistulas**) or low-pressure veins (**coronary arteriovenous malformations**) are, most often, congenital in nature (usually to RV, RA, or PAs).[6] They also may be acquired secondary to trauma or from invasive cardiac procedures, such as pacemaker implantation, endomyocardial biopsy, coronary artery bypass grafting, or coronary angiography. With larger fistulas, a diastolic run-off may occur, drawing blood

away from the normal coronary pathway with a widened pulse pressure and a coronary steal, thus creating a left-to-right or left-to-left shunt. Most coronary artery fistulas are small, and patients are asymptomatic. A continuous murmur may be audible at the left lower sternal border. Small coronary fistulas in children tend to grow with age and may cause clinical symptoms, such as angina or congestive heart failure, and, rarely, endocarditis or fistula rupture in up to 60% of older patients. Large, haemodynamically significant fistulas can be closed electively, either by surgery on a beating heart from the epicardial surface or through transcatheter occlusion techniques (Table 12.2).

Left ventricular protrusions

Congenital left ventricular outpouchings include diverticula, aneurysms, and hernias and can be seen in up to 0.8% of patients undergoing cardiac catheterization and found to have normal coronary arteries.[7] **Diverticula** have a thick wall, made up of histologically normal heart wall tissue, and are connected to the main left ventricular chamber through a narrow neck, whereas **aneurysms** are thin-walled, fibrotic, and non-contractile and have a wide communication with the main chamber. **Cardiac hernias** are defined as myocardium protruding through a pericardial defect. Left ventricular protrusions can be a source of embolic stroke.

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Chapter 13

Univentricular heart (tricuspid atresia/single ventricle)

Definition

Univentricular heart denotes malformations where either the RV or LV is missing or, if present, is hypoplastic and thus not amenable for biventricular repair, such as:

- Tricuspid atresia
- Mitral atresia
- Double-inlet left or right ventricle
- Hypoplastic left or right heart syndrome variants
- Heterotaxia syndromes.

These malformations are always associated with additional intracardiac and extracardiac lesions.[1,2]

Pathophysiology and presentation

The following haemodynamic conditions can be seen:

1. Patients with no anatomic restrictions to pulmonary blood flow with early post-natal development of a large left-to-right shunt and symptoms of congestive heart failure. This condition may be exacerbated by obstructions to systemic circulation due to additional abnormalities. Surgical treatment, such as coarctation repair and pulmonary artery banding, is usually needed early in life to avoid the development of severe pulmonary vascular disease.
2. Patients with severe cyanosis due to obstruction to pulmonary flow, frequently caused by valvular or subvalvular PS or atresia. A small number of patients, usually with the right isomerism type of heterotaxia, can also have a total anomalous pulmonary venous connection. These patients usually undergo a systemic-to-pulmonary artery shunt procedure, with repair of the total anomalous pulmonary venous connection, if needed.

A small number of patients will present with mild cyanosis and no congestive heart failure without a previous operation. Usually, adults with these conditions will

Table 13.1 ESC 2010 GL on ACHD

Special considerations and indications for intervention in univentricular hearts	
Only well-selected patients after careful evaluation (low pulmonary vascular resistances, adequate function of the AV valve(s), preserved ventricular function) should be considered candidates for a Fontan operation	IIa-C
PA banding or tightening of a previously placed band in patients with increased pulmonary blood flow (unlikely at adult age)	IIa-C
Bidirectional Glenn shunt in patients with severe cyanosis, with decreased pulmonary blood flow without elevated PVR	IIa-C
Heart transplantation and heart–lung transplantation when there is no conventional surgical option in patients with poor clinical status	IIa-C

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have undergone previous palliation with some type of a systemic-to-pulmonary shunt.

Therapy

Recommendations for management of these patients are presented in Table 13.1. Depending on the haemodynamic status, single-ventricle anomalies are initially dealt with PA banding or a Norwood procedure (modified Blalock–Taussig or RV-to-PA shunt) and later on with a Fontan operation.[3]

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Chapter 14

The Fontan patient

Definition

The Fontan operation is a generic term for a group of operations that redirect the systemic venous return to the pulmonary arteries without passing through a subpulmonary ventricle.[1,2] It is usually the final operation for 'univentricular heart' conditions described in Chapter 13. The classic Fontan consisted of a valved conduit between the right atrium and pulmonary artery. It was subsequently modified to a direct anastomosis of the right atrium to a divided pulmonary artery (Figure 14.1A). The intracardiac lateral tunnel consists of an end-to-side anastomosis of the superior vena cava to the undivided right pulmonary artery, and a composite intra-atrial tunnel that uses the right atrial lateral wall and prosthetic material to channel inferior vena caval flow to the pulmonary artery (Figure 14.1B). The 'extracardiac' variant of the total cavopulmonary connection Fontan consists of directing inferior vena caval flow to the pulmonary artery by means of an external conduit (Figure 14.1C).[3]

Pathophysiology

Fontan is usually offered to patients with single-ventricle physiology, i.e. a functionally single ventricle, or when biventricular repair is not feasible (see Chapter 13). Thus, nowadays, the so-called Fontan physiology consists of staged approaches that eventually end up in a single functional ventricle that maintains both the systemic and the passive pulmonary circulation. Symptoms develop when the single functional ventricle fails. The 12-year survival after various types of operation is 70%.[1] Extracardiac conduit, total cavopulmonary connection, and lack of clinical arrhythmia or right heart failure are good prognostic signs, whereas exercise intolerance is not associated with long-term mortality.[4] Considerable mortality is still observed during the first years of life among patients with a single ventricle. In patients with a functionally univentricular heart undergoing the Fontan procedure, RV dominance is the most important risk factor for death but only before bidirectional superior cavopulmonary anastomosis.[5]

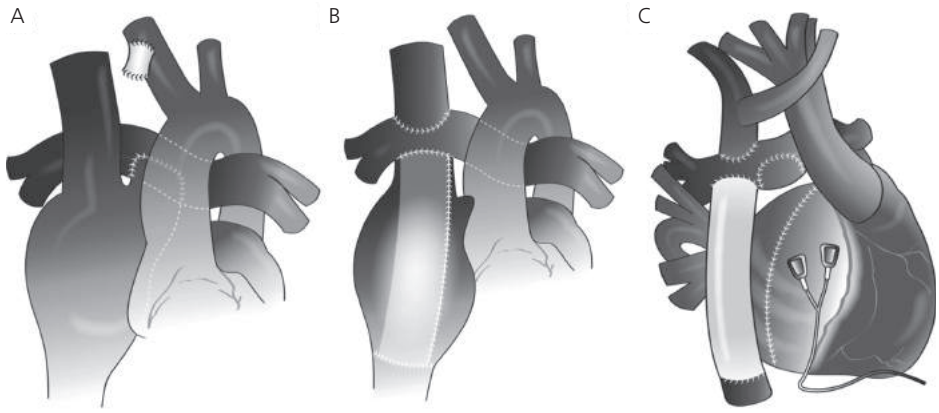

Figure 14.1 Variations of Fontan surgery. A, The modified classic Fontan. B, The intracardiac lateral tunnel Fontan. C, The extracardiac.

Khairy P, Poirier N. Is the extracardiac conduit the preferred Fontan approach for patients with univentricular hearts. *Circulation*. 2012;**126**:2516–25 with permission from Wolters Kluwer.

Table 14.1 ACC/AHA 2008 GL on ACHD. Recommendations for patients with prior Fontan repair

Recommendations for medical therapy	
Warfarin with a documented atrial shunt, atrial thrombus, atrial arrhythmias, or a thromboembolic event.	I-C
ACE inhibitors and diuretics for SV dysfunction.	IIa-C
Recommendations for surgery for adults with prior Fontan repair	
Surgeons with training and expertise in CHD should perform operations on patients with prior Fontan repair for single-ventricle physiology.	I-C
Reoperation after Fontan is indicated for : a. Unintended residual ASD that results in right-to-left shunt with symptoms and/or cyanosis not amenable to transcatheter closure. b. Haemodynamically significant residual systemic artery-to-pulmonary artery shunt, residual surgical shunt, or residual ventricle-to-pulmonary artery connection not amenable to transcatheter closure. c. Moderate to severe systemic AV valve regurgitation. d. Significant (>30 mmHg peak-to-peak) subaortic obstruction. e. Fontan pathway obstruction. f. Development of venous collateral channels or pulmonary arteriovenous malformation not amenable to transcatheter management. g. Pulmonary venous obstruction. h. Rhythm abnormalities, such as complete AV block or sick sinus syndrome, that require epicardial pacemaker insertion. i. Creation or closure of a fenestration not amenable to transcatheter intervention.	I-C
Recommendations for evaluation and follow-up after Fontan procedure	
Reoperation for Fontan conversion (i.e. revision of an atriopulmonary connection to an intracardiac lateral tunnel, intra-atrial conduit, or extracardiac conduit) for recurrent AF or flutter without haemodynamically significant anatomic abnormalities. A concomitant Maze procedure should also be performed.	IIa-C
Heart transplantation for severe SV dysfunction or protein-losing enteropathy.	IIb-C
Recommendations for electrophysiology testing/pacing issues in single-ventricle physiology and after Fontan procedure	
Electrophysiological studies in adults with Fontan physiology should be performed at centres with expertise in the management of such patients.	I-C
New-onset atrial tachyarrhythmias should prompt a comprehensive non-invasive imaging evaluation to identify associated atrial/baffle thrombus, anatomic abnormalities of the Fontan pathway, or ventricular dysfunction.	I-C
There is high risk of symptomatic intra-atrial reentrant tachycardia (IART) in adult patients. This can cause serious haemodynamic compromise and contribute to atrial thrombus formation. Treatment is often difficult, and consultation with an electrophysiologist who is experienced with CHD is recommended.	I-C

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Clinical problems

Patients present with classic right heart failure. There is a **non-pulsatile high JVP** (10 cm), with **single S2** and a **murmur** only if subaortic obstruction or significant systemic AV valve regurgitation. Luminal protein loss can manifest as either a break in the integrity of the intestinal mucosa, with the development of protein-losing enteropathy, or a break in the bronchial mucosa with the accumulation of proteinaceous material in the airways, forming bronchial casts, or plastic bronchitis.[6] Oedema and ascites may be seen as a sign of **protein-losing enteropathy** that occurs in 5–15% of patients following the Fontan operation and carries a 5-year mortality of >10%.[7] Other problems are arrhythmias due to post-operative atrial scarring such as **intra-atrial reentrant tachycardia, atrial flutter, and AF**. The most frequent of these is intra-atrial reentrant tachycardia, particularly seen with atrio-pulmonary connections. With modern techniques, its incidence has been reduced to 7%.[8] Catheter ablation is cumbersome, due to multiple circuits, and should be attempted only at experienced centres. **Sick sinus syndrome** and **AV block**, **thromboembolic complications**, progressive **AV valve deterioration**, **liver fibrosis** and **renal dysfunction**, **venous insufficiency**, and **neurocognitive deficits** may also occur.[6] **Obstruction of the Fontan connection or the pulmonary artery branches** are being dealt with by stent-based transcatheter pulmonary valve implantation. These patients need attention in experienced ACHD centres.[9,10] Pregnancy is associated with maternal and fetal complications and must be discouraged or undertaken with great deliberation.[11]

Therapy

Recommendations are presented in Table 14.1. In patients with exercise intolerance, bosentan improves exercise capacity, exercise time, and functional class in Fontan patients, without serious adverse events or hepatotoxicity.[12]

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Chapter 15

Eisenmenger syndrome

Definition

Eisenmenger syndrome results when elevated pulmonary vascular resistance becomes irreversible and leads to a reversal of shunt, desaturation, cyanosis, and secondary erythrocytosis.[1]

Pathophysiology

With long-standing left-to-right shunting, exposure of the pulmonary artery system to high pressure and increased flow lead to progressive arteriolar medial hypertrophy, intimal proliferation and fibrosis, and obliteration of pulmonary arterioles and capillaries. These changes are reversible, but more advanced morphologic changes, such as occlusion of small arterioles, plexiform lesions, and necrotizing arteritis, are irreversible. The precise pathophysiological mechanisms for this are not completely understood, but there is evidence that microvascular injury stimulates production of growth factors and enzymes that result in intimal proliferation and medial hypertrophy. Endothelial dysfunction and platelet activation may also play a role in the obliteration of pulmonary arterioles. When pulmonary vascular resistance approaches and exceeds systemic vascular resistance, shunting reverses and becomes right-to-left and cyanosis appears.

Clinical problems

Adult patients with Eisenmenger syndrome have a better haemodynamic profile and life expectancy compared to patients with idiopathic pulmonary arterial hypertension, but poorer quality of life. Patients present with fatigue, SOBOE, palpitations. Symptoms of **hyperviscosity** (headaches, visual disturbances, dizziness, paraesthesiae), **secondary polycythaemia**, **thrombocytopenia** and **iron deficiency**, **gallstones**, and **gouty arthritis** develop, and patients are at risk for both bleeding and thrombosis. **Symptomatic hypertrophic osteoarthropathy**, **haemoptysis**, **cerebrovascular accidents**, **pulmonary artery thrombosis**, **impaired renal function, and infections** such as brain abscess, pneumonia, endocarditis, and sinusitis may also be seen. Death may be sudden due to arrhythmias or heart failure, but some patients die of massive haemoptysis, brain abscess, or stroke.

Physical examination

Patients are cyanotic with clubbing, but there may be no murmur during systole or diastole because shunting may be minimal.

V waves in JVP

RV parasternal heave

S_4 and loud P_2

High-frequency diastolic decrescendo murmur of PR

Holosystolic murmur of TR

Peripheral oedema may be present late in the course of disease when right ventricular dysfunction is present.

Investigations

ECG shows RV hypertophy.

Chest radiography reveals prominent central pulmonary arteries with decreased vascular markings (pruning) of the peripheral vessels. Cardiomegaly may be seen in patients with ASD.

Echocardiography reveals RV pressure overload and pulmonary hypertension. Demonstration of shunting may be difficult with Doppler imaging because of the low velocity of the jet and often requires contrast echocardiography. RV dysfunction, as measured by tricuspid annular plane systolic excursion, and right atrial area and pressure are associated with worse outcomes in patients with Eisenmenger syndrome.[2,3]

Cardiac catheterization is mandatory for assessing the severity and potential reversibility of pulmonary vascular disease. PA pressure >2/3 of Ao pressure or PVR >2/3 of SVR (approximately 7 Wood units) that do not respond to vasodilators, such as oxygen, nitric oxide, adenosine, or epoprostenol, indicate irreversible pulmonary damage that does not allow intervention. The value of lung biopsy is not proven.

Table 15.1 ACC/AHA 2008 GL on ACHD

Recommendations for medical therapy of Eisenmenger physiology	
Avoidance of :	
a. Pregnancy.	I-B
b. Dehydration.	I-C
c. Moderate and severe strenuous exercise, particularly isometric exercise.	I-C
d. Acute exposure to excessive heat (e.g. hot tub or sauna).	I-C
e. Chronic high altitude exposure, (particularly at an elevation >5000 feet above sea level).	I-C
f. Iron deficiency.	I-B
Prompt therapy for arrhythmias and infections.	I-C
Haemoglobin, platelet count, iron stores, creatinine, and uric acid should be assessed at least yearly.	I-C
Assessment of digital oximetry, both with and without supplemental oxygen therapy, at least yearly. The presence of oxygen-responsive hypoxaemia should be investigated further.	I-C
Exclusion of air bubbles in intravenous tubing during treatment.	I-C
Non-cardiac surgery and cardiac catheterization should be performed only in centres with expertise. In emergent situations, consultation with designated caregivers should be performed.	I-C
All medications should undergo rigorous review for the potential to change systemic blood pressure, loading conditions, intravascular shunting, and renal or hepatic flow or function.	IIa-C
Pulmonary vasodilator therapy can be beneficial because of the potential for improved quality of life.	IIa-C
Recommendations for reproduction	
Patients and their partners should be counselled about the absolute avoidance of pregnancy and educated regarding safe and appropriate methods of contraception.	I-B
Women with CHD and pulmonary arterial hypertension (CHD-PAH) who become pregnant should:	I-C
a. Receive individualized counselling from cardiovascular and obstetric experts.	
b. Undergo the earliest possible pregnancy termination.	
Surgical sterilization carries some operative risk for women with CHD-PAH but is a safer option than pregnancy.	I-C
Pregnancy termination in the last two trimesters of pregnancy poses a high risk to the mother. It may be reasonable, however, after the risks of termination are balanced against the risks of continuation of the pregnancy.	IIb-C
Pregnancy in women with CHD-PAH, especially those with Eisenmenger physiology, should be absolutely avoided in view of the high risk of maternal mortality.	III-B
The use of single barrier contraception alone in women with CHD-PAH is not recommended, owing to the frequency of failure.	III-C
Oestrogen-containing contraceptives should be avoided.	III-C

ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. *J Am Coll Cardiol*. 2008;**52**:e1–e121 with permission from Elsevier.

Table 15.2 ESC 2010 GL on ACHD

Recommendations for targeted pulmonary hypertension therapy in congenital heart disease	
Targeted PAH therapy in CHD should only be performed in specialized centres.	I-C
The endothelin receptor antagonist (ERA) bosentan should be initiated in WHO functional class III* patients with Eisenmenger syndrome.	I-B
Other ERAs, phosphodiesterase type 5 inhibitors, and prostanoids in WHO functional class III* patients with Eisenmenger syndrome.	IIa-C
Combination therapy may be considered in WHO functional class III patients with Eisenmenger syndrome.	IIb-C
The use of calcium channel blockers should be avoided in patients with Eisenmenger syndrome.	III-C

* Although recent data support the use of ERAs, such as bosentan, also in WHO functional class II in patients with idiopathic PAH and PAH associated with connective tissue diseases, such data are currently not available for Eisenmenger patients. Because of marked differences in the natural history between these groups, the results cannot simply be applied to congenital patients, and further studies are required before recommendations.

ESC Guidelines for the management of grown-up congenital heart disease. *Eur Heart J*. 2010;**31**:2915–57 with permission from Oxford University Press.

Therapy

The patient with Eisenmenger syndrome needs care in specialized centres. In general, intense exercise and acute heat exposure, as in hot tubs or saunas, are avoided. Annual influenza vaccination and Pneumovax every 5 years are recommended. Pregnancy in patients with Eisenmenger syndrome is not recommended, owing to excessive maternal and fetal mortality, and should be strongly discouraged.

Long-term oxygen administration for 12–15 h/day may improve symptoms but not survival. **Diuretics** should be used with caution to avoid dehydration. **Calcium channel blockers** may increase the right-to-left shunt. The use of **anticoagulation** is controversial and should be considered only if additional indications exist. **Phlebotomy** with isovolumic replacement should be reserved for moderate to severe hyperviscosity syndromes (haematocrit >65%). Vasodilator therapy is an important adjunct to management and can provide functional improvement. The dual endothelin receptor antagonist **bosentan** has been shown to improve haemodynamics and exercise capacity, and perhaps survival, and is currently recommended to all patients by the ESC guidelines. The phosphodiesterase type V inhibitor **sildenafil** that raises cGMP levels may improve functional class, oxygen saturation, and haemodynamics.

Beneficial effects of **endothelin receptor antagonists**, and **prostacyclin (epoprostenol)** or prostacyclin analogues have also been reported (see Chapter 78). **Heart-lung transplantation** is a therapeutic option. Recommendations for pulmonary hypertension and Eisenmenger syndrome are presented in Tables 15.1 and 15.2.[4,5]

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Part II

Valve disease

Relevant guidelines

AHA/ACC 2014 Guidelines on valve disease

2014 AHA/ACC Guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

ESC 2012 Guidelines on valve disease

ESC 2012 Guidelines on the management of valvular heart disease. *Eur Heart J*. 2012;**33**:2451–96.

ACCF/AHA 2011 Guideline on CABG

2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery. *Circulation*. 2011;**124**:2610–42.

ESC 2014 Guidelines on revascularization

2014 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2014;**35**:2541–619.

ESC/ESA 2014 Guidelines on non-cardiac surgery

2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management. *Eur Heart J*. 2014;**35**:2383–431.

ESC 2011 Guidelines on pregnancy

ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**:3147–97.

Chapter 16

General principles

Epidemiology

The prevalence of any valve disease in the general population in the USA is 2.5% and increases with age, from 0.7% in persons 18–44 years old to 13.2% in those ≥75 years.[1] Data are provided by epidemiological studies such as the CARDIA (Coronary Artery Risk Development in Young Adults), ARIC (Atherosclerosis Risk in Communities), and CHS (Cardiovascular Health Study), as well as the Olmsted County community study. Survival of participants in those studies with valve disease is 79% at 5 years, compared with 93% in participants without valve disease.[2] Approximately 0.4% have aortic stenosis (AS), 0.5% aortic regurgitation (AR), 0.1% mitral stenosis (MS), and 1.7% mitral regurgitation (MR).[2] In Europe, data are collected by the EuroHeart Survey among patients with established valve disease. Prevalence is AS 43%, MR 31.5%, AR 13.3%, and MS 12.1%.[3] Table 16.1 presents the new classification of the progression of valvular heart disease (VHD) by the ACCF/AHA 2014 guidelines.[4]

Table 16.1 AHA/ACC 2014 GL on valve disease. Stages of progression of VHD

Stage	Definition	Description
A	At risk	Patients with risk factors for development of VHD
B	Progressive	Patients with progressive VHD (mild-to-moderate severity and asymptomatic)
C	Asymptomatic severe	Asymptomatic patients who have the criteria for severe VHD: C1: Asymptomatic patients with severe VHD in whom the left or right ventricle remains compensated C2: Asymptomatic patients with severe VHD, with decompensation of the left or right ventricle
D	Symptomatic severe	Patients who have developed symptoms as a result of VHD

AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185 with permission from Elsevier.

Cardiac auscultation

Heart sounds

First sound (S_1) is due to simultaneous MV and TV closure.

Loud: MS, hyperkinetic states, short PR <160 ms

Soft: long PR (>200 ms), severe MS, LV dysfunction

Widely split: RBBB.

Second sound (S_2) is due to AV followed by PV closure. Splitting normally increases with inspiration. A loud P_2 suggests pulmonary hypertension.

Single: AS or PS

Widely split: RBBB, MR

Fixed splitting: ASD

Reversed splitting: LBBB, AS, hypertrophic cardiomyopathy (HCM), RV pacing.

Third sound (S_3) is pathological over the age of 30 years. Probably due to rapid LV filling. Audible in LV failure, severe MR, VSD. A high-pitched S_3 may be heard in restrictive cardiomyopathy and pericardial constriction.

Fourth sound (S_4) corresponds to atrial contraction and is produced at end-diastole before S_1. It can be heard in conditions with LVH or after acute MI.

Ejection sound Bicuspid AV or PS.

Mid-systolic (non-ejection) click Mitral valve prolapse (MVP).

Opening snap MS, rarely TS, Ebstein's anomaly.

Murmurs

Murmurs are produced by turbulent blood flow and are described according to their location, intensity, timing, frequency, and radiation (Tables 16.2 and 16.3).

Innocent murmurs are due to pulmonary flow and can be heard in children, pregnancy, and high-flow states such as hyperthyroidism and anaemia. They are heard over the left sternal edge and are ejection systolic, and there are no added sounds or thrill. The **cervical venous hum** is a continuous murmur, common in children and typically reduced by turning the head laterally or bending the elbows back. The **mammary soufflé** is a continuous murmur that may be heard in pregnancy.

Dynamic auscultation manoeuvres may help bedside diagnosis of systolic murmurs (Table 16.3).[5,6] Murmurs originating within the right-sided chambers of the heart can be differentiated from all other murmurs by augmentation of their intensity with inspiration and diminution with expiration. The murmur of hypertrophic cardiomyopathy is distinguished from all other systolic murmurs by an increase in intensity with the Valsalva manoeuvre and during squatting-to-standing, and by a decrease in intensity during standing-to-squatting action, passive leg elevation, and handgrip. The murmurs of MR and VSD have similar responses but can be differentiated from other systolic murmurs by augmentation of their

Table 16.2 Heart murmurs

Systolic	
Early	Acute MR, VSD, TR.
Mid-systolic	AS (valvular, supra- or subvalvular), AR, HCM, PS (valvular, supra- or subvalvular), ASD.
Late systolic	MR due to MVP or chordal rupture, TR.
Pansystolic	MR, TR, VSD.
Diastolic	
Early	AR (valvular or due to dilation of the ring, bicuspid AV), PR (valvular or due to dilation of the ring, congenital).
Mid-diastolic	MS, Carey Coombs, VSD, PDA, ASD, TR, AR.
Late diastolic	Presystolic accentuation of MS, Austin Flint.
Continuous	
Coronary or intercostal AV fistula or anomalous left coronary artery, PDA, ruptured sinus of Valsalva aneurysm, ASD, cervical venous hum, mammary soufflé of pregnancy.	

intensity with handgrip and during transient arterial occlusion.[5]

Investigations

Indications for echocardiography, exercise testing, and cardiac catheterization are presented in Table 16.4. They are also discussed in individual chapters. Patients with severe VHD should be evaluated by a multidisciplinary heart valve team when intervention is considered (AHA/ACC 2014 GL on VD, I-C). Consultation with, or referral to, a heart valve centre of excellence is reasonable when discussing treatment options for: 1) asymptomatic patients with severe VHD, 2) patients who may benefit from valve repair versus valve replacement, or 3) patients with multiple comorbidities for whom valve intervention is considered (AHA/ACC 2014 GL on VD, IIa-C).

Table 16.3 Interventions used to alter the intensity of cardiac murmurs

Respiration
Right-sided murmurs generally increase with inspiration. Left-sided murmurs usually are louder during expiration.
Valsalva manoeuvre
Most murmurs decrease in length and intensity. Two exceptions are the systolic murmur of HCM, which usually becomes much louder, and that of MVP, which becomes longer and often louder. After release of the Valsalva, right-sided murmurs tend to return to baseline intensity earlier than left-sided murmurs.
Exercise
Murmurs caused by blood flow across normal or obstructed valves (e.g. PS and MS) become louder with both isotonic and isometric (handgrip) exercise.
Murmurs of MR, VSD, and AR also increase with handgrip exercise.
Positional changes
With standing, most murmurs diminish, two exceptions being the murmur of HCM, which becomes louder, and that of MVP, which lengthens and often is intensified. With brisk squatting, most murmurs become louder, but those of HCM and MVP usually soften and may disappear. Passive leg raising usually produces the same results as brisk squatting.
Post-ventricular premature beat or atrial fibrillation
Murmurs originating at normal or stenotic semilunar valves increase in intensity during the cardiac cycle after a VPB or in the beat after a long cycle length. In AF, by contrast, systolic murmurs due to atrioventricular valve regurgitation do not change, diminish (papillary muscle dysfunction), or become shorter (MVP).
Pharmacological interventions
During the initial relative hypotension after amyl nitrite inhalation, murmurs of MR, VSD, and AR decrease, whereas murmurs of AS increase because of increased stroke volume. During the later tachycardia phase, murmurs of MS and right-sided lesions also increase. This intervention may thus distinguish the murmur of the Austin Flint phenomenon from that of MS. The response in MVP often is biphasic (softer, then louder than control).
Transient arterial occlusion
Transient external compression of both arms by bilateral cuff inflation to 20 mmHg greater than peak systolic pressure augments the murmurs of MR, VSD, and AR, but not murmurs due to other causes.

AF indicates atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; HCM, hypertrophic cardiomyopathy; MR, mitral regurgitation; MS, mitral stenosis; MVP, mitral valve prolapse; PS, pulmonic stenosis; VPB, ventricular premature beat; and VSD, ventricular septal defect.

AHA/ACC 2008 Focused Update Incorporated Into the ACC/AHA 2006 Guidelines for the Management of Patients with Valvular Heart Disease. *J Am Coll Cardiol*. 2008;**52**: e1–e142 with permission from Elsevier.

Management

Indications for valve interventions and surgery are provided in individual chapters. Evaluation and management of CAD in patients undergoing valve surgery are presented in Tables 16.5 and 16.6, and Figure 16.1.

Rheumatic fever and endocarditis prophylaxis

Secondary prevention of rheumatic fever is indicated in patients with rheumatic heart disease, and especially mitral stenosis, and is discussed in detail in Chapter 82.

Prophylaxis of infective endocarditis is discussed in Chapter 81. Prophylaxis is indicated only in high-risk patients (i.e. patients with prosthetic cardiac valves), and only before dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa, and before vaginal delivery. Prophylaxis against infective endocarditis is not recommended for non-dental procedures (such as transoesophageal echocardiogram, oesophagogastroduodenoscopy, or colonoscopy) in the absence of active infection. In patients with unoperated valve disease, prophylaxis is not recommended any more for any procedure.

Table 16.4 AHA/ACC 2014 GL on valve disease. Diagnostic testing

Transthoracic echocardiography (TTE) in the initial evaluation of patients with known or suspected VHD to confirm the diagnosis, establish aetiology, determine severity, assess haemodynamic consequences, determine prognosis, and evaluate for timing of intervention.	I-B
TTE in patients with known VHD with any change in symptoms or physical examination findings.	I-C
Periodic monitoring with TTE in asymptomatic patients with known VHD at intervals, depending on valve lesion, severity, ventricular size, and ventricular function.	I-C
Cardiac catheterization for haemodynamic assessment in symptomatic patients when non-invasive tests are inconclusive or when there is a discrepancy between the findings on non-invasive testing and physical examination.	I-C
Exercise testing in selected patients with asymptomatic severe VHD to: 1) confirm the absence of symptoms, or 2) assess the haemodynamic response to exercise, or 3) determine prognosis.	IIa-B

AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

Table 16.5 Evaluation of coronary artery disease

AHA/ACC 2014 GL on valve disease. Evaluation and management of coronary disease	
Coronary angiography before valve intervention in patients with symptoms of angina, objective evidence of ischaemia, decreased LV systolic function, history of CAD, or coronary risk factors (including men age >40 years and post-menopausal women).	I-C
Coronary angiography as part of the evaluation of patients with chronic severe secondary MR.	I-C
Surgery without coronary angiography is reasonable for patients having emergency valve surgery for acute valve regurgitation, disease of the aortic sinuses or ascending aorta, or IE.	I-C
CT coronary angiography to exclude the presence of significant obstructive CAD. In selected patients with a low/intermediate pretest probability of CAD. A positive coronary CT angiogram (the presence of any epicardial CAD) is confirmed with invasive coronary angiography.	IIa-B
CABG or PCI in patients undergoing valve repair or replacement with significant CAD (≥70% reduction in luminal diameter in major coronary arteries or ≥50% reduction in luminal diameter in the left main coronary artery).	IIa-C
ACCF/AHA 2011 GL on CABG. Patients with concomitant valvular disease	
Concomitant aortic valve replacement in patients undergoing CABG who have at least moderate aortic stenosis.	I-B
Concomitant mitral valve repair or replacement at the time of CABG, in patients undergoing CABG who have severe ischaemic mitral valve regurgitation not likely to resolve with revascularization.	I-B
Concomitant mitral valve repair or replacement at the time of CABG, in patients undergoing CABG who have moderate ischaemic mitral valve regurgitation not likely to resolve with revascularization.	IIa-B
Concomitant aortic valve replacement when evidence (e.g. moderate-severe leaflet calcification) suggests that progression of the aortic stenosis may be rapid and the risk of the combined procedure is acceptable, in patients undergoing CABG who have mild aortic stenosis.	IIb-C

AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.
ACCF/AHA 2011 guideline for Coronary Artery Bypass Graft Surgery. *Circulation*. 2011;**124**:2610–42 with permission from Wolters Kluwer.

Table 16.6 ESC 2014 GL on revascularization. Combined valvular and coronary interventions*

Diagnostic modalities	
Coronary angiography is recommended before valve surgery in patients with severe valvular heart disease and any of the following: • History of coronary artery disease • Suspected myocardial ischaemia • Left ventricular systolic dysfunction • In men aged over 40 years and post-menopausal women • ≥1 cardiovascular risk factor.	I-C
Coronary angiography is recommended in the evaluation of secondary mitral regurgitation.	I-C
CT angiography should be considered before valve surgery in patients with severe valvular heart disease and low probability for CAD or in whom conventional coronary angiography is technically not feasible or of high risk.	IIa-C
Primary valve intervention and coronary revascularization	
CABG is recommended in patients with a primary indication for aortic/mitral valve surgery and coronary artery diameter stenosis >70% in a major epicardial vessel.	I-C
CABG should be considered in patients with a primary indication for aortic/mitral valve surgery and coronary artery diameter stenosis 50–70% in a major epicardial vessel.	IIa-C
PCI should be considered in patients with a primary indication to undergo TAVI and coronary artery diameter stenosis >70% in proximal segments.	IIa-C
PCI should be considered in patients with a primary indication to undergo transcatheter mitral valve interventions and coronary artery diameter stenosis >70% in proximal segments.	IIa-C
Primary revascularization and non-coronary intervention	
Mitral valve surgery is indicated in patients with severe mitral regurgitation undergoing CABG and LVEF >30%.	I-C
Mitral valve surgery should be considered in patients with moderate mitral regurgitation undergoing CABG to improve symptoms.	IIa-B
Repair of moderate-to-severe mitral regurgitation should be considered in patients with a primary indication for CABG and LVEF ≤35%.	IIa-B
Stress testing should be considered in patients with a primary indication for CABG and moderate mitral regurgitation to determine the extent of ischaemia and regurgitation.	IIa-C
Aortic valve surgery should be considered in patients with a primary indication for CABG and moderate aortic stenosis (defined as valve area 1.0–1.5 cm^2 [0.6 cm^2/m^2 to 0.9 cm^2/m^2 body surface area] or mean aortic gradient 25–40 mmHg in the presence of normal flow conditions).	IIa-C

*Similar recommendations have been provided by the ESC 2012 GL on valve disease.
CABG, coronary artery bypass grafting; CA, coronary artery disease; CT, computed tomography; LV, left ventricular; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation.
ESC 2012 guidelines on the management of valvular heart disease. *Eur Heart J.* 2012;**33**:2451–96 with permission from Oxford University Press.

Table 16.7 AHA/ACC 2014 GL on valve disease. Pregnancy and valvular heart disease*

Clinical evaluation and TTE before pregnancy for all patients with suspected valve stenosis or regurgitation.	I-C
Prepregnancy counselling by a cardiologist with expertise in managing patients with VHD during pregnancy for all patients with severe valve stenosis or regurgitation (stages C and D).	I-C
Prepregnancy counselling by a cardiologist with expertise in managing patients with VHD during pregnancy about the risks and benefits of all options for operative interventions, including mechanical prosthesis, bioprosthesis, and valve repair for all patients referred for a valve operation before pregnancy.	I-C
Pregnant patients with severe valve stenosis or regurgitation (stages C and D) should be monitored in a tertiary care centre with a dedicated heart valve team of cardiologists, surgeons, anaesthesiologists, and obstetricians with expertise in the management of high-risk cardiac patients during pregnancy.	I-C
ACE inhibitors and ARBs should not be given to pregnant patients with valve stenosis or regurgitation.	III-C
Valve operation should not be performed in pregnant patients with valve stenosis in the absence of severe HF symptoms.	III-C
Exercise testing is reasonable in asymptomatic patients with severe valve regurgitation (stage C) before pregnancy.	IIa-C
Valve repair or replacement before pregnancy for symptomatic women with severe valve regurgitation (stage D).	I-C
Valve operation for pregnant patients with severe valve regurgitation only if there are refractory NYHA class IV HF symptoms (stage D).	IIa-C
Valve operations in pregnant patients with valve regurgitation or stenosis in the absence of severe intractable HF symptoms.	III-C

* See also individual chapters.
AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol.* 2014;**63**:e57–185.

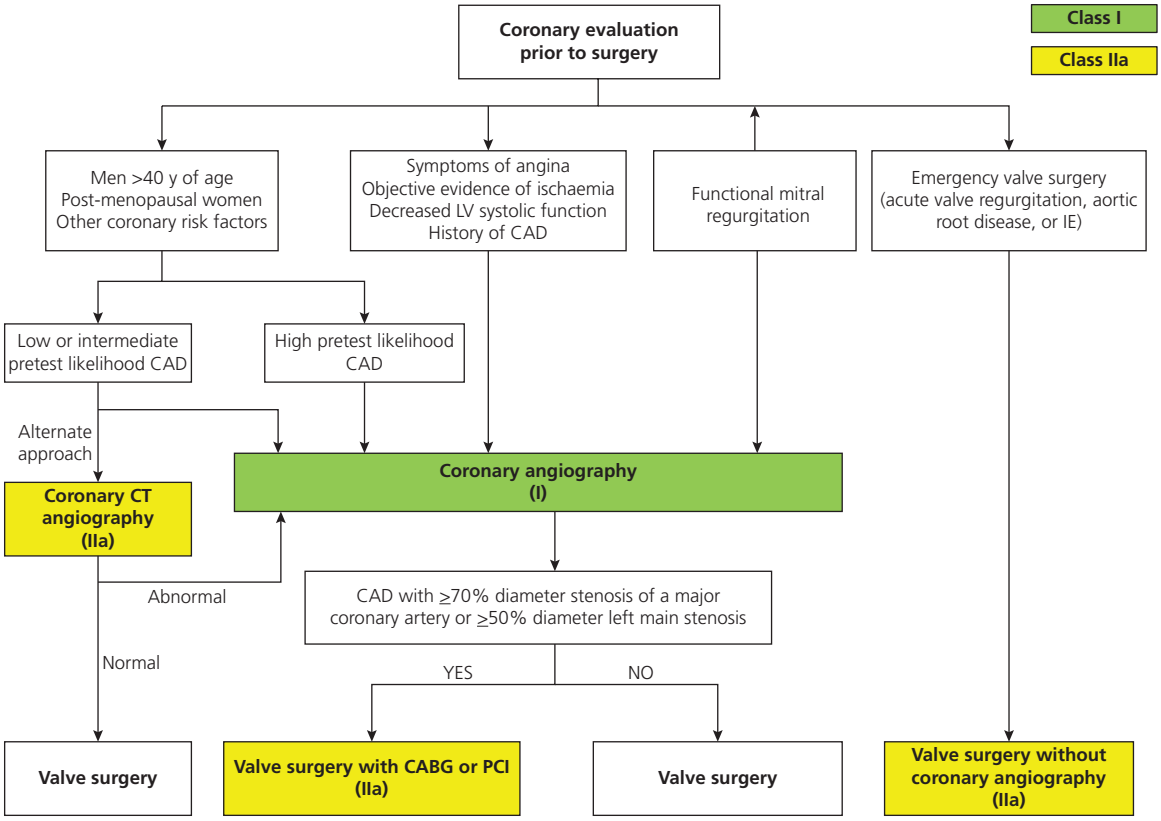

Figure 16.1 AHA/ACC 2014 GL on valve disease. Evaluation and management of CAD in patients undergoing valve surgery

AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol.* 2014;**63**:e57–185.

Pregnancy

Valvular lesions associated with high maternal and/or fetal risk during pregnancy are:[7,8]

- MS with NYHA functional class II–IV symptoms
- Severe AS with or without symptoms
- AR or MR with NYHA functional class III–IV symptoms
- Severe pulmonary hypertension (pulmonary pressure >2/3 of systemic pressures) or LV dysfunction (LVEF <40%)
- Mechanical prosthetic valve requiring anticoagulation
- Marfan's syndrome with or without aortic regurgitation.

General recommendations are provided in Table 16.7. Valve disease in pregnancy is also discussed in chapters on specific valve diseases. Pregnancy in patients with prosthetic valves is discussed in Chapter 22.

Non-cardiac surgery

Recommendations are discussed in chapters on specific valve diseases.

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Chapter 17

Mitral stenosis

Epidemiology

Mitral stenosis (MS) is highly prevalent in developing countries because of its association with rheumatic fever (6/1000 children in India vs 0.5/1000 in developed countries), but is also seen in developed countries where patients are of increased age.[1,2] In developed countries, the prevalence of MS detected by echocardiography is about 0.1–0.2%.[3,4] Although the attack rate for rheumatic fever is roughly equal among genders, MS is 2–3 times more common in women.

Aetiology

Rheumatic fever is the main cause of MS, although less than 60% of affected patients provide a relevant history.[1,2] The M protein antigen held in common between the heart and group A haemolytic *Streptococcus* results in an autoimmune attack of the heart in response to streptococcal infection. The rheumatic process leads to inflammation of the endocardium, myocardium, and pericardium, but the disease affects mainly the endocardium. Persistent inflammatory valve damage results in gradual progression that is strongly associated with repeated episodes of rheumatic fever. In the western world, symptoms of MS usually appear after 15–20 years following the rheumatic fever attack. **Degenerative** causes may be identified in up to 12.5% in developed countries.[5] In 6–8% of patients with severe **mitral annular calcification**, who are often elderly or dialysis-dependent, calcium encroaching into the valve leaflets causes mitral stenosis. Other rare causes are **congenital MS** (**Lutembacher syndrome when combined with ASD**, **mucopolysaccharidoses**, **Fabry's disease**, **systemic lupus erythematosus**, **rheumatoid arthritis**, **anorectic drugs**, and disorders associated with abnormal serotonin metabolism (**carcinoid and methysergide treatment**).[1]

Pathophysiology and natural history

The main features are leaflet thickening and calcification with chordal shortening and fusion. Patients usually have a dilated and stiff LA and may develop systolic and diastolic LV dysfunction. Procoagulation abnormalities are

Table 17.1 Classification of MS

AHA/ACC 2014 GL on valve disease. Stages of MS

Stage	Definition	Valve anatomy	Valve haemodynamics	Haemodynamic consequences	Symptoms
A	At risk of MS	• Mild valve doming during diastole	Normal transmitral flow velocity	None	None
B	Progressive MS	• Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets • Planimetered MVA >1.5 cm^2	• Increased transmitral flow velocities • MVA >1.5 cm^2 • Diastolic pressure half-time <150 ms	• Mild-to-moderate LA enlargement • Normal pulmonary pressure at rest	None
C	Asymptomatic severe MS	• Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets • Planimetered MVA ≤1.5 cm^2 • (MVA ≤1.0 cm^2 with very severe MS)	• MVA ≤1.5 cm^2 • (MVA ≤1.0 cm^2 with very severe MS) • Diastolic pressure half-time ≥150 ms • (Diastolic pressure half-time ≥220 ms with very severe MS)	• Severe LA enlargement • Elevated PASP >30 mm Hg	None
D	Symptomatic severe MS	• Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets • Planimetered MVA ≤1.5 cm^2	• MVA ≤1.5 cm^2 • (MVA ≤1.0 cm^2 with very severe MS) • Diastolic pressure half-time ≥150 ms • (Diastolic pressure half-time ≥220 ms with very severe MS)	• Severe LA enlargement • Elevated PASP >30 mm Hg	• Decreased exercise tolerance • Exertional dyspnoea

The transmitral mean pressure gradient should be obtained to further determine the haemodynamic effect of the MS and is usually >5 mm Hg to 10 mm Hg in severe MS; however, due to the variability of the mean pressure gradient with heart rate and forward flow, it has not been included in the criteria for severity.

LA indicates left atrial; LV, left ventricular; MS, mitral stenosis; MVA, mitral valve area; and PASP, pulmonary artery systolic pressure.

ESC 2012 GL on valve disease. Definition of severe MS

Valve area < 1 cm^2

Mean gradient >10 mm Hg (in patients with sinus rhythm, to be interpreted according to heart rate)

AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol.* 2014;**63**:e57–185.
ESC 2014 guidelines on the management of valvular heart disease. *Eur Heart J.* 2012;**33**:2451–96 with permission from Oxford University Press.

common. The normal mitral valve area is 4–5 cm^2, and a gradient is rare, unless the valve is less than 2 cm^2. The valve area narrows gradually by 0.1–0.3 cm^2 per year, and symptoms start when the mitral valve area becomes less than 1.5 cm^2. Pulmonary oedema may develop with valve areas <1 cm^2 (Table 17.1). Patients with pulmonary oedema rarely have severe pulmonary arterial hypertension, whereas those with severe hypertension (pulmonary vascular resistance >6–8 Wood units) seem to present with right heart failure, rather than pulmonary oedema. The 10-year survival of untreated patients presenting with MS is 50–60%, depending on symptoms on presentation. Death in neglected cases is mainly due to heart failure or systemic embolism.

Presentation

Patients usually present with **SOBOE** or **fatigue**. Later symptoms include **haemoptysis** (pulmonary oedema or bronchial vein rupture), **chest pain**, and **systemic embolism**. The enlarged left atrium may impinge on the left recurrent laryngeal nerve, causing hoarseness (**Ortner's syndrome**). **Atrial fibrillation** occurs in approximately 50% of patients with mitral stenosis, precipitates such symptoms, greatly increases the risk of systemic embolization, and reduces cardiac output and exercise capacity. **Pulmonary arterial hypertension** is reversible and resolves after intervention. Moderate to severe **tricuspid regurgitation** is seen in up to a third of patients with mitral stenosis and may not be improved with valvuloplasty. Severe TR requires ring annuloplasty at time of mitral surgery. **Rheumatic AR** may be associated with MS that may blunt the presentation of AR due to reduced cardiac output.

Physical examination

Mitral facies with plethoric bluish cheeks with telangiectases are now rarely seen.

A diastolic thrill may be palpated in the left lateral decubitus position.

Increased intensity of the S_1 because the transmitral gradient holds the mitral valve open for all of diastole so that ventricular systole closes the mitral valve forcefully. In advanced disease, S_1 may become soft.

Mitral valve opening snap The distance from S_2 is a measure of MS severity. An S_2 opening snap interval <0.08 s usually indicates severe disease.

A low-pitched mitral rumble follows the opening snap. **Presystolic accentuation** of the murmur audible in normal sinus rhythm or during long RR intervals in atrial fibrillation indicates tight stenosis.

A high-pitched blowing murmur (**Graham Steell**) may be heard at the cardiac base. Although this murmur is thought to represent the PR of pulmonary hypertension, in reality, it is more often due to concomitant AR.[6]

Pulse pressure may also be reduced in advanced disease.

Elevated JVP, **TR**, **hepatomegaly**, **ascites**, **and peripheral oedema** may be found in severe pulmonary hypertension and RV failure.

P_2 increased in pulmonary hypertension.

Investigations

ECG Left atrial enlargement (P wave >0.12 s in lead II) and RV hypertrophy, often with AF.

Chest radiography Left atrial enlargement and, in long-standing MS, pulmonary congestion and pulmonary arterial hypertension. Interstitial oedema is manifested as Kerley A lines (dense, short, horizontal lines at the costophrenic angles) or Kerley B lines (straight, dense lines towards the hilum).

Echocardiography is used to exclude conditions that mimic mitral stenosis (atrial myxoma, tricuspid stenosis, ball-valve thrombus, or ASD), calculate valve area, assess mitral regurgitation, and provide information about suitability for percutaneous balloon valvuloplasty (PBV).

Stenosis severity is determined by:

Planimetry The most reliable method to calculate valve area is planimetry with 2D or 3D echocardiography. 2D echocardiography underestimates the severity of mitral stenosis, especially moderate to severe disease and underestimates the extent of commissural splitting by PBV.

Doppler-derived pressure half-time Valve area is given by the empirical formula 220/PHT (Figures 17.1 and 17.2). This method is affected by left ventricular chamber compliance and heart rate.

The AHA/ACC recommended frequency of echocardiograms in asymptomatic patients with normal LV function is every 3–5 years for MVA >1.5 cm^2, every 1–2 years for MVA 1.0–1.5 cm^2 and once every year for MVA <1.0 cm.[2,7]

Transoesophageal echocardiography provides an improved image of the commissural anatomy and calcification and allows detection of left atrial appendage thrombus and calculation of the echo score (Tables 17.2 and 17.3 and Figure 17.3).

Exercise or dobutamine stress echocardiography is needed for patients with inconclusive symptoms or haemodynamics.

Cardiac catheterization is rarely needed, with imaging methods now available (echo, cardiac CT and MRI). It is indicated when the non-invasive tests are inconclusive to resolve the issue of stenosis severity and evaluate MR. Cardiac output and transvalvular gradient measurements are used to calculate valve area with the Gorlin formula to reassess stenosis severity (Figure 17.4). It may also be used to assess the response of PA and LA pressures to exercise or to assess the cause of pulmonary arterial hypertension when it is inproportional to MS severity.

Coronary angiography is indicated only in patients with evidence of myocardial ischaemia.

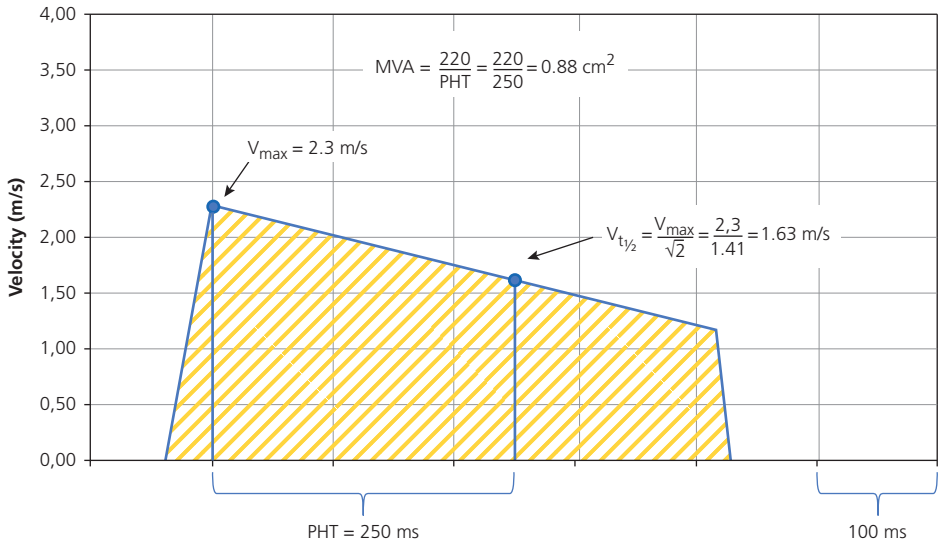

Figure 17.1 Pressure half-time is the time taken for the pressure to halve from the peak value. It is the same as the time for peak velocity to decrease to a velocity equal to the peak velocity divided by the square root of 2 (=1.4).

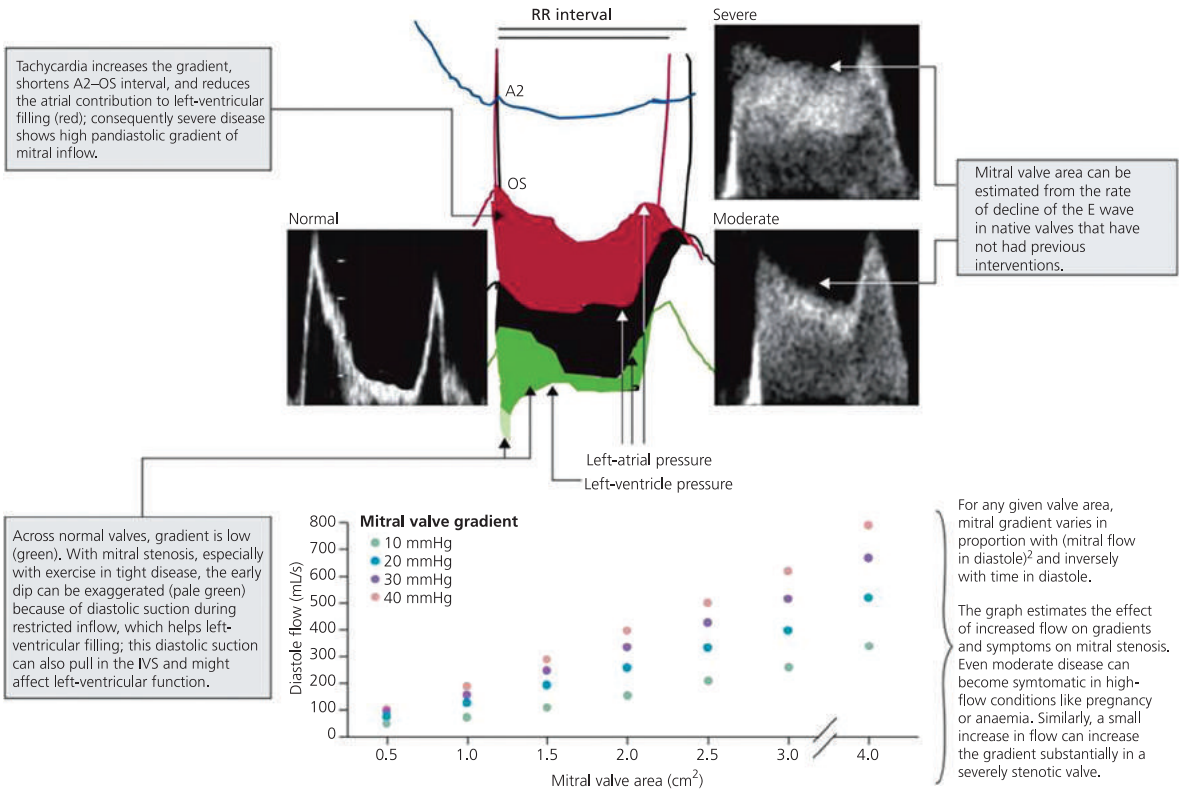

Figure 17.2 Physiology of severity of mitral stenosis. Gradient between left atrium and left ventricle is shown as normal to very low (green), moderate (black), and severe (red). Arrows indicate the extent of gradient towards the end of diastole. A2–OS=A2 to opening snap interval. IVS=interventricular septum.

Chandrashekhar Y, *et al*. Mitral stenosis. *Lancet*. 2009;**374**:1271–83 with permission from Elsevier.

Table 17.2. Mitral valve scoring systems

Wilkins echocardiographic mitral valve score

Grade	Mobility	Subvalvular thickening	Thickening	Calcification
1	Highly mobile valve with only leaflet tips restricted	Minimal thickening just below the mitral leaflets	Leaflets near normal in thickness (4 to 5 mm)	A single area of increased echo brightness
2	Leaflet mid and base portions have normal mobility	Thickening of chordal structures extending up to one-third of the chordal length	Midleaflets normal, considerable thickening of margins (5 to 8 mm)	Scattered areas of brightness confined to leaflet margins
3	Valve continues to move forward in diastole, mainly from the base	Thickening extending to the distal third of the chords	Thickening extending through the entire leaflet (5–8 mm)	Brightness extending into the mid-portions of the leaflets
4	No or minimal forward movement of the leaflets in diastole	Extensive thickening and shortening of all chordal structures extending down to the papillary muscles	Considerable thickening of all leaflet tissue (>8–10 mm)	Extensive brightness throughout much of the leaflet tissue

Wilkins GT, *et al. British Heart J*. 1988;60:299-308 with permission from BMJ Publishing Group.

Scoring System Proposed by Nunes *et al.*

Predictors of outcome	Points
MV area ≤1 cm^2	2
Maximum leaflets displacement ≤12 mm	3
Commissural area ratio ≥ 1.25	3
Subvalvular involvement	3

Nunes MCP, *et al*. Valvular Heart Disease: The Echo Score Revisited. *Circulation*. 2014;**129**:886–95 with permission Wolters Kluwer.

Table 17.3 AHA/ACC 2014 GL on valve disease

Diagnostic testing

Transthoracic echocardiography (TTE) to establish the diagnosis, quantify mean pressure gradient, mitral valve area, and pulmonary artery pressure, assess concomitant valvular lesions, and determine suitability for mitral commissurotomy	I-B
Transoesophageal echocardiography (TOE) in patients considered for percutaneous mitral balloon commissurotomy to search for left atrial thrombus and evaluate the severity of MR	I-B
Exercise testing with Doppler or invasive haemodynamic assessment to evaluate the response of the mean mitral gradient and pulmonary artery pressure when there is a discrepancy between resting Doppler echocardiographic findings and clinical symptoms or signs.	I-C

AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

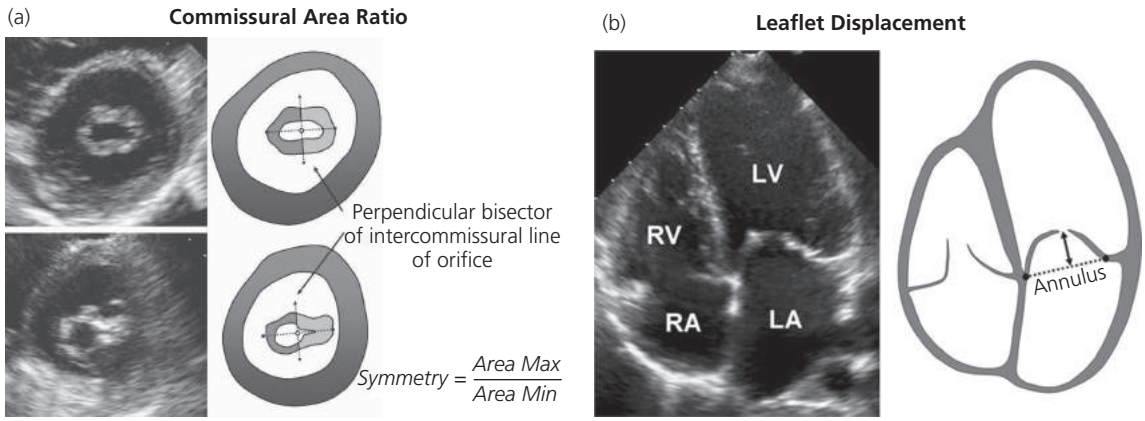

Figure 17.3 (a) Echocardiographic parasternal short-axis view showing two traced areas to calculate the commissural area ratio. Asymmetry of commissural thickening was quantified by the ratio between the largest to the smallest area. (b) Echocardiographic apical four-chamber view showing maximum apical displacement of the leaflets relative to the mitral annulus.

Nunes MCP, *et al*. Valvular Heart Disease: The Echo Score Revisited. *Circulation*. 2014;**129**:886–95 with permission Wolters Kluwer.

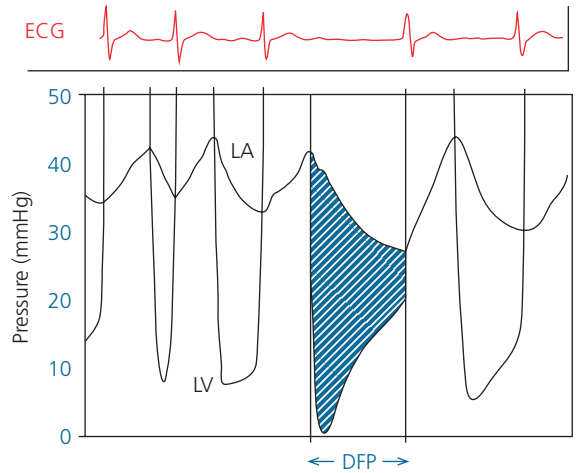

Figure 17.4 Calculation of mitral valve area (MVA) in the catheter laboratory.

MVA = Mitral valve flow (ml/s)/31√ mean mitral gradient (mm Hg). Mitral valve flow = Angiographic cardiac output (ml/min)/diastolic filling period (s/min). 31 is the Gorlin constant assuming LVEDP of 5 mm Hg.

Table 17.4 AHA/ACC 2014 GL on valve disease

Medical therapy	
Anticoagulation (vitamin K antagonist or heparin) in AF (paroxysmal, persistent, or permanent), or a prior embolic event, or a left atrial thrombus	I-B
Heart rate control in AF and fast ventricular response.	IIa-C
Heart rate control in normal sinus rhythm and symptoms associated with exercise	IIb-B

AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

Therapy

Medical

Diuretics and beta blockers or rate-slowing calcium channel blockers (e.g. diltiazem) are the mainstay for control of heart rate. The role of statins in slowing progression of MS is under investigation.

Anticoagulation is indicated in AF or prior embolic event or left atrial thrombus (Table 17.4).

Systemic embolization may occur in 10–20% of patients with MS, even in the absence of left atrial thrombi. Retrospective studies indicate a 4- to 15-fold decrease in the incidence of embolic events with anticoagulation.[7]

AF develops in 30–40% of patients and is associated with a poorer prognosis (10-year survival 25%, compared to 46% in SR). Pharmaceutical or electrical cardioversion is recommended after transoesophageal exclusion of left appendix thrombi under heparin (1mg/kg) or following 3 weeks of warfarin. Warfarin is continued after cardioversion for, at least, 1 month or indefinitely, if indicated.

Interventional/surgical

As with all valvular heart disease, no randomized trials have been performed to ascertain the best timing of intervention. Recommendations are based on observational data.[7,8]

Percutaneous mitral balloon valvotomy (PMBV) or commisurotomy (PMC) improves survival, especially in patients with NYHA class III or IV (Tables 17.5 to 17.7, and Figures 17.5 and 17.6). The technique is as effective as open valvotomy and more effective than closed valvotomy.[9] Nearly half of all patients who undergo percutaneous mitral commissurotomy remain free from cardiovascular death or surgery at 20 years, and 25% of them need a repeat procedure.[10] Successful PMBV is usually defined as a post-procedure mitral valve area of >1.5 cm^2 with no more than moderate mitral regurgitation. Suitability for PMBV is determined by valve morphology and the amount of mitral regurgitation present. The Wilkins score (Table 17.2) is the most widely used echo score and gives a rough guide to the suitability of

Table 17.5 AHA/ACC 2014 GL on valve disease

Intervention in mitral stenosis	
Percutaneous mitral balloon commissurotomy (PMBC) in severe MS (MVA <1.5 cm^2, stage D) and favourable valve morphology in the absence of left atrial thrombus or moderate-to-severe MR	I-A
Mitral valve surgery in severely symptomatic patients (NYHA class III/IV) with severe MS (MVA <1.5 cm^2, stage D) who are not high risk for surgery and who are not candidates for or failed previous PMBC	I-B
Concomitant mitral valve surgery in patients with severe MS (MVA ≤1.5 cm^2, stage C or D) undergoing other cardiac surgery	I-C
PMBC for asymptomatic patients in very severe MS (MVA <1.0 cm^2, stage C) and favourable valve morphology in the absence of left atrial thrombus or moderate-to-severe MR	IIa-C
Mitral valve surgery for severely symptomatic patients (NYHA class III/IV) with severe MS (MVA ≤1.5 cm^2, stage D), provided there are other cardiac operative indications	IIa-C
PMBC for asymptomatic patients with severe MS (MVA ≤1.5 cm^2, stage C) and favourable valve morphology who have new onset of AF in the absence of contraindications	IIb-C
PMBC for symptomatic patients with MVA >1.5 cm^2 if there is pulmonary artery wedge pressure >25 mmHg or mean valve gradient >15 mmHg during exercise	IIb-C
PMBC for severely symptomatic patients (NYHA class III/IV) with severe MS (MVA ≤1.5 cm^2, stage D) who have suboptimal valve anatomy and are not candidates for surgery or at high risk for surgery	IIb-C
Concomitant mitral valve surgery for patients with moderate MS (MVA 1.6–2.0 cm^2) undergoing other cardiac surgery	IIb-C
Mitral valve surgery and excision of the left atrial appendage for patients with severe MS (MVA ≤1.5 cm^2, stages C and D) who have had recurrent embolic events while receiving adequate anticoagulation	IIb-C

AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

Table 17.6 ESC 2012 GL on valve disease. Indications for percutaneous mitral commissurotomy (PMC) in mitral stenosis with valve area ≤1.5 cm^2

Symptomatic patients with favourable characteristics* for PMC	I-B
Symptomatic patients with contraindication or high risk for surgery	I-C
As initial treatment in symptomatic patients with unfavourable anatomy but favourable clinical characteristics	IIa-C
Asymptomatic patients without unfavourable characteristics and: - high thrombo-embolic risk (previous history of embolism, dense spontaneous contrast in the left atrium, recent or paroxysmal AF and/or high risk of haemodynamic decompensation (systolic pulmonary pressure >50 mmHg at rest), need for major non-cardiac surgery, desire of pregnancy	IIa-C

*: Unfavourable characteristics for percutaneous mitral commissurotomy can be defined by the presence of several of the following characteristics:
– Clinical characteristics: old age, history of commissurotomy, NYHA class IV, permanent atrial fibrillation, severe pulmonary hypertension.
– Anatomical characteristics: echo score >8, Cormier score 3 (calcification of mitral valve of any extent, as assessed by fluoroscopy), very small mitral valve area, severe tricuspid regurgitation.

ESC 2012 guidelines on the management of valvular heart disease. *Eur Heart J*. 2012;**33**:2451–96 with permission from Oxford University Press.

Table 17.7 ESC 2012 GL on valve disease. Contraindications to percutaneous mitral commissurotomy

Mitral valve area **>**1.5 cm^2
Left atrial thrombus
More than mild MR
Severe or bicommissural calcification
Absence of commissural fusion
Severe concomitant aortic valve disease or severe combined TS and TR
Concomitant coronary artery disease requiring bypass surgery

ESC 2012 guidelines on the management of valvular heart disease. *Eur Heart J*. 2012;**33**:2451–96 with permission from Oxford University Press.

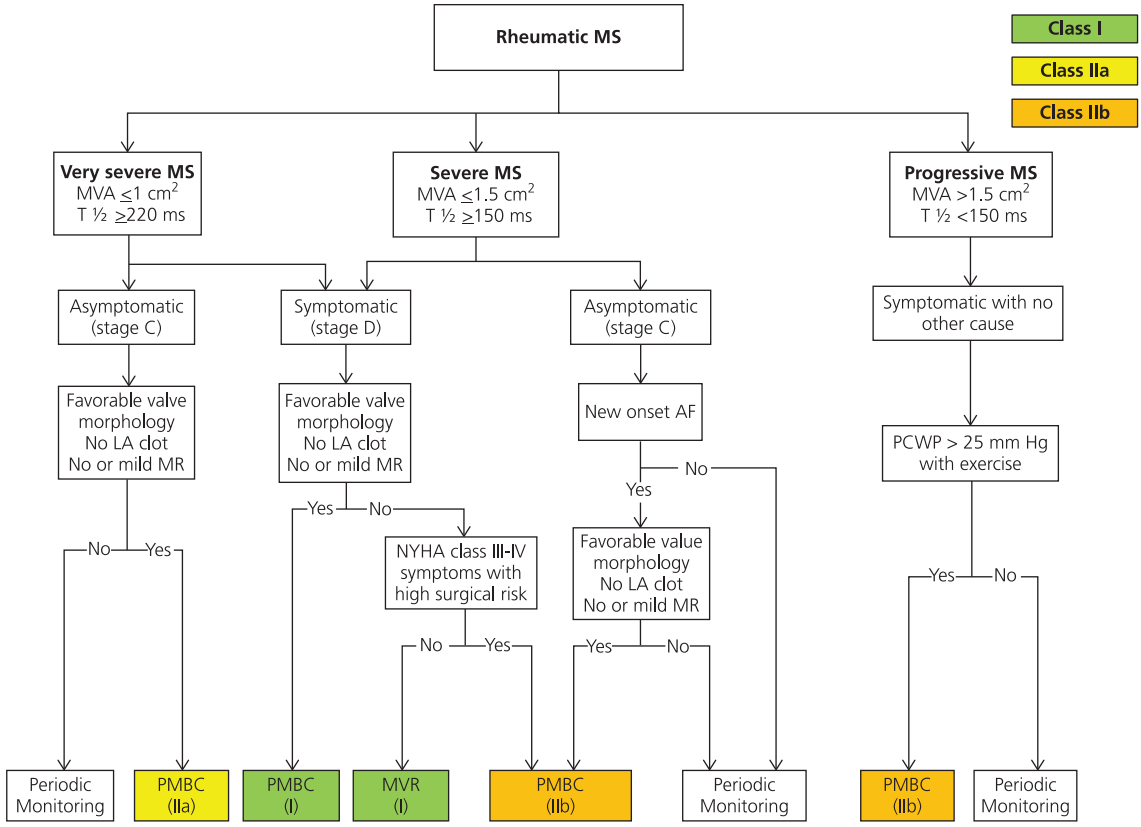

Figure 17.5 Indications for Intervention for Rheumatic MS.

AF indicates atrial fibrillation; LA, left atrial; MR, mitral regurgitation; MS, mitral stenosis; MVA, mitral valve area; MVR, mitral valve surgery (repair or replacement); NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PMBC, percutaneous mitral balloon commissurotomy; and T ½, pressure half-time.

AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

the valve morphology for PMBV. This scoring system assigns a point value from 1 to 4 for each of (1) valve calcification, (2) leaflet mobility, (3) leaflet thickening, and (4) disease of the subvalvular apparatus. In general, patients with a score of <8–9, with no calcification and less than moderate mitral regurgitation, have the best outcomes, although many patients have benefited from PMBV despite higher valve scores. A novel scoring system incorporating new quantitative echocardiographic parameters is more accurate in predicting outcome following PMBV (Table 17.2 and Figures 17.3).[11] According to this scoring system, three risk groups were defined: low (score of 0–3), intermediate (score of 5), and high (score of 6–11) with observed suboptimal PMBV results of 16.9%, 56.3%, and 73.8%, respectively. Recent data suggest that severe valve calcification, especially when it is unilateral, is not necessarily a contraindication for the procedure.[12,13] Patients with favourable morphology have more than 90% procedural success, very low occurrence of complications (<2%), and acceptably low frequency of re-stenosis on follow-up. Procedural mortality is nowadays <1% and is mainly due to tamponade or severe mitral regurgitation. Complications include severe mitral regurgitation (2–10%, although 25% of patients increase severity by one grade), most often due to non-commissural tear, urgent surgery (<1%), haemopericardium (0.5–12%), embolism (0.5–5%), and residual ASD (<5%). Re-stenosis can often be treated with repeat PMBV, but results are poorer than those after the first intervention. Recently, a benefit of PMBV was demonstrated in asymptomatic patients with moderate MS (<1.5 m^2) and suitable morphology, even in the absence of other conventional indication for intervention.[14] Of patients with a good result, 10% will require re-PBV, and 30% surgery in the next 20 years.[10] Recommendations for the management of AF are provided in Chapter 53.

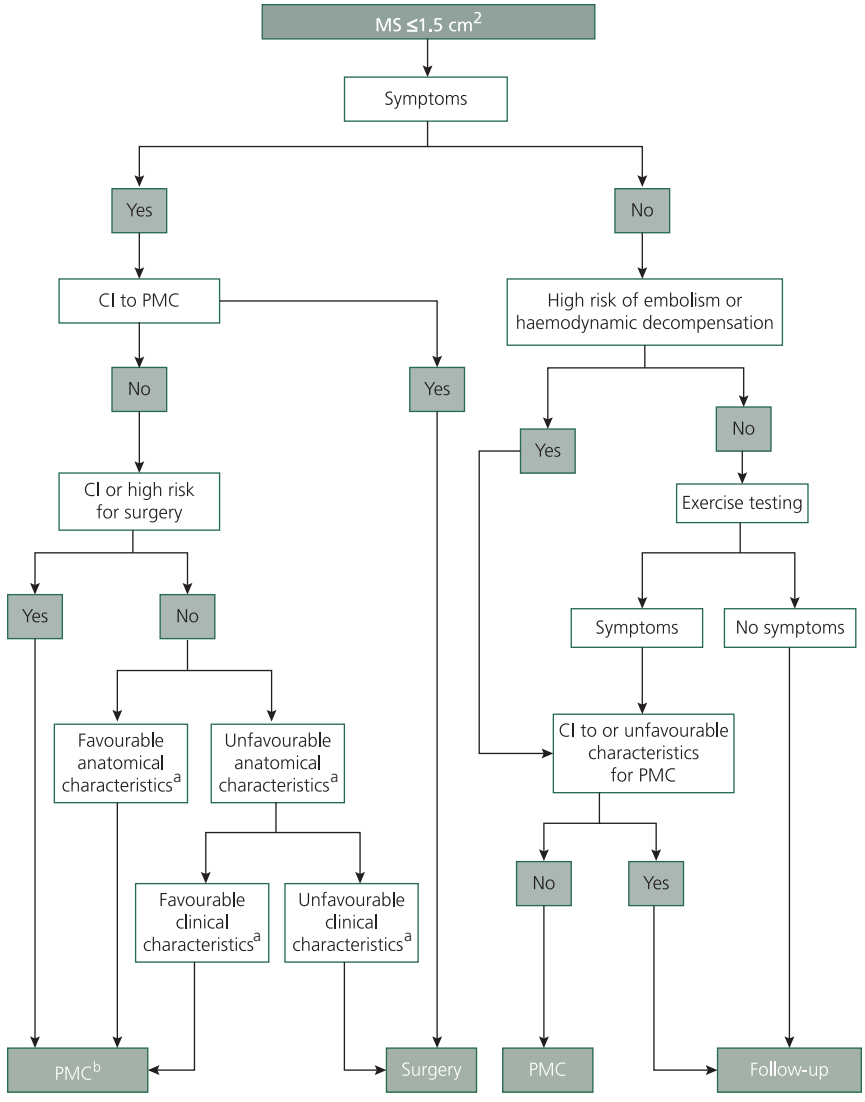

Figure 17.6 Management of clinically significant mitral stenosis.

CI: contraindication; MS: mitral stenosis; PMC: percutaneous mitral commissurotomy.
a: See indications for PMC.
b: Surgical commissurotomy may be considered by experienced surgical teams or in patients with contraindications to percutaneous mitral commissurotomy.
ESC 2012 guidelines on the management of valvular heart disease. *Eur Heart J*. 2012;**33**:2451–96 with permission from Oxford University Press.

Open valvotomy is attractive in cases unsuitable for PMBV; it allows conservation of the native valve and allows controlled reconstruction of the valves and simultaneous tricuspid valve repair or mitral valve replacement, if necessary. The risk of surgery is 1–3%.[7,8] Patients with mitral stenosis and severe tricuspid regurgitation do better with surgical repair than with PMBV.

Mitral valve replacement with preservation of the subvalvar apparatus is the treatment of choice in elderly patients with anatomy that is unfavourable for other options. Patient prosthesis mismatch and prosthesis stenosis due to ingrowth of pannus are the main problems. The operative risk is <5% in the absence of other co-morbidities but may reach 20% in the elderly with pulmonary hypertension.[7,8] The choice of prosthesis is based on patient age and the risk of anticoagulation (see Chapter 23 on prosthetic valves). **Congenital MS** is rare. Surgery is indicated with a mean MV gradient >10 mmHg in the presence of symptoms or a PA pressure >50 mmHg. Concomitant surgical ablation with a modification of the

MAZE or alternative procedures may be needed in the case of drug-refractory AF.[15]

Transcatheter transapical mitral valve-in-valve implantation for dysfunctional biological mitral prosthesis is also a recent possibility.[16]

Non-cardiac surgery

In asymptomatic patients with significant MS and a systolic pulmonary artery pressure <50 mmHg, non-cardiac surgery can be performed safely.[8] In symptomatic patients or in patients with systolic pulmonary artery pressure >50 mmHg, percutaneous mitral commissurotomy should be attempted before non-cardiac surgery if it is intermediate- or high-risk (ESC 2014 GL on non-cardiac surgery, IIa-C).[17] If valve replacement is needed, the decision should be individualized. If valve morphology is not favourable for percutaneous commissurotomy, moderate-risk elective non-cardiac surgery can be performed in asymptomatic, severe MS with appropriate intraoperative and post-operative haemodynamic monitoring (AHA/ACC 2014 GL on VD, IIb-C).

Pregnancy

Mitral stenosis in pregnancy is associated with substantial morbidity (including pulmonary oedema), even in asymptomatic or minimally symptomatic patients with mild to moderate disease (mitral valve area 1–1.5 cm^2). Indications for intervention are the occurrence of severe symptoms (NYHA class III/IV or pulmonary oedema) that are refractory to medical treatment. PBV is the treatment of choice.[18] Recommendations on pregnancy are presented in Tables 16.7 and 17.8.

Table 17.8 2014 AHA/ACC GL on valve disease. Mitral stenosis in pregnancy*

Anticoagulation in pregnant patients with AF unless contraindicated.	I-C
Beta blockers as required for rate control in the absence of contraindication if tolerated.	IIa-C
Diuretics for HF symptoms (stage D).	IIa-C
Valve intervention before pregnancy for symptomatic patients with severe MS (mitral valve area ≤1.5 cm^2, stage D).	I-C
Percutaneous mitral balloon commissurotomy (PMBC) before pregnancy for asymptomatic patients with severe MS (mitral valve area ≤1.5 cm^2, stage C) and favourable morphology.	I-C
PMBC for patients with severe MS (mitral valve area ≤1.5 cm^2, stage D) with favourable valve morphology who remain symptomatic with NYHA class III to IV HF symptoms despite medical therapy	IIa-B
Valve intervention for patients with severe MS (mitral valve area ≤1.5 cm^2, stage D) and valve morphology not favourable only if there are refractory NYHA class IV HF symptoms.	IIa-C

*: See also Table 16.7

2014 AHA/ACC guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

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Chapter 18

Mitral regurgitation

Classification

Mechanisms of MR are classified as functional (mitral valve is structurally normal, and disease results from valve deformation caused by ventricular or atrial remodelling) or organic (intrinsic valve lesions) (Table 18.1).[1]

Epidemiology

Although a trivial form of this valve disease is often seen in healthy people, moderate or severe MR is the most frequent valve disease, and is the second most common form of valvular heart disease (after aortic stenosis) needing surgery.[2–4] Degenerative changes and prolapse might be non-familial or genetically transmitted as an autosomal trait or X chromosome-linked. The prevalence of moderate or severe MR in the general population in the USA is estimated 1.6% (0.5% in age 18–44 years to 9.3% in ≥75 years).[4] The prevalence of mitral valve prolapse is approximately 2.4%, and half of them have maximal leaflet thickness of at least 5 mm.[5]

Aetiology

Primary mitral regurgitation (MR) may result from disorders of the valve leaflets or the mitral apparatus (chordae tendinae, papillary muscles, annulus). The main causes in the western world are **degenerative disease** (60–70% of cases) and **ischaemic** mitral regurgitation (20%), usually due to an inferior infarction involving the inferolateral and the posteromedial papillary muscle.[1] Degenerative disease is rarely due to annular calcification. **Mitral valve prolapse** (MVP) is defined on echocardiography as systolic atrial displacement of the mitral valve, such that it extends above a saddle-shaped annulus by a minimum of 2 mm. It is the most common functional abnormality associated with degenerative mitral valve disease, resulting from both leaflet redundancy and chordal elongation, and often overdiagnosed. Patients with typical **Barlow's syndrome** (initial description of MVP) have diffuse, generalized thickening and billowing of the leaflets, whereas, in those with **fibroelastic dysplasia**, the disease is localized to isolated regions of the valve.[6,7] The chordae tendineae may be elongated and prone to rupture. MVP may be detected in 2% of the population and can be familial or sporadic. Parental MVP is associated with increased prevalence of offspring MVP,[8] and multiple loci for autosomal dominant non-syndromic MVP and a gene responsible for a rare X-linked form have been described.[7] Less common causes are **rheumatic disease** (2–5% in western countries, but the leading cause in developing countries), **endocarditis** (2–5%), **cardiomyopathies, congenital anomalies, carcinoid disease, systemic lupus erythematosus (Libman–Sacks)**, **atrial fibrillation**, and **anorectic drugs**. Amphetamine derivatives, such as fenfluramine, phentermine, and benfluorex, may account for up to 7% with regurgitant valve disease in general.[9] Acute MI (45% of acute MR cases), endocarditis (28%), chordal or papillary muscle rupture (26%) or dysfunction due to ischaemia, acute rheumatic carditis, myocarditis, Takotsubo cardiomyopathy, and prosthetic valve dysfunction may lead to **acute MR**.[10]

Table 18.1 Types of MR according to Carpentier classification

	Organic		Functional	
	Type I*	**Type II†**	**Type IIIa‡**	**Type I*/Type IIIb‡**
Non-ischaemic	Endocarditis (perforation); degenerative (annular calcification), congenital (cleft leaflet)	Degenerative (billowing/flail leaflets); endocarditis (ruptured chordae); traumatic (ruptured chord/PM); rheumatic (acute RH)	Rheumatic (chronic RF); iatrogenic (radiation/drug); inflammatory (lupus/anticardiolipin, eosinophilic endocardial disease, endomyocardial fibrosis)	Cardiomyopathy; myocarditis; left ventricular; dysfunction (any cause)
Ischaemic		Ruptured PM	–	Functional ischaemic

MR, mitral regurgitation; PM, papillary muscle; RF, rheumatic fever.
* Mechanism involves normal leaflet movement.
† Mechanism involves excessive valve movement.
‡ Restricted valve movement, IIIa in diastole, IIIb in systole.
Carpentier A. Cardiac valve surgery—the "French Correction". *J Thor Cardiovasc Surg*. 1983;**86**:323–37 with permission from Elsevier.

Secondary or functional MR is due to cardiomyopathies or chronic ischaemic heart disease.[11] The abnormal and dilated left ventricle causes papillary muscle displacement, which in turn results in leaflet tethering with associated annular dilation that prevents coaptation. The prognosis of these patients is worse than other kinds of MR, and the therapeutic approach is not established.

Pathophysiology and natural history

In **acute MR**, the unprepared left atrium and left ventricle cannot accommodate the regurgitant volume, which causes large v waves in the left atrium and results in pulmonary congestion. Patients with chronic MR and preserved LV function may tolerate the marked increase in volume better, whereas patients with impaired ventricular function may quickly decompensate with acute worsening of MR.

In **chronic** cases, the adaptive changes to volume overload include LV dilatation and eccentric hypertrophy and left atrial enlargement that allows accommodation of the regurgitant volume at a lower pressure. Regurgitant fractions <40% may be tolerated indefinitely. The LV ejection fraction in chronic MR is usually greater than normal because of the increase in preload and the afterload-reducing effect of ejection into the low-impedance left atrium. Thus, LV dysfunction in severe MR is defined as LVEF ≤60% or an elevated end-systolic dimension (>40 mm by ACC/AHA and >45 mm by ESC). Advanced myocardial dysfunction may occur while LV ejection fraction appears normal. Ventricular dysfunction should be suspected when end-systolic dimensions are large, but is often masked by a large ejection volume and is revealed after surgical elimination of mitral regurgitation, with a post-operative average immediate ejection fraction drop of about 10%. In patients with organic MR, RV function impairment is frequent (30%), constitutes a predictor of post-operative cardiovascular survival, and depends weakly on pulmonary artery systolic pressure but mainly on LV remodelling and septal function.[12] Thus, biventricular impairment is a powerful predictor of both cardiovascular and overall survival. The risk of AF and heart failure increases with severity of MR. Patients with severe MR usually develop symptoms within the next 6–10 years and have an increased risk for sudden death. The rate of death from cardiovascular causes among asymptomatic patients with, at least, moderate MR or an LVEF <50% exceeds 3% per year.[13–15] Patients with severe MR and flail leaflets have an annual mortality of 6–7%, and, in 10 years, 90% of them are dead or require MV operation.

The prognosis of **mitral valve prolapse** is benign in the absence of moderate to severe MR or LVEF <50%, and thickened mitral leaflets (>5 mm), with survival similar to that of people without prolapse.[5,6] Recent data indicate that mitral leaflet thickness, as opposed to LV dysfunction and the presence of MR, may not be an independent predictor of mortality.[7] The prognostic significance of a flail leaflet is controversial. Infective endocarditis (100 cases per 100 000 patient-years of follow-up), spontaneous chordal rupture, and sudden death are higher than in the general population. In the presence of flail leaflets, the rate of infective endocarditis is 1.5% per year and that of sudden death 1.8% per year.[6] Fibrin emboli, as well as the increased incidence of MVP in von Willebrand's disease and other coagulopathies, are responsible for visual symptoms with involvement of the ophthalmic or posterior cerebral circulation. MR of MVP that is purely mid-late systolic has more benign consequences and outcomes than holosystolic MR.[16] Sudden cardiac death may also occur in young athletes and women with arrhythmias. Patients with MVP who may experience sudden cardiac death are mostly females with bileaflet prolapse, ventricular arrhythmias of LV origin (outflow tract alternating with papillary muscle/fascicular origin), and frequent ECG repolarization abnormalities on inferior leads.[17,18] Contrast-enhanced CMR may identify fibrosis of the papillary muscles and inferobasal LV free wall, which correlates well with arrhythmia morphology, pointing to a myocardial stretch by the prolapsing leaflets and elongated chordae.[18]

Presentation

Acute MR Patients who develop acute severe MR usually present with symptomatic heart failure, because their ventricles are not prepared to accept the sudden increase in volume load. Some patients may present solely with new-onset dyspnoea, without evidence of impending cardiovascular collapse, and may be misdiagnosed.

Chronic MR The patient may be entirely asymptomatic, even during vigorous exercise, or present with dyspnoea (Table 18.2 and Table 18.3).

Physical examination

Acute MR

Physical examination of the precordium may be misleading, because a normal-sized left ventricle does not produce a hyperdynamic apical impulse.

The **systolic murmur** of MR may not be holosystolic and may even be absent.

A **third heart sound** or **early diastolic flow rumble** may be the only abnormal physical finding.

Chronic MR

Displaced apical impulse in severe MR

Soft S_1 and **widely split S_2**

Late systolic murmur in MVP or papillary muscle dysfunction

Mid-systolic click in the presence of MVP

Holosystolic murmur in chordal rupture and flail leaflet. The radiation of the murmur follows the direction of the regurgitant jet. With a flail posterior leaflet, the murmur radiates anteriorly and may mimic aortic

stenosis, whereas a murmur associated with a flail anterior leaflet radiates to the back.

- A **diastolic rumble and S_3** may be present and do not necessarily indicate LV dysfunction.
- **Loud P_2** due to pulmonary venous hypertension indicates advanced disease.

Investigations

Chest radiography Cardiomegaly due to LV and left atrial enlargement in chronic MR. Kerley B lines and interstitial oedema can be seen in acute MR or progressive LV failure. Predominant MS is suggested by mild cardiomegaly and significant changes in the lung fields. A unilateral pattern that is found in 2% of cases of pulmonary oedema, usually of the right upper lobe, is always associated with severe functional or organic MR.[19] This entity should be differentiated from lobar pneumonia.

Electrocardiography Left atrial enlargement and atrial fibrillation may be present. LV enlargement is seen in approximately 30% of patients and RV hypertrophy in 15%. AF is associated with increased mortality.[20]

Transthoracic echocardiography demonstrates the disruption of the MV but may underestimate lesion severity by inadequate imaging of the colour flow jet. Thus, if there is normal or hyperdynamic systolic function of the left ventricle on echocardiography in a patient with acute heart failure, the suspicion of severe MR should be raised. Quantitative assessment of regurgitation is feasible by quantitative Doppler, based on mitral and aortic stroke volumes, or quantitative 2D echo, based on LV volumes, or flow convergence analysis with colour flow imaging proximal to the regurgitant orifice (PISA, proximal isovelocity surface area method) (Tables 18.2 to 18.5, and Figure 18.1). However, they should be always interpreted within the clinical context.[21] Measures of effective regurgitant orifice area (ERO) and regurgitant volume depend on LV size and LV-LA pressure gradient, and can be inaccurate in acute MR, particularly in the context of tachycardia. Assessment of mid or late MR in the context of mitral leaflet prolapse

Table 18.2 ACC/AHA 2014 GL on valve disease. Stages of primary MR

Grade	Definition	Valve anatomy	Valve haemodynamics*	Haemodynamic consequences	Symptoms
A	At risk of MR	Mild mitral valve prolapse with normal coaptation Mild valve thickening and leaflet restriction	No MR jet or small central jet area <20% LA on Doppler Small vena contracta <0.3 cm	None	None
B	Progressive MR	Severe mitral valve prolapse with normal coaptation Rheumatic valve changes with leaflet restriction and loss of central coaptation Prior IE	Central jet MR 20–40% LA or late systolic eccentric jet MR Vena contracta <0.7 cm Regurgitant volume <60 mL Regurgitant fraction <50% ERO <0.40 cm^2 Angiographic grade 1–2+	Mild LA enlargement No LV enlargement Normal pulmonary pressure	None
C	Asymptomatic severe MR	Severe mitral valve prolapse with loss of coaptation or flail leaflet Rheumatic valve changes with leaflet restriction and loss of central coaptation Prior IE Thickening of leaflets with radiation heart disease	Central jet MR >40% LA or holosystolic eccentric jet MR Vena contracta ≥0.7 cm Regurgitant volume ≥60 mL Regurgitant fraction ≥50% ERO ≥0.40 cm^2 Angiographic grade 3–4+	Moderate or severe LA enlargement LV enlargement Pulmonary hypertension may be present at rest or with exercise **C1**: LVEF >60% and LVESD <40 mm **C2**: LVEF ≤60% and LVESD ≥40 mm	None
D	Symptomatic severe MR	Severe mitral valve prolapse with loss of coaptation or flail leaflet Rheumatic valve changes with leaflet restriction and loss of central coaptation Prior IE Thickening of leaflets with radiation heart disease	Central jet MR >40% LA or holosystolic eccentric jet MR Vena contracta ≥0.7 cm Regurgitant volume ≥60 mL Regurgitant fraction ≥50% ERO ≥0.40 cm^2 Angiographic grade 3–4+	Moderate or severe LA enlargement LV enlargement Pulmonary hypertension present	Decreased exercise tolerance Exertional dyspnoea

* Several valve haemodynamic criteria are provided for assessment of MR severity, but not all criteria for each category will be present in each patient. Categorization of MR severity as mild, moderate, or severe depends on data quality and integration of these parameters in conjunction with other clinical evidence.

ERO indicates effective regurgitant orifice; IE, infective endocarditis; LA, left atrium/atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD; left ventricular end-systolic dimension; and MR, mitral regurgitation.

AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

Table 18.3 ACC/AHA 2014 GL on valve disease. Stages of secondary MR

Grade	Definition	Valve anatomy	Valve haemodynamics*	Haemodynamic consequences	Symptoms
A	At risk of MR	Normal valve leaflets, chords, and annulus in a patient with coronary disease or cardiomyopathy	No MR jet or small central jet area <20% LA on Doppler Small vena contracta <0.3 cm	Normal or mildly dilated LV size with fixed (infarction) or inducible (ischaemia) regional wall motion abnormalities Primary myocardial disease with LV dilation and systolic dysfunction	Symptoms due to coronary ischaemia or HF may be present that respond to revascularization and appropriate medical therapy
B	Progressive MR	Regional wall motion abnormalities with mild tethering of mitral leaflet Annular dilation with mild loss of central coaptation of the mitral leaflets	ERO <0.20 $cm^{2\dagger}$ Regurgitant volume <30 mL Regurgitant fraction <50%	Regional wall motion abnormalities with reduced LV systolic function LV dilation and systolic dysfunction due to primary myocardial disease	Symptoms due to coronary ischaemia or HF may be present that respond to revascularization and appropriate medical therapy
C	Asymptomatic severe MR	Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet Annular dilation with severe loss of central coaptation of the mitral leaflets	ERO ≥0.20 $cm^{2\dagger}$ Regurgitant volume ≥30 mL Regurgitant fraction ≥50%	Regional wall motion abnormalities with reduced LV systolic function LV dilation and systolic dysfunction due to primary myocardial disease	Symptoms due to coronary ischaemia or HF may be present that respond to revascularization and appropriate medical therapy
D	Symptomatic severe MR	Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet Annular dilation with severe loss of central coaptation of the mitral leaflets	ERO ≥0.20 $cm^{2\dagger}$ Regurgitant volume ≥30 mL Regurgitant fraction ≥50%	Regional wall motion abnormalities with reduced LV systolic function LV dilation and systolic dysfunction due to primary myocardial disease	HF symptoms due to MR persist even after revascularization and optimization of medical therapy Decreased exercise tolerance Exertional dyspnoea

* Several valve haemodynamic criteria are provided for assessment of MR severity, but not all criteria for each category will be present in each patient. Categorization of MR severity as mild, moderate, or severe depends on data quality and integration of these parameters in conjunction with other clinical evidence.

† The measurement of the proximal isovelocity surface area by 2D TTE in patients with secondary MR underestimates the true ERO due to the crescentic shape of the proximal convergence.

† 2D indicates 2-dimensional; ERO, effective regurgitant orifice; HF, heart failure; LA, left atrium; LV, left ventricular; MR, mitral regurgitation; and TTE, transthoracic echocardiogram.

AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

may also be misleading, because jet area and ERO by flow convergence appear similar to those of holosystolic MR. 3D measurement of vena contracta area and regurgitant volume is superior to 2D methods.[22] 3-D analysis of the annular shape has also been shown prognostically significant; flattening of the annular saddle (normal) shape is associated with progressive leaflet billowing and increased chordal rupture.[23] In asymptomatic primary MR, absence of LV contractile reserve, that is better assessed using exercise-induced changes in LV myocardial longitudinal function, rather than in LVEF, is independently associated with a twofold increase in risk of cardiac events.[24]

The AHA/ACC recommended frequency of echocardiograms in asymptomatic patients with normal LV function is every 3–5 years for MR of mild severity, every 1–2 years for moderate severity, every 6–12 months for severe MR, and more frequently for a dilating LV.[25]

Transoesophageal echocardiography can more accurately assess the colour flow jet and direct successful surgical repair, particularly in acute MR.

Exercise testing, with or without Doppler assessment, before and after exercise in symptomatic patients in whom there is a discrepancy between symptoms and resting measures of LV function and pulmonary artery pressure. It is very helpful in identifying patients who develop pulmonary hypertension (>60 mmHg) with exercise. Impaired exercise capacity (age- and sex-matched predicted METS) can develop in the absence of significant overt symptoms and is associated with adverse long-term outcomes.[26]

Cardiac catheterization is indicated when the non-invasive tests are inconclusive to resolve the severity of MR.

Coronary angiography is necessary before surgery in the haemodynamically stable patient over 40 years of age or with risk factors or clinical suspicion of coronary artery

Table 18.4 ESC 2012 GL on valve disease. Echocardiographic criteria for definition of severe MR

Qualitative		
Valve morphology	Flail leaflet/ruptured papillary muscle/ large coaptation defect	
Colour flow regurgitant jet	Very large central jet or eccentric jet adhering, swirling, and reaching the posterior wall of the left atrium	
CW signal of regurgitant jet	Dense/triangular	
Other	Large flow convergence zone[a]	
Semi-quantitative		
Vena contracta width (mm)	>7 (>8 for biplane)[b]	
Upstream vein flow[c]	Systolic pulmonary vein flow reversal	
Inflow	E wave dominant >1.5 m/s[d]	
Other	TVI mitral/TVI aortic >1.4	
Quantitative		
	Primary	**Secondary**[e]
EROA (mm^2)	>40	>20
RVol (mL/beat)	>60	>30
+ enlargement of cardiac chambers/vessels	LV, LA	

a: At a Nyquist limit of 50–60 cm/s.
b: For average between apical four- and two-chamber views.
c: Unless other reasons for systolic blunting (atrial fibrillation, elevated atrial pressure).
d: In the absence of other causes of elevated left atrial pressure and of mitral stenosis.
e: Different thresholds are used in secondary MR where an EROA >20 mm^2 and regurgitant volume >30 mL identify a subset of patients at increased risk of cardiac events.
ESC 2012 guidelines on the management of valvular heart disease. *Eur Heart J.* 2012;**33**:2451–96 with permission from Oxford University Press.

Table 18.5 AHA/ACC 2014 GL on valve disease. Diagnostic testing

Chronic primary MR	
Transthoracic echocardiograph (TTE) for evaluation of LV size and function, RV function and left atrial size, pulmonary artery pressure, and mechanism and severity of primary MR (stages A to D)	I-B
Cardiac magnetic resonance (CMR) when TTE not satisfactory	I-B
Intraoperative transoesophageal echocardiograph (TOE) to establish the anatomic basis for chronic primary MR (stages C and D) and to guide repair	I-B
TOE for evaluation of patients with chronic primary MR (stages B to D) in whom non-invasive imaging provides non-diagnostic information	I-C
Exercise haemodynamics with either Doppler echocardiography or cardiac catheterization in symptomatic patients where there is a discrepancy between symptoms and the severity of MR at rest (stages B and C)	IIa-B
Exercise treadmill testing to establish symptom status and exercise tolerance (stages B and C)	IIa-C
Chronic secondary MR	
TTE to establish the aetiology of MR (stages B to D) and the extent and location of wall motion abnormalities and to assess global LV function, severity of MR, and magnitude of pulmonary hypertension	I-C
Non-invasive imaging (stress nuclear/positron emission tomography, CMR, or stress echocardiography), cardiac CT angiography, or cardiac catheterization, including coronary arteriography, to establish aetiology of MR (stages B to D) and/or to assess myocardial viability	I-C

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disease. LV angiography at the RAO projection allows visualization and quantification of the regurgitant jet, but the method depends on the amount of contrast injected and the size of the LA.

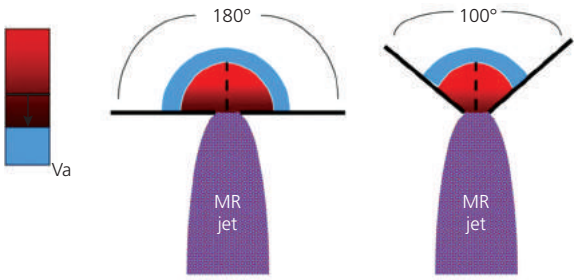
Cardiac magnetic resonance provides accurate measurement of regurgitant flow and LV volumes and is an emerging modality of increasing significance. Preliminary data suggest that is more accurate than echocardiography in assessing the severity of MR.[27] It might be also useful for risk stratification of patients with mitral leaflet prolapse, ECG depolarization abnormalities on inferior or inferolateral leads, complex ventricular arrhythmias with right bundle-branch block morphology on 12-lead ECG Holter monitoring, and a history of presyncope or syncope.[18]

Biomarkers, such as B-natriuretic peptide, are related to functional class, but their value for risk stratification is limited.

Therapy

Acute MR

Medical therapy is aimed at stabilizing haemodynamics in preparation for surgical repair or MV replacement (usually with endocarditis). Nitroprusside in the normotensive patient and dopamine with or without nitroprusside in hypotension are administered. Aortic balloon counterpulsation increases forward output and mean arterial pressure while diminishing regurgitant volume and LV filling pressure and can also be used. MV repair or replacement, combined with CABG for papillary muscle rupture-induced MR, can now be offered, with <10% mortality.[10] Surgical mortality for endocarditis-induced acute MR is 10–20%. The prognosis of patients with ischaemic cardiogenic shock is inversely related to the



Peak MR flow rate = $2\pi r^2 \times Va \times (angle/180°)$
EROA = peak MR flow rate/peak velocity of MR Jet

Figure 18.1 Schematic example of the proximal isovelocity surface area (PISA) method. Left, the colour Doppler baseline is shifted downward (in the direction of the mitral regurgitation (MR) jet) until the proximal convergence zone (middle) appears hemispheric. The aliasing velocity (Va) is used to calculate peak regurgitant flow rate from the formula, where r is the radius from the blue-red alias line to the orifice. Note that this formula assumes that peak flow rate from the PISA radius occurs at the same time as peak velocity of the MR jet by continuous wave Doppler. If the proximal flow convergence does not occur over a flat (180°) plane, angle correction must be used (right). It is important to shift the baseline in the direction of the MR jet, not to merely lower the aliasing velocity. It is also important to turn off variance, which makes the red-blue alias line easier to identify.

EROA indicates effective regurgitant orifice area.
Grayburn PA, *et al*. Quantitation of mitral regurgitation. *Circulation*. 2012;**126**:2005–17 with permission from Wolters Kluwer.

degree of MR and also argues for aggressive revascularization when feasible.[28]

Chronic MR

Medical therapy is aimed at reducing the afterload and pulmonary congestion with ACE/ARB and diuretics (Table 18.6). In asymptomatic and normotensive patients with normal LV function vasodilators are not indicated, since by decreasing LV size and mitral closing force they may increase mitral prolapse. Beta blockers in MR may increase LVEDD and were thought to be contraindicated, but recent evidence indicated beneficial reverse remodelling, especially in functional MR, but also in degenerative disease.[29] They are also recommended in patients with MVP, no severe MR, and palpitations. Aspirin (75–325 mg od) or warfarin in non-responders is recommended for patients with MVP and TIAs.

Surgery is mainly recommended for (Tables 18.7 and 18.8, and Figures 18.2 and 18.3):[25,30]

Symptomatic patients with severe MR and preserved LV function (i.e. LVEF >30% and LVEDD <55 mm)

Table 18.6 AHA/ACC 2014 GL on valve disease. Medical therapy

Chronic primary MR	
Medical therapy for systolic dysfunction in symptomatic patients (stage D) and LVEF less than 60% in whom surgery is not contemplated	IIa-B
Vasodilator therapy is not indicated for normotensive asymptomatic patients (stages B and C1) with normal systolic LV function	III-B
Chronic secondary MR	
Patients (stages B to D) and HF with reduced LVEF should receive ACE inhibitors, ARBs, beta blockers, and/or aldosterone antagonists as indicated	I-A
Cardiac resynchronization therapy with biventricular pacing for symptomatic patients (stages B to D) who meet the indications for device therapy	I-A

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Asymptomatic patients with severe MR and mild to moderate LV dysfunction (LVEF 30–60% and/or LVESD ≥40 mm) or development of AF or PA hypertension (>50 mmHg)

Mitral valve repair is also recommended for asymptomatic patients with severe MR and well preserved LV function (LVEF >60% and LVESD <40 mm). This last recommendation is somehow debatable, since no randomized data exist to allow certain conclusions.[16,31]

Most retrospective studies support early repair, particularly in the context of organic MR[32,33] and before the establishment of pulmonary hypertension.[34] These patients should be referred to centres with known expertise and a greater than 90% likelihood of successful repair. A watchful waiting approach should probably be preferred if the likelihood of a high-quality repair is low and in the presence of high surgical risk and/or low probability of a durable repair, which is typically the case in very elderly patients with relevant co-morbidities and/or complex valve lesions.[35] However, early surgery has been associated with better outcomes in patients who are older than 50 years and have ERO ≥0.4 cm^2 or flail mitral leaflets,[36] and in a recent analysis of the Medicare database, elderly patients (≥75 years) who underwent repair had a life expectancy similar to that of the age- and sex-matched US population.[37] Operative mortality for patients who underwent repair was 3.9%, compared with 8.9% for replacement. In addition, in patients of the MIDA registry with MR due to flail mitral leaflet but without class I indication for surgery, early surgery was associated with greater long-term survival and lower risk of heart failure compared to initial conservative management.[38] Thus, an approach of early identification

Table 18.7 AHA/ACC 2014 GL on valve disease. Intervention for MR

Chronic Primary MR	
MV surgery for symptomatic patients with severe MR (stage D) and LVEF >30%	I-B
MV surgery for asymptomatic patients with MR and LV dysfunction (LVEF 30–60% and/or LVESD ≥40 mm, stage C2)	I-B
MV repair in preference to MVR when surgical treatment is indicated for severe MR limited to the posterior leaflet	I-B
MV repair in preference to MVR when surgical treatment is indicated for severe MR involving the anterior leaflet or both leaflets when a successful and durable repair can be accomplished	I-B
Concomitant MV repair or replacement in patients with severe MR undergoing cardiac surgery for other indications	I-B
MV repair in asymptomatic patients with severe MR (stage C1) with LVEF >60% and LVESD <40 mm, in whom the likelihood of a successful and durable repair without residual MR is >95% with an expected mortality rate of <1% when performed at a Heart Valve Centre of Excellence	IIa-B
Mitral valve repair for asymptomatic patients with severe nonrheumatic MR (stage C1) and LVEF >60% and LVESD <40 mm, in whom there is a high likelihood of a successful and durable repair with 1) new onset of AF or 2) resting pulmonary hypertension (pulmonary artery systolic arterial pressure >50 mm Hg)	IIa-B
Concomitant MV repair in patients with moderate MR (stage B) undergoing cardiac surgery for other indications	IIa-C
MV surgery in symptomatic patients with severe MR and LVEF ≤30% (stage D)	IIb-C
MV repair in patients with rheumatic mitral valve disease when surgical treatment is indicated if a durable and successful repair is likely or if the reliability of long-term anticoagulation management is questionable	IIb-B
Transcatheter MV repair may be considered for severely symptomatic patients (NYHA class III/IV) with severe MR (stage D) who have favourable anatomy and a reasonable life expectancy but a prohibitive surgical risk because of severe comorbidities	IIb-B
MVR should not be performed for treatment of isolated severe MR limited to less than one half of the posterior leaflet unless MV repair has been attempted and was unsuccessful	III-B (Harm)
Chronic Secondary MR	
MV surgery for patients with severe MR (stages C and D) who are undergoing CABG or AVR	IIa-C
MV repair or replacement for severely symptomatic patients (NYHA class III/IV) despite optimum therapy with severe MR (stage D)	IIb-B
MV repair for patients with moderate MR (stage B) who are undergoing other cardiac surgery	IIb-C

AF indicates atrial fibrillation; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation; MVR, mitral valve replacement; PA, pulmonary artery.
AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

Table 18.8 ESC 2012 GL on valve disease. Surgery for MR

Indications for surgery in severe primary mitral regurgitation	
Mitral repair is preferred when expected to be durable.	I-C
Symptomatic patients with LVEF >30% and ESD <55 mm.	I-B
Asymptomatic patients with LV dysfunction (ESD ≥45 mm and/or LVEF ≤60%).	I-C
Asymptomatic patients with preserved LV function and new-onset AF or pulmonary hypertension (systolic pulmonary artery pressure >50 mmHg at rest).	IIa-C
Asymptomatic patients with preserved LV function, high likelihood of durable repair, and low risk for surgery and flail leaflet, and LVESD ≥40 mm.	IIa-C
Patients with severe LV dysfunction (LVEF <30% and/or LVESD >55 mm) and/or refractory to medical therapy with high likelihood of durable repair and low co-morbidity.	IIa-C
Patients with severe LV dysfunction (LVEF <30% and/or ESD >55 mm) refractory to medical therapy with low likelihood of repair and low co-morbidity.	IIb-C
Asymptomatic patients with preserved LV function, high likelihood of durable repair, low surgical risk and: Left atrial dilatation (volume index ≥60 mL/m^2 BSA) and sinus rhythm, or Pulmonary hypertension on exercise (systolic PA pressure ≥60 mmHg at exercise).	IIb-C
Indications for surgery in chronic secondary mitral regurgitation	
Patients with severe MR,[1] undergoing CABG, and LVEF >30%	I-C
Patients with moderate MR undergoing CABG[2]	IIa-C

(*continued*)

Table 18.8 Continued

Symptomatic patients with severe MR, LVEF <30%, option for revascularization, and evidence for viability	IIa-C
Patients with severe MR, LVEF >30%, refractory to medical therapy (including CRT if indicated), and low co-morbidity, when revascularization is not indicated	IIb-C

* Lower values can be considered for patients of small stature.
[1] The thresholds for severity (EROA ≥20 mm^2; R Vol >30 ml) differ from that of primary MR and are based on the prognostic value of these thresholds to predict poor outcome.
[2] When exercise echocardiography is feasible, the development of dyspnoea and increased severity of MR associated with pulmonary hypertension are further incentives to surgery.
ESC 2012 guidelines on the management of valvular heart disease. *Eur Heart J*. 2012;**33**:2451–96 with permission from Oxford University Press.

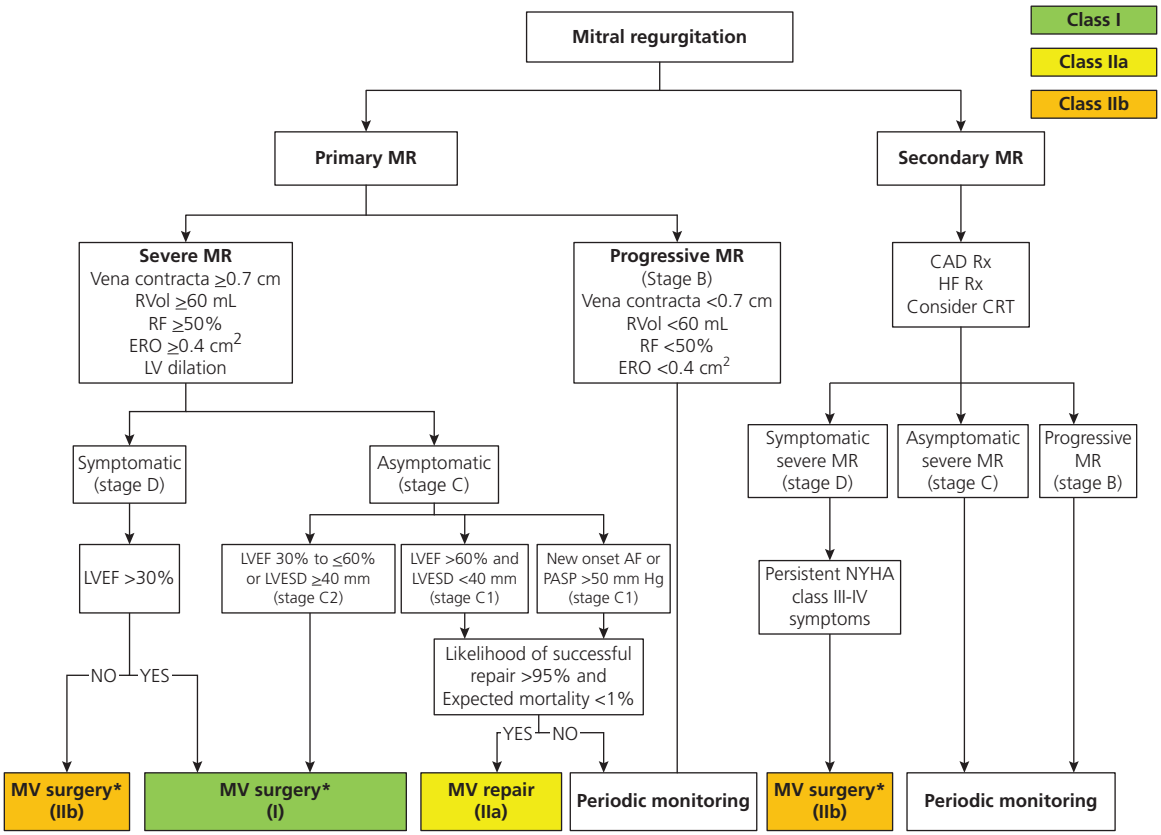

Figure 18.2 AHA/ACC 2014 on valve disease. Indications for surgery for mitral regurgitation.

* Mitral valve (MV) repair is preferred over MVR when possible.
AF indicates atrial fibrillation; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; ERO, effective regurgitant orifice; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation, MV, mitral valve; MVR, mitral valve replacement; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RF, regurgitant fraction; RVol, regurgitant volume; and Rx, therapy.
AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

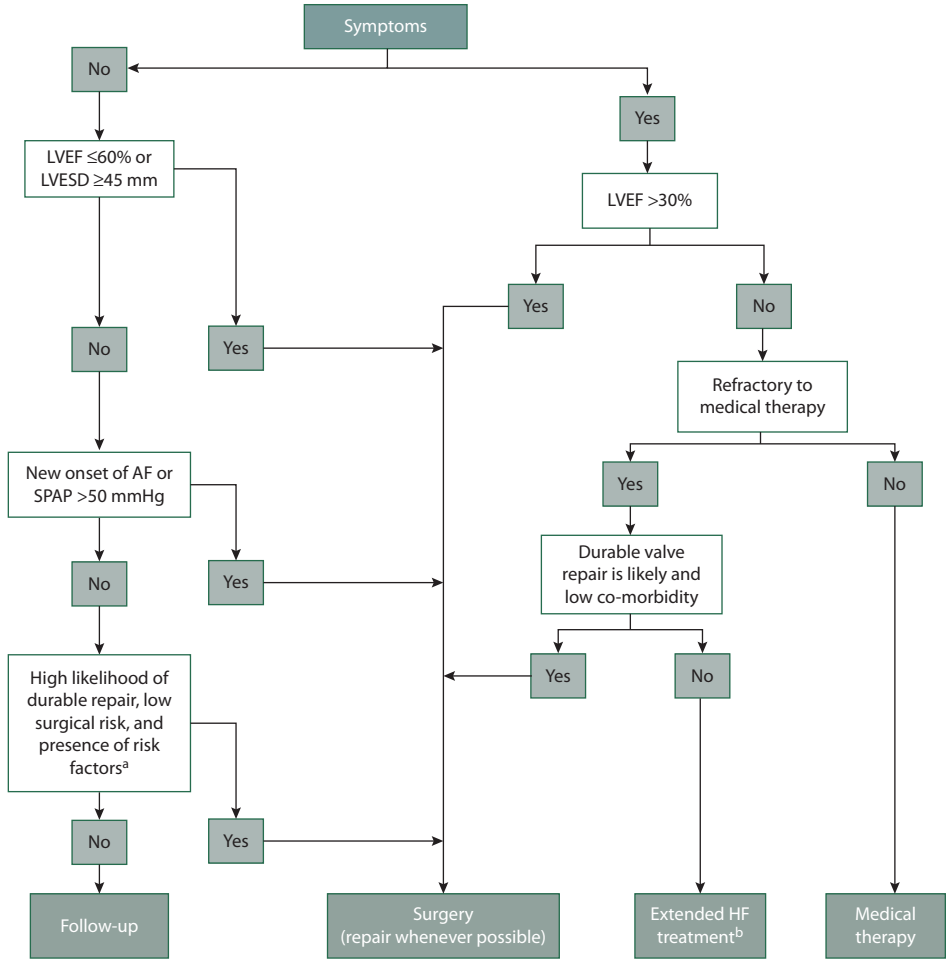

Figure 18.3 ESC 2012 GL on valve disease. Management of severe organic MR.

BSA, body surface area; SPAP, systolic pulmonary arterial pressure.
a: When there is a high likelihood of durable valve repair at a low risk, valve repair should be considered (IIaC) in patients with flail leaflet and LVESD ≥40 mm; valve repair may be considered (IIbC) if one of the following is present: LA volume ≥60 mL/m² BSA and sinus rhythm or pulmonary hypertension on exercise (SPAP ≥60 mmHg).
b: Extended HF management includes the following: cardiac resynchronization therapy: ventricular assist devices; cardiac restraint devices; heart transplantation.
ESC 2012 guidelines on the management of valvular heart disease. *Eur Heart J.* 2012;**33**:2451–96 with permission from Oxford University Press.

and surgical referral should be probably considered, regardless of age.

MV repair is recommended over **MV replacement**,[39,40] although, in a recent RCT, chordal-sparing replacement and repair were not different by means of survival and LV reverse remodelling at 12 months.[41] Calcified mitral annulus, rheumatic disease, and involvement of the anterior leaflet diminish the likelihood of repair. In experienced centres, reoperation after 10 years is necessary in 5% of patients with repaired posterior leaflet prolapse and 10% of those with anterior leaflet repair. MV repair for degenerative MR restores lifespan to normal, except in patients with symptoms at rest and impaired left ventricular function. Advanced age and complex mitral valve pathologies increase the risk of late recurrent MR.[42] In patients with moderate TR or tricuspid annular dilation who are undergoing degenerative mitral repair, concomitant tricuspid annuloplasty may improve outcomes.[43] When repair is not feasible, **MV replacement** with preservation of the subvalvar apparatus is preferred. The choice of prosthesis is based on patient age and the risk of anticoagulation (see Chapter 23 on prosthetic valves). Recommendations for the management of AF are provided in Chapter 53.

The prognosis of patients with **secondary (functional) MR** is worse than other kinds of MR, and the role of surgery is

controversial.[11,44] Although CABG may improve MR in some patients,[45] moderate ischaemic MR does not reliably resolve,[46] and development of significant MR may be seen following isolated CABG.[47] Recently, an analysis of the STICH trial cohort suggested potentially improved survival when MV repair with an annuloplasty ring was added to CABG in ischaemic patients with LVEF ≤35% and moderate to severe MR.[48] However, no effect on mortality with the addition of annuloplasty has been seen in the three RCTs conducted so far.[49–51] In the most recent of these, in patients with moderate ischaemic MR, the addition of mitral valve repair to CABG did not even result in a higher degree of LV reverse remodelling.[51] Again, the value of adding MV surgery (repair or replacement) to CABG is controversial.[44] In addition, a recent retrospective analysis of the Duke Databank demonstrated that in patients with significant CAD and moderate or severe MR, CABG alone had the lowest risk of death.[52] Cardiac resynchronization therapy is a potential therapeutic option in heart failure patients with moderate to severe functional MR and high risk for surgery.[53] Recommendations for surgery are given in Table 18.7 and Table 18.8. See also Table 16.6 and Table 16.7 of Chapter 16.

In patients with **persistent AF** who undergo mitral surgery, PV isolation or a Maze procedure provides a higher rate of freedom from AF (63 vs 29%), but the risk of implantation of a permanent pacemaker is also increased.[54]. In the US, concomitant surgical ablation is performed in approximately 60% of patients with AF who undergo mitral valve operations (see Chapter 53).[55]

Percutaneous techniques for MR, such as edge-to-edge anterior and posterior leaflet attachment with a clip and coronary sinus cinching, are under investigation.[56,57] The EVEREST II randomized controlled trial failed to show convincing benefits of the Mitraclip technique in comparison with surgical repair in all-comers with severe MR.[58] However, subsequent analysis of outcomes in higher risk subjects within the trial, compared with registry controls receiving medical therapy alone, and data from registries have suggested a possible role for percutaneous treatment in mainly functional MR.[59–61] The clinical effectiveness of this and other percutaneous approaches, such as the Mitralign device, are under study.[62–64] In March 2016, the FDA issued a recall for MitraClip Clip Delivery System after reports of issues in detaching the delivery system from the clip, and the system is being reconsidered. A consensus approach to clinical trial design and uniform endpoint definitions to evaluate outcomes in patients with MR has been offered by the Mitral Valve Academic Research Consortium.[65, 66]

Transapical mitral valve implantation for severe MR or dysfunctional biological mitral prosthesis is also a recent possibility.[67,68]

Non-cardiac surgery

Moderate-risk elective non-cardiac surgery with appropriate intraoperative and post-operative haemodynamic monitoring can be performed in patients with asymptomatic severe MR and normal LV function (AHA/ACC 2014 GL on VD and ESC 2014 GL on non-cardiac surgery IIa-C).[26,69] If LV dysfunction is severe (EF <30%), non-cardiac surgery should only be performed, if strictly necessary, after optimization of medical therapy for HF.

Pregnancy

Valve repair before pregnancy may be considered in the asymptomatic patient with severe MR (stage C) and a valve suitable for valve repair, but only after detailed discussion with the patient about the risks and benefits of the operation and its outcome on future pregnancies (AHA/ACC 2014 GL on VD, IIb-C). For general recommendations, see also Table 15.9.

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Chapter 19

Aortic stenosis

Epidemiology

Aortic stenosis (AS) is the most prevalent form of cardiovascular disease in the western world after hypertension, coronary artery disease, and mitral regurgitation.[1,2,3] It is the most common form of valvular heart disease needing surgery in Europe.[2] In the USA, approximately 652 000 patients were subjected to aortic valve surgical replacement in 2010, mainly for AS.[4] Aortic sclerosis, defined as irregular valve thickening without obstruction to LV outflow, is present in about 25% of adults over 65 years of age and is associated with clinical factors, such as age, sex, hypertension, smoking, serum low-density lipoprotein and lipoprotein(a) levels, and diabetes mellitus.[5]

Aetiology

The most common cause of AS in adults is calcification of a normal trileaflet or congenital bicuspid valve. The disease process is characterized by lipid accumulation, inflammation, and calcification, with many similarities to atherosclerosis, although the pathophysiological processes in calcific AS are locally determined and regulated.[5] Lipoprotein(a) has been associated with calcific aortic valve disease.[6] Metabolic syndrome is an independent predictor of AS progression, especially in younger patients.[7] Rheumatic AS, due to fusion of the commissures with scarring and eventual calcification of the cusps, is less common in developed countries and is invariably accompanied by mitral valve disease. Progression of aortic valve stenosis is

associated with bone remodelling and secondary hyperparathyroidism in elderly patients.[8] In the young, AS is due to congenital malformations, such as bicuspid aortic valve, the presence of which significantly increases the risk of AS, discrete subvalvular obstruction, or supravalvular stenosis (see Chapter 1). Calcific valvular disease is known to cluster within families, and recently the CHARGE Extracoronary Calcium Working Group reported one single nucleotide polymorphism in the lipoprotein(a) locus that is associated with aortic valve calcification.[9]

Pathophysiology and natural history

Inflammation, fibrosis, and calcification contribute to the development of AS. The trilayered structure of the AV matrix may be disrupted because of an imbalance in the expression of matrix metalloproteinases and their inhibitors, and eventually, the expression of bone-related proteins increases and results in osteoblastic differentiation of the valve interstitial cells.[10] The calcific disease progresses gradually over many years from the base of the cusps to the leaflets with formation of hydroxyapatite nodules, cartilage, and bone tissue, eventually causing a reduction in leaflet motion and effective valve area without commissural fusion.[4] The LV adapts to the obstruction by increasing wall thickness while maintaining normal chamber size. The consequent concentric hypertrophy is a compensatory mechanism to normalize the LV wall stress. As a result of increased wall thickness and diminished compliance of the chamber, LV end-diastolic pressure increases without chamber dilatation. LV systolic function is usually preserved, and cardiac output is maintained for many years. If LV systolic dysfunction is present, it usually improves after aortic valve replacement (AVR). Irreversible LV dysfunction is possible but cannot be easily diagnosed by preoperative imaging. Impaired platelet function and decreased levels of von Willebrand factor develop with severe disease and predispose to epistaxis and ecchymosis.[7]

The narrowed AV orifice and restricted leaflet opening create an acceleration of blood through the valve, from a low velocity (V <1 m/s) in the LVOT to the maximum velocity at the vena contracta (VC) of the jet (Figure 19.1). The area formed by the free edges of the AV leaflets is known as the geometric orifice area (GOA) of the valve, whereas the area of the flow jet at the VC is known as the effective orifice area (EOA). GOA is greater than EOA, or equal when GOA and LVOT area are equal, and it is measured at peak systole with planimetric methods at echocardiography or CT scanning. EOA is probably the most important parameter because it represents the workload imposed on the LV, but some uncertainty still exists.[11] ΔP_{rec} is the pressure difference as measured between LVOT and ascending aorta during cardiac catheterization, especially when it is done with pullback of one catheter), and is usually less than the ΔP_{max} measured between LVOT and EOA at the vena contracta measured

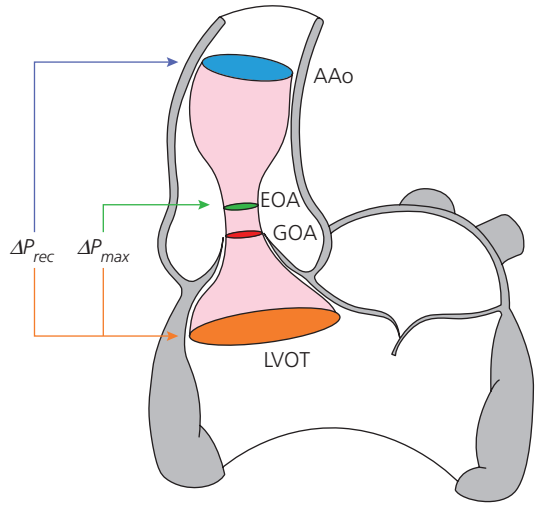

Figure 19.1 Schematic of flow through a stenotic aortic valve. ΔP_{max} (pressure difference between LVOT and EOA at the vena contracta) is larger than ΔP_{rec} (pressure difference between LVOT and ascending aorta), due to pressure recovery.

AAo indicates ascending aorta; EOA, effective orifice area at the vena contracta; GOA, geometric orifice area; and LVOT, left ventricular outflow tract. Saikrishnan N, *et al.* Accurate assessment of aortic stenosis: a review of diagnostic modalities and hemodynamics. *Circulation*. 2014;**129**:244–53 with permission from Wolters Kluwer.

by Doppler echocardiography. This is because the blood flow contracts to pass through the stenotic orifice, and a portion of the potential energy of the blood (i.e, pressure) is converted into kinetic energy (i.e, velocity). Downstream of the vena contracta, a part of the kinetic energy is irreversibly dissipated as heat because of flow turbulences. The remaining portion of the kinetic energy is recovered back to potential energy and represents the so-called 'pressure recovery' (Figure 19.2).[11,12] Thus, Doppler-derived gradients may be theoretically more accurate in the absence of conditions that violate the assumptions of the modified Bernoulli (continuity) equation, such as aortic regurgitation or anaemia/fever/thyrotoxicosis where flow velocity in LVOT is >1 m/s. They are subject to error, however, because echocardiography may underestimate the LV outflow tract diameter, an integral component of the continuity equation, that is not circular but oval. The combination of CT with Doppler assessment has been proposed, but clinical experience is limited.[13]

Severe aortic stenosis is defined as an effective orifice area ≤1 cm^2 (0.6 cm^2/m^2 BSA) in the context of a mean transvalvular gradient ≥40 mmHg (Tables 19.1 and 19.2). It should be noted that the value of 40 mmHg may represent an inconsistency of current guidelines, since, in the context of normal cardiac output, an EOA of 1 cm^2 corresponds to a gradient of 30–35 mmHg.[11] However, gradients are a squared function of flow, as expressed by the stroke volume, and even a modest decrease of flow may

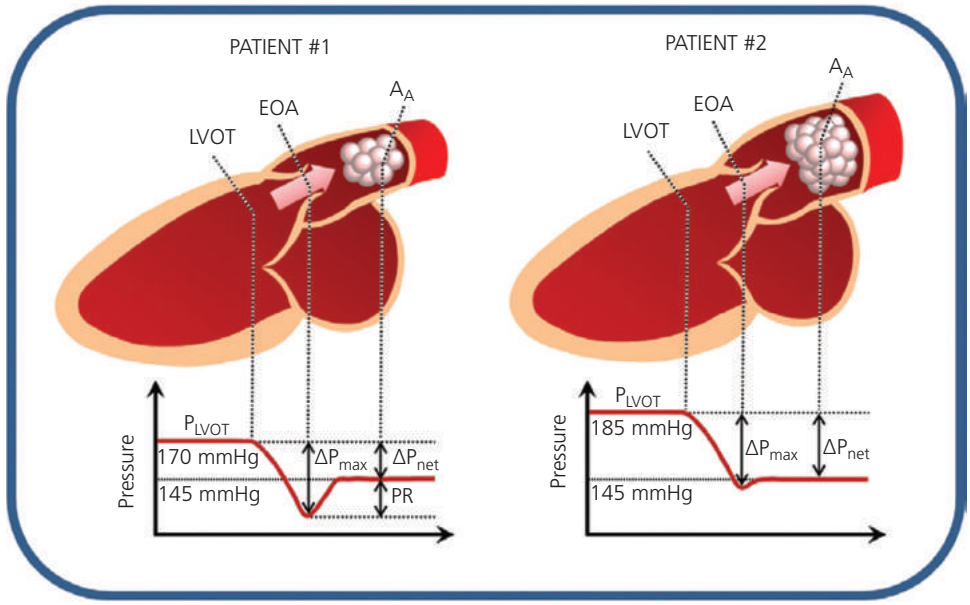

Figure 19.2 The phenomenon of pressure recovery in aortic stenosis. Schematic representation of flow and blood pressure across the left ventricular outflow tract (PLVOT), aortic valve, and ascending aorta (AA) during systole in two theoretical patients having the same stroke volume (80 mL) and valve effective orifice area (EOA; 0.9 cm^2) but different sizes of ascending aorta (2.0 cm diameter in patient 1 vs 4.0 cm in patient 2). The maximum pressure gradient recorded at vena contracta (ΔPmax, i.e. the mean gradient measured by Doppler) is the same in the two patients, but patient 1, with the small aorta, has a large amount of pressure recovery (PR) downstream of the valve, whereas patient 2 has minimal pressure recovery. Consequently, the net 'irreversible' gradient (ΔPnet, i.e. measured by catheter), and thus the left ventricular systolic pressure, is significantly higher in patient 2 than in patient 1.

LVOT indicates left ventricular outflow tract. Please note that in this figure EOA is indicated at the level of GOA (Figure 19.1).
Pibarot P, *et al.* Energy Loss Index in Aortic Stenosis: From Fluid Mechanics Concept to Clinical Application. *Circulation*. 2013;**127**:1101–4 with permission from Wolters Kluwer.

lead to an important reduction in gradient, even in the presence of a severe stenosis. Thus, there has been a tendency to characterize severe aortic stenosis in terms of flow and gradient.[14]

Severe AS with reduced LVEF (≤40%). This can be secondary to the valve disease or due to unrelated myocardial dysfunction. Low-flow/low-gradient severe AS with reduced LVEF is defined as effective orifice area < 1 cm^2 (≤0.6 cm^2/m^2), mean gradient < 40 mm Hg, SVi <35 mL/m^2,

Table 19.1 ESC 2012 GL on valve disease. Definition of severe AS

Valve area (cm^2)	<1.0
Indexed valve area (cm^2/m^2 BSA)	<0.6
Mean gradient (mmHg) (in patients with normal cardiac output/transvalvular flow)	>40
Maximum jet velocity (m/s) (in patients with normal cardiac output/transvalvular flow)	>4.0
Velocity ratio	<0.25

ESC 2012 guidelines on the management of valvular heart disease. *Eur Heart J.* 2012;**33**:2451–96 with permission from Oxford University Press.

and LVEF (≤40%) due to myocardial dysfunction that is caused by the valve disease (Table 19.2).[14] Approximately 20–30% of these patients have **pseudosevere AS** due to intrinsic cardiomyopathy unrelated to the valve disease. Pseudosevere AS is diagnosed by dobutamine infusion that increases the valve area without significantly affecting the gradient of dobutamine infusion (see Diagnosis).

Severe AS with preserved LVEF (>50%). These patients have been classified into 4 groups according to flow-F (Stroke volume index, SVi <35 or ≥35 ml/m^2) and gradient-G (<40 mmHg or ≥40 mm Hg):[15]

1. Normal F/Low G
2. Normal F/High G
3. Low F/Low G
4. Low F/High G

Low-flow, low-gradient severe AS with normal LVEF or **paradoxical low-flow, low-gradient severe AS** is characterized by an effective orifice area < 1 cm^2 (0.6 cm^2/m^2), mean gradient <40 mmHg, SVi <35 mL/m^2, and LVEF ≥50%.[16] This pattern is seen in 3–24% of patients with severe AS, and 30–50% of patients with severe AS in the

Table 19.2 AHA/ACC 2014 GL on valve disease. Stages of valvular AS

Stage	Definition	Valve anatomy	Valve haemodynamics	Haemodynamic consequences	Symptoms
A	At risk of AS	Bicuspid aortic valve (or other congential valve anomaly) Aortic valve sclerosis	Aortic V_{max} <2 m/s	None	None
B	Progressive AS	Mild-to-moderate leaflet calcification of a bicuspid or trileaflet valve with some reduction in systolic motion or rheumatic valve changes with commissural fusion	Mild AS: aortic V_{max} 2.0–2.9 m/s or mean ΔP <20 mmHg Moderate AS: aortic V_{max} 3.0–3.9 m/s or mean ΔP 20–39 mmHg	Early LV diastolic dysfunction may be present Normal LVEF	None
C: Asymptomatic severe AS					
C1	Asymptomatic severe AS	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	Aortic V_{max} 4 m/s or mean ΔP ≥40 mmHg AVA typically is ≤1.0 cm^2 (or AVAi ≤0.6 cm^2/m^2 Very severe AS is an aortic V_{max} ≥5 m/s or mean ΔP ≥60 mmHg	LV diastolic dysfunction Mild LV hypertrophy Normal LVEF	None: exercise testing is reasonable to confirm symptom status
C2	Asymptomatic severe AS with LV dysfunction	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	Aortic V_{max} ≥ 4 m/s or mean ΔP ≥40 mmHg AVA typically is ≤1.0 cm^2 (or AVAi ≤0.6 cm^2/m^2	LVEF <50%	None
D: Symptomatic severe AS					
D1	Symptomatic severe high-gradient AS	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	Aortic V_{max} ≥4 m/s or mean ΔP ≥40 mmHg AVA typically is ≤1.0 cm^2 (or AVAi ≤0.6 cm^2/m^2 but may be larger with mixed AS/AR	LV diastolic dysfunction LV hypertrophy Pulmonary hypertension may be present	Exertional dyspnoea or decreased exercise tolerance Exertional angina Exertional syncope or presyncope
D2	Symptomatic severe low-flow/ low-gradient AS with reduced LVEF	Severe leaflet calcification or congenital stenosis with severely reduced leaflet motion	AVA ≤1.0 cm^2 (or AVAi ≤0.6 cm^2/m^2 but may be larger with mixed AS/AR Dobutamine stress echocardiography shows AVA ≤1.0 cm^2 with V_{max} ≥4 m/s at any flow rate	LV diastolic dysfunction LV hypertrophy LVEF <50%	HF Angina Syncope or presyncope
D3	Symptomatic severe low-gradient AS with normal LVEF or paradoxical low-flow severe AS	Severe leaflet calcification with severely reduced leaflet motion	AVA ≤1.0cm^2 with aortic V_{max} <4 m/s or mean ΔP <40 mmHg Indexed AVA ≤0.6 cm^2/m^2 and Stroke volume index <35 mL/m^2 Measured when patient is normotensive (systolic BP <140 mmHg)	Increased LV relative wall thickness Small LV chamber with low stroke volume Restrictive diastolic filling LVEF ≥50%	HF Angina Syncope or presyncope

AR indicates aortic regurgitation; AS, aortic stenosis; AVA, aortic valve area; AVAi, aortic valve area indexed to body surface area; BP, blood pressure; HF, heart failure; LV, left ventricular; LVED, left ventricular ejection fraction; ΔP, pressure gradient; and V_{max}, maximum aortic velocity.
AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

context of preserved LVEF. The discrepancy between LVEF and stroke volume has been confirmed by invasive haemodynamics,[17] and is attributed to high global afterload and restricted physiology with pronounced concentric remodelling and myocardial fibrosis that are mainly reflected in impaired longitudinal function.[18,19] Atrial fibrillation and coexistent mitral valve disease may also cause reduced forward stroke volume.

Aortic sclerosis is characterized by focal areas of valve thickening, typically located in the leaflet centre with commissural sparing and normal leaflet mobility. Jet velocity in aortic sclerosis is <2.5 m/s. Diffuse leaflet thickening is not seen in aortic sclerosis, being suggestive of normal ageing changes, significant AS, or imaging artefact. In AS, the aortic valve is usually thickened and calcified, with limited excursion and a reduced aortic valve area. Its prevalence increases with age (up to 40% in patients >80 years), there is a low (1.9% per year) rate of progression to clinical AS, but an independent increase of coronary events, stroke, and mortality in these patients.[20]

Once even moderate stenosis is present (jet velocity >3.0 m/s), the average rate of progression is an increase in the mean pressure gradient of 7 mmHg per year, and a decrease in the valve area of 0.1 cm^2 per year.[21] An annual increase in jet velocity >0.32 m/s indicates rapid haemodynamic progression.[22] Most patients with AV velocity of 4 m/s become symptomatic within the next 5 years and carry a 1% risk of sudden death per year.[23] Asymptomatic patients with very severe aortic stenosis (jet velocity >5 m/s) have a poor prognosis with a high event rate (75% at 3 years have AVR or die) and a risk of rapid functional deterioration.[24]

Presentation

Patients, even with severe AS, may be asymptomatic. Usually with progression of stenosis severity, SOBOE or heart failure (50%), angina (35%), and syncope (15%) appear. Once symptoms develop, AVR is needed because the average survival is only 2–3 years, with an increased risk of sudden death.

Physical examination

Slow arterial pulse (pulsus parvus et tardus) in severe AS. May not be present with AR, in hypertension, or in the elderly due to rigid vasculature.

Prominent a waves in JVP in severe AS (reduced RV compliance due to hypertrophy of the interventricular septum). The **v wave** may be prominent if there is RV failure.

Soft S_1 and **single S_2** (late or absent A_2)

S_4 (vigorous atrial contraction) indicates severe AS.

A **thrill** may be present.

Hyperdynamic LV suggests concomitant MR or AR.

Crescendo–decrescendo systolic murmur along the left sternal border that radiates to the upper right sternal border and the carotids. It may also radiate to the LV apex (the Gallavardin phenomenon) and may be mistaken for MR.

The intensity of the murmur does not correspond to the severity of AS.

Diastolic murmur if AR is also present.

Systolic ejection click in young patients with bicuspid valve.[26]

Investigations

ECG LV hypertrophy may be seen. The additional presence of ECG strain (≥1-mm concave downsloping ST-segment depression with asymmetrical T-wave inversion in the lateral leads) indicates myocardial fibrosis and adverse clinical outcome.[25] Left atrial enlargement in severe AS and AF is in <15% of patients. Various degrees of AV and intraventricular block may be seen, as well as arrhythmias, especially in the elderly (up to 20%), mainly AF, NSVT and AV block.[27]

Chest radiography Usually normal. Cardiomegaly is a late feature in AS, and calcification is a universal finding, but rarely visible on chest X-ray. The proximal ascending aorta may be dilated, particularly in patients with bicuspid valves.

Echocardiography is the standard imaging procedure. 2D echocardiography establishes the diagnosis and usually identifies a bicuspid valve. Doming of the aortic leaflets due to asymmetry and restriction is often seen in young patients with bicuspid aortic valves. Planimetric systolic geometric orifice areas can also be obtained, but they may not accurately represent AS severity.[11] Doppler echocardiography allows quantification of jet velocity, pressure gradient derived as 4 × (jet velocity)^2, and valve area (Table 19.3). In patients with mixed AS and AR, peak aortic jet velocity reflects both stenosis and regurgitation and represents a useful predictive parameter.[27] Doppler-derived gradients tend to be higher and effective orifice area lower, compared to those derived by cardiac catheterization, due to the pressure recovery effect (Figures 19.1 and 19.2). This can be accounted for by calculating the energy loss index (***ELI***). (ELI = [EOA × A_A / A_A - EOA]/BSA, where EOA = is the effective orifice area by conventional echocardiography, A_A is the cross-sectional area of the aorta measured at 1 cm downstream of the sinotunular junction, and BSA is the body surface area). In asymptomatic patients with inconsistent grading of stenosis and obtained by catheterization, it provides additional prognostic information independently of the aortic gradient.[28]

The AHA/ACC recommended frequency of echocardiograms in asymptomatic patients with normal LV function and normal stroke volume is every 3–5 years for mild AS (V_{max} 2–2.9 m/s), every 1–2 years for moderate severity (V_{max} 3–3.9 m/s), and every 6–12 months for severe AS (V_{max} ≥4 m/s).[21]

Low-dose dobutamine haemodynamic measurements or **exercise echocardiography** is useful in cases of ***low-flow/low-gradient severe AS*** in order to differentiate patients with anatomically severe AS from those with pseudosevere AS. Dobutamine (5–20 microgram/kg/min) in AS with LV dysfunction and gradient <40 mmHg produces an increment in stroke volume (>20%) and valve area (>1 cm^2 and/or an increase ≥0.3 cm^2) but no change in gradient, in haemodynamically non-significant stenosis (pseudosevere AS). In significant AS, the valve area remains unchanged (or increases <0.2 cm^2 but remains <1 cm^2), whereas the gradient and stroke volume increase (mean gradient >40 mmHg). In ambiguous response, calculation of the projected orifice area that would have occurred at a standardized flow rate of 250 mL/s may be useful (TOPAS trial).[29]

In ***paradoxical low-flow, low-gradient severe AS***, detailed echocardiographic examination to avoid miscalculation of the stroke volume, evaluation of the systemic

Table 19.3 AHA/ACC 2014 GL on valve disease. Diagnostic testing

Transthoracic echocardiography (TTE) in patients with signs or symptoms of AS or a bicuspid aortic valve for accurate diagnosis of the cause of AS, haemodynamic severity, LV size and systolic function, and for determining prognosis and timing of valve intervention	I-B
Low-dose dobutamine stress testing using echocardiographic or invasive haemodynamic measurements is reasonable in patients with stage D2 AS with all of the following: a. Calcified aortic valve with reduced systolic opening; b. LVEF <50%; c. Calculated valve area ≤1.0 cm^2 d. Aortic velocity <4.0 m/s or mean pressure gradient <40 mmHg.	IIa-B
Exercise testing to assess physiological changes with exercise and to confirm the absence of symptoms in asymptomatic patients with a calcified aortic valve and an aortic velocity ≥4.0 m/s or mean pressure gradient ≥40 mmHg (stage C)	IIa-B
Exercise testing should not be performed in symptomatic patients with AS when the aortic velocity is ≥4.0 m/s or mean pressure gradient ≥40 mmHg (stage D)	III-B

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arterial compliance and valvuloarterial impedance ($\mathbf{Z}_{VA}$), and interpretation of findings in the context of peripheral blood pressure are recommended.[15] It has been proposed that, for the measure of Doppler stroke volume, the LV outflow tract diameter should be measured preferably at the insertion of the aortic valve cusps, rather than at 5–10 mm below the aortic annulus, as proposed by the European Society of Echocardiography/American Society of Echocardiography.[30] Impaired longitudinal function, i.e. lower basal longitudinal strain and tissue velocities and mitral plane excursion, as assessed by speckle-tracking echocardiography, are markers of worse prognosis.[31] The aortic valve calcification load, as assessed by multidetector computed tomography, may also be of value in this case.

Plasma BNP A high value (>550 pg/mL) is a powerful predictor of mortality in patients with low-flow/low-gradient AS, regardless of medical or surgical treatment or the presence and/or absence of flow reserve.[32]

Treadmill exercise testing (closely supervised) is no longer contraindicated in asymptomatic AS[33] and may be considered to elicit exercise-induced symptoms and abnormal blood pressure responses. Development of symptoms or a hypotensive response are predictors of sudden death and indicate the need of valve replacement. Exercise testing is contraindicated in symptomatic AS. Truly severe AS shows only small changes in valve area (increase <0.2 cm^2 and remaining <1 cm^2), with increasing flow rate but a significant increase in gradients (mean gradient >40 mmHg), whereas pseudosevere AS shows a marked increase in valve area but only minor changes in gradients. In addition, this test may detect the presence of flow reserve, which has favourable prognostic implications.

Multidetector computed tomography is useful for the assessment of aortic root dilatation and assessment of calcification. Severe calcification detected by multi-slice tomography is useful in establishing the diagnosis of paradoxical low-flow, low-gradient AS. Aortic valve calcification ≥1274 AU in women and 2065 AU in men or with AVC density (indexed to annulus cross-sectional area) ≥292 AU/cm^2 in women and 476 AU/cm^2 in men.[34] CT is also useful for valve sizing and prediction of paravalvular leakage with TAVI procedures.

Cardiac magnetic resonance allows anatomic measurement of the valve area and estimation of jet velocity and stroke volume (especially in paradoxical low-flow, low-gradient AS). It has lower spatial resolution than CT.[11]

Cardiac catheterization may be necessary for assessment of the gradient in the case of inconclusive non-invasive tests results. Simultaneous pressure measurements across the valve (and not pull back) are necessary. Dobutamine can also be used to identify low-flow/low-gradient AS.

Coronary angiography is necessary before surgery in patients with risk factors or clinical suspicion of coronary artery disease (Tables 16.5 and 16.6 in Chapter 16) and occasionally before a Ross procedure to identify the origins of the coronaries.

Therapy

Medical therapy consists of exercise restriction and cautious use of diuretics and ACE/ARB that may delay progression of AS (Table 19.4).[35] Vasodilators can cause an increase in cardiac output that helps offset the drop in systemic vascular resistance, even in severe AS.[36] Systemic hypertension in low-gradient severe aortic stenosis with preserved ejection fraction is associated with elevated LV filling pressures and pulmonary hypertension, and vasodilator therapy in this setting appears to be beneficial.[37] Initial evidence about the beneficial effect of statins in reducing progression of AS has not been verified.[38] Osteoporotic and antifibrotic therapies are also under consideration.[6,8] The use of ACE inhibitors or ARBs is associated with improved survival after surgical valve replacement.[39]

Surgical therapy indications for AVR are presented in Tables 19.5 and 19.6, and Figures 19.3 and 19.4. **AVR** is indicated in symptomatic patients with severe AS, even in the presence of LVEF <35%, unless this is due to previous myocardial infarctions.[21,40] AVR may also be advisable in asymptomatic patients with severe AS.[24] AVR should also be considered in patients with moderate aortic stenosis (mean gradient 30–50 mmHg or Doppler velocity 3–4 m/s or heavily calcified aortic valve even when Doppler velocity 2.5–3 m/s) who undergo CABG (ESC/EACTS 2010 GL on revascularization, IIa-C).[41] Perioperative

Table 19.4 AHA/ACC 2014 GL on valve disease. Medical therapy

Hypertension in patients at risk for developing AS (stage A) and in patients with asymptomatic AS (stages B and C) should be treated according to standard guidelines-directed medical therapy (GDMT), started at a low dose, and gradually titrated upward as needed with frequent clinical monitoring	I-B
Vasodilator therapy may be reasonable if used with invasive haemodynamic monitoring in the acute management of patients with severe decompensated AS (stage D) with NYHA class IV HF symptoms	IIb-C
Statin therapy is not indicated for prevention of haemodynamic progression of AS in patients with mild-to-moderate calcific valve disease (stages B to D)	III-A

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Table 19.5 ESC 2012 GL on valve disease

Indications for aortic valve replacement in aortic stenosis	
Patients with severe AS and symptoms related to AS.	I-B
Patients with severe AS undergoing coronary artery bypass surgery, surgery of the ascending aorta or on another valve.	I-C
Asymptomatic patients with severe AS and systolic LV dysfunction (LVEF <50%) not due to other cause.	I-C
Asymptomatic patients with severe AS and abnormal exercise test showing symptoms on exercise related to AS	I-C
AVR in high-risk patients with severe symptomatic AS who are suitable for TAVI but in whom surgery is favoured by a 'heart team', based on the individual risk profile and anatomic suitability.	IIa-B
Asymptomatic patients with severe AS and abnormal exercise test showing fall in blood pressure below baseline.	IIa-C
Patients with moderate AS* undergoing coronary artery bypass surgery, surgery of the ascending aorta or another valve.	IIa-C
Symptomatic patients with low-flow, low-gradient (<40 mmHg) AS with normal EF only after careful confirmation of severe AS.**	IIa-C
Symptomatic patients with severe AS, low-flow, low-gradient with reduced EF, and evidence of flow (contractile) reserve.	IIa-C
Asymptomatic patients, with normal EF and none of the above mentioned exercise test abnormalities, if the surgical risk is low, and one or more of the following findings is present: • Very severe AS defined by a peak transvalvular velocity >5.5 m/s or, • Severe valve calcification and a rate of peak transvalvular velocity progression ≥0.3 m/s per year.	IIa-C
Symptomatic patients with severe AS low-flow, low-gradient and LV dysfunction without flow (contractile) reserve.	IIb-C
Asymptomatic patients with severe AS, normal EF, and none of the above mentioned exercise test abnormalities, if surgical risk is low, and one or more of the following findings is present: • Markedly elevated natriuretic peptide levels confirmed by repeated measurements and without other explanations • Increase of mean pressure gradient with exercise by >20 mmHg • Excessive LV hypertrophy in the absence of hypertension.	IIb-C

* Moderate AS is defined as valve area 1.0–1.5 cm^2 (0.6–0.9 cm^2/m^2 BSA) or mean aortic gradient 25–40 mmHg in the presence of normal flow conditions. However, clinical judgement is required.
** Patients with a small valve area, but low gradient despite preserved LVEF, explanations for this finding (other than the presence of severe AS) are frequent and must be carefully excluded.
ESC 2012 guidelines on the management of valvular heart disease. *Eur Heart J*. 2012;**33**:2451–96 with permission from Oxford University Press.

Table 19.6 AHA/ACC 2014 GL on valve disease. Timing of intervention in AS

Very severe AS (decreased systolic opening of a calcified or congenitally stenotic aortic valve with velocity ≥5 m/s or mean gradient ≥60 mmHg)	
Asymptomatic patients (stage C1) and low surgical risk	IIa-B
Severe AS (decreased systolic opening of a calcified or congenitally stenotic aortic valve with velocity ≥4 m/s or mean gradient ≥40 mmHg)	
Symptoms of heart failure, syncope, exertional dyspnoea, angina, or presyncope by history or on exercise testing (stage D1)	I-B
Asymptomatic patients and LVEF <50% (stage C2)	I-B
Patients (stages C and D) undergoing other cardiac surgery	I-B
Asymptomatic patients (stage C1) and decreased exercise tolerance or a fall in systolic BP on exercise testing	IIa-B
Asymptomatic patients with low surgical risk and serial testing shows an increase in aortic velocity ≥0.3 m/s/year.	IIb-C
Moderate AS (velocity 3–3.9 m/s or mean gradient 20–39 mmHg)	
Asymptomatic patients (stage B) undergoing other cardiac surgery	IIa-C
Low-flow/low-gradient severe AS (calcified valve with reduced systolic opening, with valve area ≤1 cm^2, Velocity <4 m/s, or mean gradient <40 mmHg)	
Symptomatic patients and LVEF <50% (stage D2) and a low-dose dobutamine study that shows velocity ≥4 m/s or mean gradient ≥40 mmHg with valve area ≤1 cm^2, at any dobutamine dose	IIa-B
Paradoxical low-flow/low-gradient severe AS (calcified valve with significantly reduced leaflet motion, LVEF ≥50%, velocity <4 m/s or mean gradient <40 mmHg, stroke volume <35 mL/m^2, and valve area ≤0.6 cm^2/m^2 when systolic BP <140 mmHg)	
Symptomatic patients (stage D3) if clinical, haemodynamic, and anatomic data support valve obstruction as the most likely cause of symptoms	IIa-C

AS indicates aortic stenosis; AVR, aortic valve replacement by either surgical or transcatheter approach; BP, blood pressure; LVEF, left ventricular ejection fraction.
AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

mortality in patients >65 years old is 3.9 for AVR alone and 5.9 for AVR plus CABG. Long-term survival after surgical aortic valve replacement in the elderly is excellent, although patients with a high (≥10) STS perioperative risk of mortality and those with certain comorbidities (lung disease and renal failure, particularly dialysis-dependent renal failure) carry a particularly poor long-term prognosis.[42] According to the STS National Database, the operative mortality for isolated AVR has constantly declined in the last decade to <3% today in the US (http://www.sts.org).

Patients with ***low-flow/low-gradient severe AS and LVEF ≤40%*** have poor prognosis, with medical therapy (survival rates <50% at 3-year follow-up).[14] Operative risk is 22–33% in those with no flow reserve (increase in stroke volume <20% with dobutamine), but 5–8% in the presence of preserved flow reserve.[14]

Patients with ***pseudosevere AS*** have a 5-year survival under medical therapy better than patients with true severe AS, and similar to patients with systolic heart failure and no evidence of valve disease.[43]

The prognosis of patients with ***paradoxical low-flow, low-gradient severe AS, and LVEF >50%*** is controversial. It has been reported to be worse than those with high-gradient severe AS or those with moderate AS and improves with surgery,[44,45] but in other studies outcome was similar to that of patients with moderate stenosis and did not improve with surgery.[30,46,47] Patients with paradoxical low-flow/low-gradient severe AS can be managed medically with special attention to treating concomitant hypertension,[37] and with serial (6–12 months) clinical and echocardiographic evaluations. The SVi is a predictor of perioperative mortality in all patients with low flow/low gradient AS.[48]

The **choice of prosthesis** is based on patient age and the risk of anticoagulation (see Chapter 23 on prosthetic valves). Indications for **concomitant CABG** are presented in Tables 16.6 and 16.7 in Chapter 16.

Indications for combined valvular and coronary interventions are provided in Tables 16.5 and 16.6 in Chapter 16.

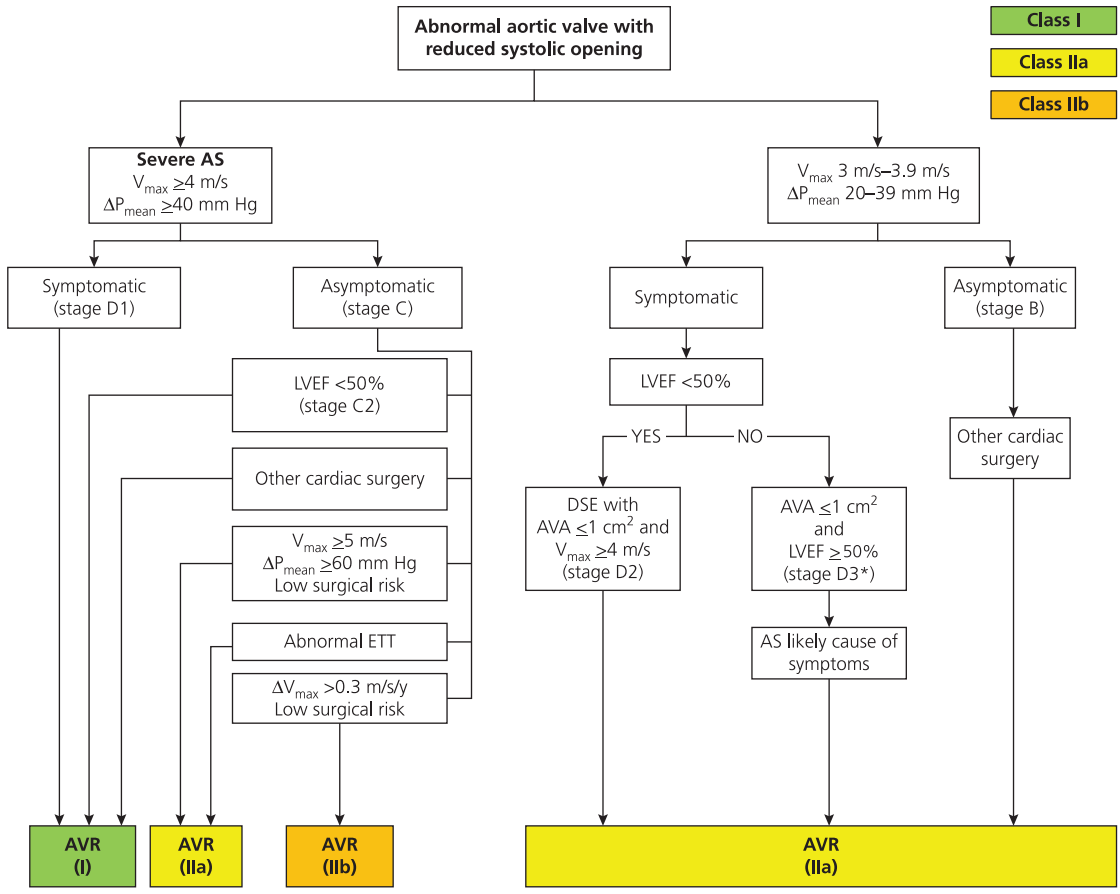

Figure 19.3 AHA/ACC 2014 GL on valve disease. Indications for AVR in patients with AS.

Arrows show the decision pathways that result in a recommendation for AVR. Periodic monitoring is indicated for all patients in whom AVR is not yet indicated, including those with asymptomatic AS (stage D or C) and those with low gradient AS (stage D2 or D3) who do not meet the criteria for intervention.

* AVR should be considered with stage D3 AS only if valve obstruction is the most likely cause of symptoms, stroke volume index is <35 mL/m^2, indexed AVA is ≤0.6 cm^2/m^2, and data are recorded when the patient is normotensive (systolic BP <140 mmHg).

AS indicates aortic stenosis; AVA; aortic valve area; AVR, aortic valve replacement by either surgical or transcatheter approach; BP, blood pressure; DSE, dobutamine stress echocardiography; ETT, exercise treadmill test; LVEF, left ventricular ejection fraction; DPmean, mean pressure gradient; and Vmax, maximum velocity.

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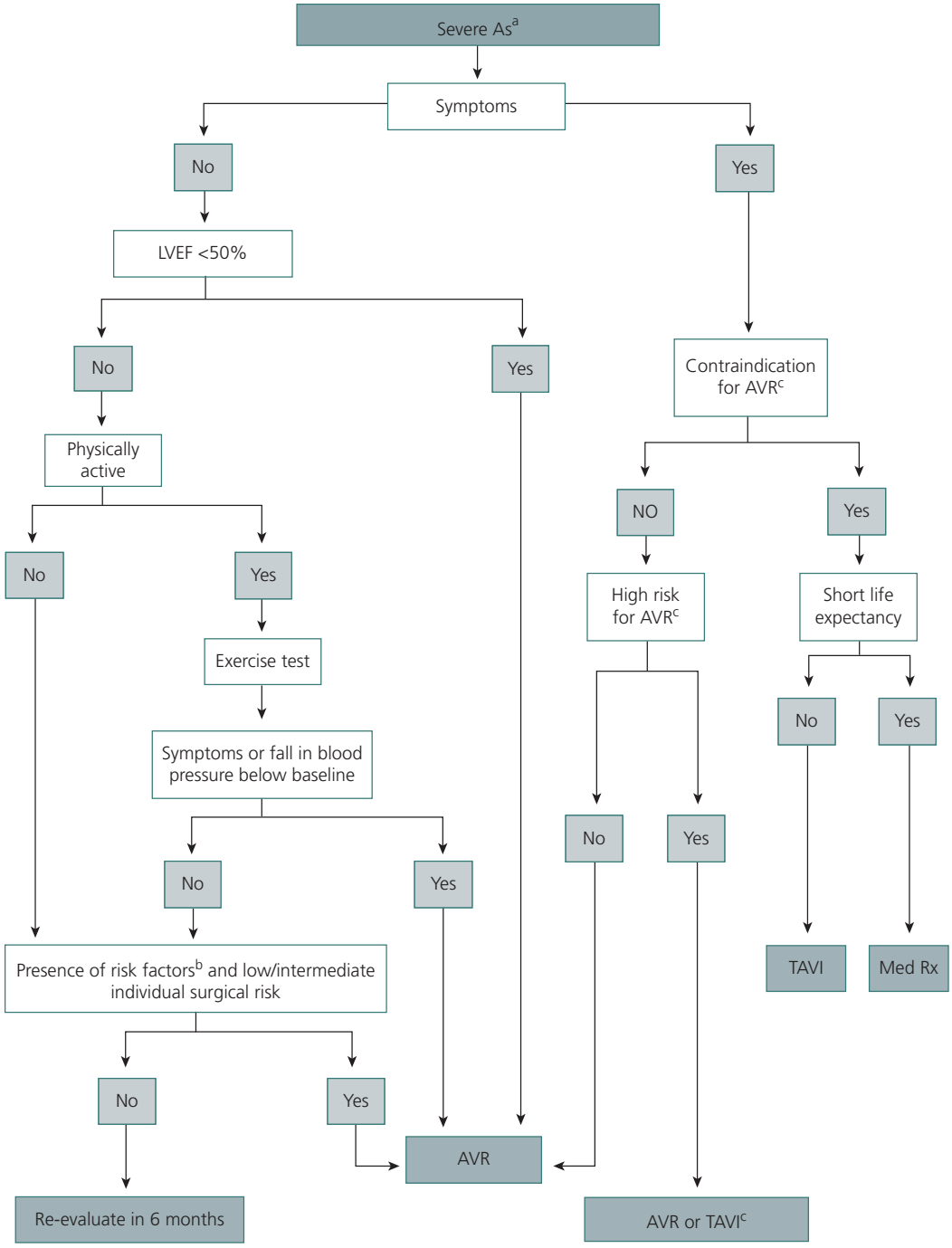

Figure 19.4 ESC 2012 GL on valve disease. Management of severe AS.

AS, aortic stenosis; AVR, aortic valve replacement; BSA, body surface area; LVEF, left ventricular ejection fraction; Med Rx, medical therapy; TAVI, transcatheter aortic valve implantation. a: See Table 19.1 for definition of severe AS. b: Surgery should be considered (IIaC) if one of the following is present: peak velocity >5.5 m/s; severe valve calcification + peak velocity progression ≥0.3 m/s/year. Surgery may be considered (IIbC) if one of the following is present: markedly elevated natriuretic peptide levels; mean gradient increase with exercise >20 mmHg; excessive LV hypertrophy. c: The decision should be made by the 'heart team', according to individual clinical characteristics and anatomy.

ESC 2012 guidelines on the management of valvular heart disease. *Eur Heart J.* 2012;**33**:2451–96 with permission from Oxford University Press.

Transcatheter aortic valve implantation (TAVI/TAVR)

Percutaneous implantation of bioprosthetic valves is evolving fast, with very promising results in selected inoperable (STS score >10 or logistic EuroSCORE >20%) or high-risk patients as judged by a team of surgeons and cardiologists.[49–51] It is a safe option for patients with porcelain aorta,[52] and also an option for failed bioprosthetic valves.[53] The Edwards SAPIEN valve system (Edwards Lifesciences Inc, Irvine, CA) is a trileaflet bovine pericardial valve mounted on a cobalt chromium stent frame (Figure 19.5). The CoreValve system (Medtronic, Minneapolis, MN) is a trileaflet porcine pericardial valve mounted in a self-expanding nitinol stent. They are both FDA-approved now, while other devices are also under study (Portico by St Jude, and Lotus by Boston Scientific).[54] The devices are usually implanted by a transfemoral retrograde approach; the alternatives are a subclavian or transaortic approach. The transapical approach is also an option but carries a higher complication rate.[55,56]

In the first randomized trial published, which used the SAPIEN (PARTNER), TAVI offered better survival than medical therapy in ***inoperable*** patients (PARTNER B). Five-year mortality was 71.8% vs 93.6% for medical therapy, P <0.0001. Risk of stroke was higher with TAVI in the first 30 days (6.7% vs 1.7%, P = 0.02) but not at 5-year follow-up.[50] Inoperable patients were defined as patients with a ≥50% risk of mortality or irreversible morbidity, as judged by two surgeons and one cardiologist. The STS score was 11.2 ± 5.8, but other factors, such a porcelain aorta, chest wall deformities, COPD, and frailty, were also considered. In ***high-risk*** patients (PARTNER A), with predicted risk of mortality ≥15% by two surgeons, STS score 11.8 ± 3.3, and logistic Euroscore 29.3 ± 16, there was similar 5-year mortality with TAVI and surgery (67.8% vs 62.4%). Moderate or severe AR was significantly higher with TAVI (14% vs 1%) and this predicted increased mortality.[51] Strokes were more frequent with TAVI at 30 days (4.6% vs 2.4%, *P* = 0.12), but, at 2 years, they did not differ significantly between the two approaches. Perivalvular regurgitation was more frequent with TAVI and was associated with increased late mortality. In the second randomized trial that used the CoreValve in patients at ***high risk*** for surgery (mean STS score 7.4% and mean logistic EuroSCORE of 18.1), TAVI was found to be superior to surgical AVR.[49] At 1 year, TAVI had lower mortality (14.2% vs 19.1%, *P* = 0.04). At 30 days, mortality (3.3% vs 4.5%) and strokes (4.9% vs 6.2%) were similar, while the need for permanent pacemaker (19.8% vs 7.1%, *P* <0.001) was worse with TAVI. Currently, decisions about TAVI are based on an overall assessment of the patient's risk. This is notable especially since functional decline after TAVI (20%) is mainly predicted by measures of frailty and cognitive impairment, rather than the STS and EuroSCORE.[57]. In the NOTION randomized clinical trial that used the CoreValve in low risk patients (STS 2.9 ± 1.6 and logistic

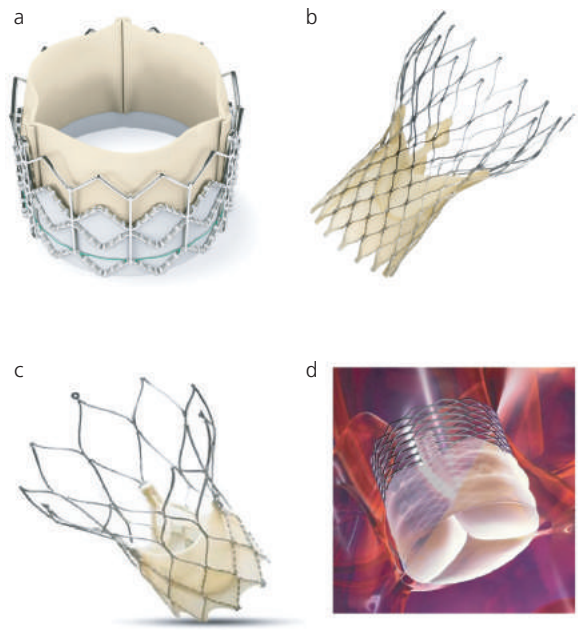

Figure 19.5 a) Sapien (Edwards Lifesciences), b) CoreValve (Medtronic), c) Portico (St Jude), d) Lotus (Boston Scientific).

Euroscore 7.4 ± 1.4), ≥ 70 years old, and without significant coronary artery disease, no significant difference in cardiac death (2.1 vs 3.7%) or the composite rate of death from any cause, stroke, or myocardial infarction at 1 year was found (13.1% vs. 16.3% for TAVI and surgery, respectively). TAVI was significantly better than the surgical group regarding bleeding, acute heart failure, acute kidney injury, new-onset or worsening atrial fibrillation, effective orifice area, and number of days hospitalized. Surgery was better regarding conduction abnormalities requiring permanent pacemaker, NYHA functional class at 1 year, and aortic valve regurgitation.[58]

Procedural complications, including death (approximately 5% 30-day mortality), stroke (3–4%), renal failure (5%), vascular complications (5%), and myocardial infarction (2%), are not significantly different between SAPIEN and CoreValve).[59–65] Valve compression and late embolization are rare complications mainly seen with the SAPIEN valve.[59] Although, in the CHOICE trial, a trend towards reduced stroke rate with the CoreValve was seen (5.8% vs 2.6%, $P = 0.33$),[61] most probably there is no difference between the two valve designs as far as stroke risk is considered.[63] Stroke rates may be higher than previously thought following surgical AVR in patients ≥65 years. The DeNOVO study revealed a 17% incidence, as opposed to 7% provided by the STS database.[66] In the recent report of the US National Registry (STS/ACC TVT) on 12182 patients who underwent TAVI at 1-year follow-up, overall mortality was 23.7%, the stroke rate was 4.1%, and the rate of the composite outcome of death and stroke was 26.0%.[63] Similar stroke rates were reported by the French registry, but lower (<3%) by the German and UK registries in relatively lower risk patients.[60,67] Neuroprotection devices by means of a mesh filter used during TAVI are under study.[68]

Coronary artery occlusion (0.7%) is more common with the SAPIEN and occurs mainly in patients with lower lying coronary ostium and shallow sinuses of Valsalva (10.7 ± 0.4 mm vs 13.3 ± 0.3 mm, and 28.3 ± 0.8 mm vs 31.3 ± 0.6 mm, compared to matched controls, respectively).[69] CMR may detect myocardial injury in up to 18% of patients subjected to TAVI.[70] Extensive LVOT calcification and aggressive annular area oversizing are associated with an increased risk of aortic root rupture during TAVI with balloon expandable prostheses.[71] Moderate AR (grade ≥2) occurs in 13–21% with CoreValve, and 4–13% with SAPIEN, and carries adverse prognostic significance.[61,72] The severity of the dimensionless AR index = ([diastolic blood pressure – left ventricular end-diastolic pressure]/systolic blood pressure) × 100 is of prognostic significance. Patients with AR index <25 have a significantly increased 1-year mortality rate compared with patients with AR index ≥ 25.[73] Pulmonary hypertension indicates increased mortality although it may not be an absolute contraindication for TAVI.[74] There is a higher incidence of the need for permanent pacing with the CoreValve (approximately 25% vs 7%, with rates declining with accumulating experience), and probably LBBB that may occur in up to 30% of patients.[61,75,76] The prognostic significance of LBBB following TAVI is adverse, as also is a QRS duration >160 ms.[76–78] Male sex, baseline conduction disturbances, and intraprocedural AV block are predictors of permanent pacing after TAVI.[79] Permanent pacing does not affect mortality or the need for hospitalization but is detrimental for LV function.[80] Thrombocytopenia (platelet count $<150 \times 10^9$/L) after the procedure is a marker of adverse prognosis.[81] In a recent registry, the incidence of infective endocarditis at one year after TAVI was 0.50%, compared to 0.1–2.3% following surgery. The risk increased with the use of orotracheal intubation and a self-expandable valve system, and staphylococci and enterococci were the most common agents.[82] Valve thrombosis is rare (0.6%) presenting with dyspnoea and increased gradient, and responds to anticoagulant therapy.[83] Moderate or severe MR is not a contraindication and may improve following TAVI,[84] but the expected benefit is smaller with respect to patients with no/mild MR.[85] AF is lower with TAVI than surgical AVR due to avoidance of pericardiotomy.[58,86] Long-term (5 years) results following TAVI have detected a valve failure rate of 3.4%.[87]

Table 19.7 AHA/ACC 2014 GL on valve disease. Choice of surgical or transcatheter intervention in AS

Surgical AVR in patients who meet an indication for AVR with low or intermediate surgical risk	I-A
For patients in whom TAVR or high-risk surgical AVR is being considered, a heart valve team consisting of an integrated, multidisciplinary group of healthcare professionals with expertise in VHD, cardiac imaging, interventional cardiology, cardiac anaesthesia, and cardiac surgery should collaborate to provide optimal patient care.	I-C
TAVR is recommended in patients who meet an indication for AVR who have a prohibitive surgical risk, and a predicted post-TAVR survival >12 months	I-B
TAVR is a reasonable alternative to surgical AVR in patients who meet an indication for AVR and who have high surgical risk	IIa-B
Percutaneous aortic balloon dilation as a bridge to surgical or transcatheter AVR in severely symptomatic patients with severe AS	IIb-C
TAVR is not recommended in patients in whom existing co-morbidities would preclude the expected benefit from correction of AS	III-B

AS indicates aortic stenosis; AVR, aortic valve replacement and TAVR, transcatheter aortic valve replacement.
AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

Table 19.8 ESC 2012 on valve disease. Transcatheter aortic valve implantation (TAVI)

Recommendations for the use of TAVI	
TAVI should only be undertaken with a multidisciplinary 'heart team', including cardiologists and cardiac surgeons and other specialists, if necessary	I-C
TAVI should only be performed in hospitals with cardiac surgery on site	I-C
TAVI is indicated in patients with severe symptomatic AS who are not suitable for AVR as assessed by a 'heart team' and who are likely to gain improvement in their quality of life and to have a life expectancy of >1 year after consideration of their comorbidities	I-B
TAVI should be considered in high-risk patients with severe symptomatic AS who may still be suitable for surgery, but in whom TAVI is favoured by a 'heart team' based on the individual risk profile and anatomic suitability	IIa-B
Contraindications for TAVI	
Absolute contraindications	Absence of a 'heart team' and no cardiac surgery on the site Appropriateness of TAVI, as an alternative to AVR, not confirmed by a 'heart team'
Clinical	Estimated life expectancy <1 year Improvement of quality of life by TAVI unlikely because of co-morbidities Severe primary associated disease of other valves with major contribution to the patient's symptoms, that can be treated only by surgery
Anatomical	Inadequate annulus size (<18 mm, >29 mm*) Thrombus in the left ventricle Active endocarditis Elevated risk of coronary ostium obstruction (asymmetric valve calcification, short distance between annulus and coronary ostium, small aortic sinuses) For transfemoral/subclavian approach: inadequate vascular access (vessel size, calcification, tortuosity)
Relative contraindications	Bicuspid or non-calcified valves Untreated coronary artery disease requiring revascularization Haemodynamic instability LVEF <20% For transapical approach: severe pulmonary disease, LV apex not accessible

* Contraindication when using the current devices.
ESC 2012 guidelines on the management of valvular heart disease. *Eur Heart J*. 2012;**33**:2451–96 with permission from Oxford University Press.

PCI, if indicated, may be performed before TAVI to improve procedural safety. Risk factors are LVEF ≤30% and a STS ≥10).[88] The ESC and ACC/AHA recommendations for TAVI are presented in Tables 19.7 and 19.8.

Balloon valvotomy has only a palliative role or acts as a bridge for surgery in adults with tricuspid stenotic aortic valve.

Bicuspid aortic valve

Patients with a **bicuspid aortic valve** may also have an associated aortopathy consisting of aortic dilation, coarctation, or even aortic dissection. Recommendations are provided in Table 19.9 and a detailed discussion of the condition in Chapter 7. Balloon valvotomy may be the treatment of choice in **congenital (bicuspid or unicuspid) AS** (see also Chapter 7).

Non-cardiac surgery

In patients with severe AS needing elective non-cardiac surgery, the management depends mainly on the presence of symptoms and the type of surgery (Figure 19.6). Guidelines recommend that moderate-risk elective non-cardiac surgery with appropriate intraoperative and post-operative haemodynamic monitoring can be undertaken in asymptomatic severe AS (Table 19.10). Recent data indicate that even high-risk non-cardiac surgery can be performed safely in patients with severe, asymptomatic AS.[90]

Table 19.9 AHA/ACC 2014 GL on valve disease. Bicuspid aortic valve

Diagnostic testing	
An initial TTE to evaluate valve morphology, to measure the severity of AS and AR, and to assess the shape and diameter of the aortic sinuses and ascending aorta	I-B
Aortic magnetic resonance angiography or CT angiography when morphology of the aortic sinuses, sinotubular junction, or ascending aorta cannot be assessed accurately or fully by echocardiography	I-C
Serial evaluation of the size and morphology of the aortic sinuses and ascending aorta by echocardiography, CMR, or CT angiography in patients with a bicuspid aortic valve and an aortic diameter >4.0 cm, with the examination interval determined by the degree and rate of progression of aortic dilation and by family history. In patients with an aortic diameter >4.5 cm, this evaluation should be performed annually	I-C
Intervention	
Operative intervention to repair the aortic sinuses or replace the ascending aorta in patients with a bicuspid aortic valve if the diameter of the aortic sinuses or ascending aorta is >5.5 cm	I-B
Operative intervention to repair the aortic sinuses or replace the ascending aorta is reasonable if the diameter of the aortic sinuses or ascending aorta is >5.0 cm and a risk factor for dissection is present (family history of aortic dissection or if the rate of increase in diameter is ≥0.5 cm per year)	IIa-C
TAVR is not recommended in patients in whom existing co-morbidities would preclude the expected benefit from correction of AS	III-B

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Table 19.10 Non-cardiac surgery in AS

2014 AHA/ACC GL on valve disease	
Moderate-risk elective non-cardiac surgery with appropriate intraoperative and post-operative haemodynamic monitoring in asymptomatic severe AS.	IIa-B
2014 ESC/ESA GL on non-cardiac surgery	
AVR in symptomatic patients with severe AS, scheduled for elective non-cardiac surgery, provided that they are not at high risk of an adverse outcome from valvular surgery.	I-B
AVR in asymptomatic patients with severe AS, scheduled for elective non-cardiac surgery, provided that they are not at high risk of an adverse outcome from valvular surgery.	IIa-C
Elective low- or intermediate-risk non-cardiac surgery in asymptomatic patients with severe AS if there has been no previous intervention on the aortic valve.	IIa-C
In symptomatic patients with severe AS who are scheduled for elective non-cardiac surgery, TAVI or balloon aortic valvuloplasty should be considered by the expert team if they are at high risk of an adverse outcome from valvular surgery.	IIa-C

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ESC/ESA 2014 guidelines on noncardiac surgery: cardiovascular assessment and management. *Eur Heart J*. 2014;**35**:2383–431 with permission from Oxford University Press.

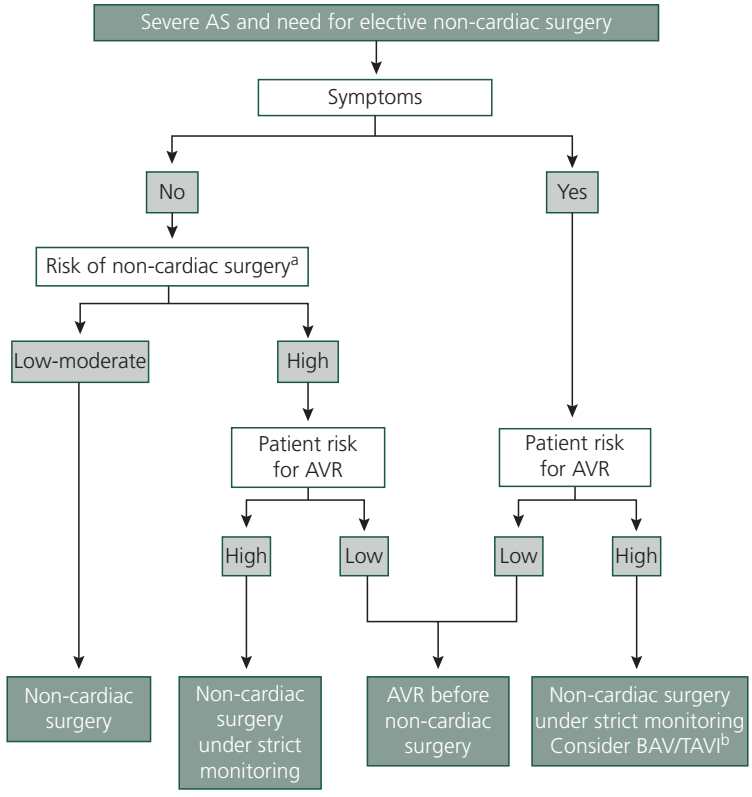

Figure 19.6 ESC 2012 GL on valve disease. Management of severe aortic stenosis and elective non-cardiac surgery according to patient characteristics and the type of surgery.

AS, aortic stenosis; AVR, aortic valve replacement; BAV, balloon aortic valvuloplasty; TAVI, transcatheter aortic valve implantation.
a: Classification into three groups according to the risk of cardiac complications (30-day death and myocardial infarction) for non-cardiac surgery (high risk >5%; intermediate risk 1–5%; low risk <1%) b: Non-cardiac surgery performed only if strictly needed. The choice between balloon aortic valvuloplasty and transcatheter aortic valve implantation should take into account patient life expectancy.
ESC 2012 guidelines on the management of valvular heart disease. *Eur Heart J.* 2012;**33**:2451–96 with permission from Oxford University Press.

Table 19.11 Pregnancy and AS

ESC 2011 GL on pregnancy	
Patients with severe AS should undergo intervention pre-pregnancy if:	
They are symptomatic	I-B
Or LVEF <50% is present	I-C
Asymptomatic patients with severe AS should undergo intervention pre-pregnancy when during exercise testing :	
They develop symptoms	I-C
Or a fall in blood pressure below baseline occurs	IIa-C
AHA/ACC 2014 GL on valve disease	
Exercise testing is reasonable in asymptomatic patients with severe AS (aortic velocity ≥4.0 m/s or mean pressure gradient ≥40 mmHg, stage C) before pregnancy	IIa-C
Valve intervention before pregnancy for symptomatic patients with severe AS (aortic velocity ≥4.0 m/s or mean pressure gradient ≥40 mmHg, stage D)	I-C
Valve intervention before pregnancy for asymptomatic patients with severe AS (aortic velocity ≥4.0 m/s or mean pressure gradient ≥40 mmHg, stage C)	IIa-C
Valve intervention is reasonable for pregnant patients with severe AS (mean pressure gradient ≥40 mm Hg, stage D) only if there is haemodynamic deterioration or NYHA class III to IV HF symptoms	IIa-B

AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol.* 2014;**63**:e57–185.
ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J.* 2011;**32**:3147–97 with permission from Oxford University Press.

Pregnancy

Usually, aortic stenosis in women of childbearing age is congenital (see Chapter 7). In mothers with severe AS with stable severity of stenosis, absence of symptoms of stress testing, and normal BP response, pregnancy outcomes are adequate. Heart failure symptoms may develop in 10% and arrhythmias may occur in 2–35%, but maternal mortality is rare.[91] Fetal complications may also occur in up to 25% of mothers with severe stenosis, including intrauterine growth retardation, preterm birth, and low birth weight. Delivery should be planned in advance, with vaginal delivery preferred for most patients. Early delivery by Caesarean, followed by urgent surgical valve replacement, may be required for life-threatening symptoms if a percutaneous approach is not feasible.[91] Recommendations for pregnancy in patients with valve disease and specifically AS are provided in Tables 16.7 and 19.11.

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Chapter 20

Aortic regurgitation

Epidemiology

The prevalence of aortic regurgitation in the western world ranges from 0.1% in subjects 45–54 years old to 2% in those ≥75 years.[1–3]

Aetiology

Aortic regurgitation (AR) results from abnormalities of the aortic leaflets or the aortic root and annulus (Table 20.1). Degenerative and congenital conditions are the most prevalent causes of **chronic AR** in the western world, although no cause can be identified in certain occasions. Rheumatic heart disease is the most common cause worldwide.[4,5] Amphetamine derivatives, such as fenfluramine, phentermine, and benfluorex, may account for up to 7% with regurgitant valve disease in general.[6] **Acute AR** is most commonly caused by endocarditis, aortic dissection, ruptured fenestration of an aortic leaflet, chest trauma, or prosthetic valve dysfunction.[7] Hypertension is associated with aortic root dilation rather than AR itself. Bicuspid aortic valve is discussed in Chapter 1 on GUCH.

Table 20.1 Aetiology of AR

Diseases that primarily affect the leaflets
Congenital AV abnormalities (mainly bicuspid aortic valve, jet lesion due to subaortic stenosis)
Rheumatic heart disease
Myxomatous degeneration
Atherosclerotic degeneration
Infective endocarditis
VSD
Connective tissue or inflammatory diseases (ankylosing spondylitis, systemic lupus erythematosus, giant cell arteritis, Takayasu's arteritis, Whipple's disease, Crohn's disease)
Antiphospholipid syndrome
Trauma
Anorectic drugs
Diseases that primarily affect the annulus or aortic root
Congenital abnormalities (bicuspid aortic valve, Marfan's)
Idiopathic aortic root dilation
Ehlers–Danlos syndrome
Osteogenesis imperfecta
Aortic dissection
Syphilitic aortitis
Connective tissue diseases (ankylosing spondylitis, psoriatic arthritis, giant cell arteritis, Behçet's syndrome, relapsing polychonditis, Reiter's syndrome)
Ulcerative colitis

Pathophysiology and natural history

Acute AR leads to rapid decompensation due to low forward cardiac output and pulmonary congestion. There is no time for compensatory LV dilation to occur, and there is marked increase in end-diastolic pressure. Although there is some degree of compensation by the Frank–Starling mechanism, the ventricle is functioning on a steep pressure–volume curve because of the lack of chamber dilation. Thus, severe hypotension with a narrow pulse pressure occurs rather

than the systolic hypertension and widened pulse pressure that are characteristics of chronic severe AR. Mitral regurgitation in acute AR may occur either in diastole or in systole (when LVEDP exceeds LA pressure). Diastolic MR results in increased LA pressure and pulmonary oedema and is a specific indicator of acute severe AR.[8]

Chronic AR results in combined volume and pressure overload of the LV that is related to the severity of the regurgitant flow (Tables 20.2 and 20.3). Systolic hypertension can contribute to progressive dilation of the aortic root and subsequent worsening of AR. In early, compensated severe AR, the LV adapts to the volume overload by eccentric hypertrophy with replication of sarcomeres in series and elongation of myofibres. Over time, progressive LV dilation and systolic hypertension increase wall stress and the volume/mass ratio that eventually leads to overt LV systolic dysfunction. In decompensated severe AR, LV systolic dysfunction is accompanied by decreased LV diastolic compliance as a result of hypertrophy and fibrosis, leading to high filling pressures and heart failure symptoms. Asymptomatic patients with AR and normal LV function, but LVESD >50 mm, may develop LV dysfunction and symptoms and a risk of sudden death of 7–19% per year. Asymptomatic patients with LV systolic dysfunction have a higher rate of events, but the LV function may improve following AVR. Symptomatic patients with severe AR have a 25% yearly mortality rate.[9]

Table 20.2 AHA/ACC 2014 GL on valve disease. Stages of chronic AR

Stage	Definition	Valve anatomy	Valve haemodynamics	Haemodynamic consequences	Symptoms
Specific signs					
A	At risk of AR	Bicuspid aortic valve (or other congenital valve anomaly) Aortic valve sclerosis Diseases of the aortic sinuses or ascending aorta History of rheumatic fever or known rheumatic heart disease IE	AR severity: none or trace	None	None
B	Progressive AR	Mild-to-moderate calcification of a trileaflet valve bicuspid aortic valve (or other congenital valve anomaly) Dilated aortic sinuses Rheumatic valve changes Previous IE	**Mild AR:** Jet width <25% of LVOT Vena contracta <0.3 cm RVol <30 mL/beat RF <30% ERO <0.10 cm^2 Angiography grade 1+ **Moderate AR:** Jet width 25–64% of LVOT Vena contracta 0.3–0.6 cm RVol 30–59 mL/beat RF 30–49% ERO 0.10–0.29 cm^2 Angiography grade 2+	Normal LV systolic function Normal LV volume or mild LV dilation	None
C	Asymptomatic severe AR	Calcific aortic valve disease Bicuspid valve (or other congenital abnormality) Dilated aortic sinuses or ascending aorta Rheumatic valve changes IE with abnormal leaflet closure or perforation	**Severe AR:** Jet width >65% of LVOT Vena contracta >0.6 cm Holodiastolic flow reversal in the proximal abdominal aorta RVol ≥60 mL/beat RF ≥50% ERO ≥0.3 cm^2 Angiography grade 3+ to 4+ In addition, diagnosis of chronic severe AR requires evidence of LV dilation	**C1:** Normal LVEF (≥50%) and mild-to-moderate LV dilation (LVESD ≤50 mm) **C2:** Abnormal LV systolic function with depressed LVEF (<50%) or severe LV dilatation (LVESD >50 mm or indexed LVESD <25 mm/m^2)	None: exercise testing is reasonable to confirm status

(*continued*)

Table 20.2 Continued

D	Symptomatic severe AR	Calcific valve disease Bicuspid valve (or other congenital abnormality) Dilated aortic sinuses or ascending aorta Rheumatic valve changes IE with abnormal leaflet closure or perforation	**Severe AR:** Jet width <65% of LVOT Vena contracta >0.6 cm Holodiastolic flow reversal in the proximal abdominal aorta RVol ≥60 mL/beat RF ≥50% ERO ≥0.3 cm^2 Angiography grade 3+ to 4+ In addition, diagnosis of chronic severe AR requires evidence of LV dilation	Symptomatic severe AR may occur with normal systolic function (LVEF ≥50%), mild-to-moderate LV dysfunction (LVEF 40% to 50%), or severe LV dysfunction (LVEF <40%) Moderate-to-severe LV dilation is present	Exertional dyspnoea or angina or more severe HF symptoms

AR indicates aortic regurgitation; ERO, effective regurgitant orifice; HF, heart failure; IE, infective endocarditis; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVOT, left ventricular outflow tract; RF, regurgitant fraction; and RVol, regurgitant volume.

Colour flow jets are composed of three distinct segments: the proximal flow convergence zone (the area of flow acceleration into the orifice), the vena contracta (the narrowest and highest velocity central flow region of the jet), and the jet itself distal to the orifice. Jet and vena contracta estimations at a Nyquist limit of 50–60 cm/s.

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Presentation

Acute AR is usually catastrophic, and the patient may present in cardiogenic shock.

In **chronic AR**, exertional dyspnoea is the most common manifestation, but angina can also occur because of a reduction in coronary flow reserve with predominantly systolic coronary flow.

Physical examination

In **acute AR**, auscultation can be confusing due to the difficulty in distinguishing diastole from systole, and the diastolic murmur may be absent because of rapid equilibration of aortic and LV diastolic pressures. The only clue may be an **absent S_2** in the setting of tachycardia, hypotension, and pulmonary oedema. S_1 may be soft due to early MV closure that is an ominous prognostic sign calling for urgent surgery.

In **chronic AR**, physical findings are related to increased stroke volume and widened blood pressure:

Bounding carotid pulse (**Corrigan's pulse**), head bobbing (**de Musset's sign**), pulsation of the uvula (**Muller's sign**), pistol shot sounds over the femoral artery with compression (**Traube's sign**), and capillary pulsations on the fingernail during compression with a glass slide (**Quincke's sign**) have been described with severe AR.

Diffuse, **hyperdynamic apical impulse** and perhaps **systolic thrill** may be present.

Soft or absent or paradoxically splitted **S_2**.

S_3 may be present that does not necessarily indicates a failing LV.

Decrescendo diastolic murmur at the aortic area or the left sternal border with the patient leaning forward in expiration.

Mid-diastolic apical rumble (**Austin Flint murmur**), possibly due to restriction of the MV opening by the high-pressure AR jet or to vibrations of the anterior mitral leaflet by a posteriorly directed AR jet.

Systolic ejection murmur due to high ejection volume.

Ejection click with bicuspid aortic valve.

Investigations

ECG Normal or LV hypertrophy. With early volume overload, there may be prominent Q waves in leads I, aVL, and V_3 to V_6. With progressive disease, the Q waves decrease, but the total QRS amplitude increases.

Chest radiography Usually normal. Cardiomegaly is a late feature in AS, and calcification is a universal finding but rarely visible on chest X-ray. The proximal ascending aorta may be dilated, particularly in patients with bicuspid valves.

Echocardiography is the standard imaging procedure for assessment of the leaflets and the aortic root and quantitation of the severity of AR (Tables 20.3 and 20.4). M-mode echo is also very useful in demonstrating premature mitral valve closure. Doppler colour flow mapping is used for quantification of AR (Tables 20.2 and 20.3). Vena contracta imaging and assessment of jet eccentricity are used, whereas PISA is less reliable than in MR. Volumetric LV measures and regurgitant fraction are superior to linear diameters in identifying patients at higher risk.[10] In patients with mixed AS and AR, peak aortic jet velocity

Table 20.3 ESC 2012 GL on valve disease

Echocardiographic criteria for definition of severe AR	
Qualitative	
Valve morphology	Abnormal/flail/large coaptation defect
Colour flow regurgitant jet	Large in central jets, variable in eccentric jets[a]
CW signal of regurgitant jet	Dense
Other	Holodiastolic flow reversal in descending aorta (EDV >20 cm/s)
Semi-quantitative	
Vena contracta width (mm)	>6
Upstream vein flow[b]	–
Inflow	–
Other	Pressure half-time <200 ms[c]
Quantitative	
EROA (mm^2)	≥30
RVol (mL/beat)	≥60
+ enlargement of cardiac chambers/vessels	LV

a: At a Nyquist limit of 50–60 cm/s.
b: Unless other reasons for systolic blunting (atrial fibrillation, elevated atrial pressure).
c: Pressure half-time is shortened with increasing left ventricular diastolic pressure, vasodilator therapy, and in patients with a dilated compliant aorta or lengthened in chronic aortic regurgitation.
ESC 2012 guidelines on the management of valvular heart disease. *Eur Heart J.* 2012;**33**:2451–96 with permission from Oxford University Press.

Table 20.4 AHA/ACC 2014 GL on valve disease. Diagnostic testing

Transthoracic echocardiography (TTE) in signs or symptoms of AR (stages A to D) for accurate diagnosis of the cause of regurgitation, regurgitant severity, and LV size and systolic function	I-B
TTE in dilated aortic sinuses or ascending aorta or with a bicuspid aortic valve (stages A and B) to evaluate the presence and severity of AR	I-B
CMR in moderate or severe AR (stages B, C, and D) and suboptimal echocardiographic images for the assessment of LV systolic function, systolic and diastolic volumes, and measurement of AR severity	I-B

ESC 2012 guidelines on the management of valvular heart disease. *Eur Heart J.* 2012;**33**:2451–96 with permission from Oxford University Press.

reflects both stenosis and regurgitation and represents a useful predictive parameter.[11] Transoesophageal echocardiography may be necessary for accurate assessment and particularly when dissection is suspected. The AHA/ACC recommended the frequency of echocardiograms in asymptomatic patients with normal LV function is every 3–5 years for AR of mild severity, every 1–2 years for moderate severity, every 6–12 months for severe AR, and more frequently for a dilating LV.[9]

Computed tomography is useful for the assessment of aortic root dilatation.

Cardiac magnetic resonance is the most promising technique for LV volumes, EF, and regurgitant fraction assessment.[12]

Cardiac catheterization Aortography allows visualization and quantification of the regurgitant jet. Grade 1 AR is contrast appearing in the LV but clearing with each beat. Grade 2 AR is faint opacification of the entire LV over several cardiac cycles. Grade 3 AR is opacification of the entire LV with the same intensity as in the aorta. Grade 4 AR is opacification of the entire LV on the first heart beat with an intensity higher than in the aorta. This method is subjective and depends on the amount of contrast injected and the size of the LV, particularly in significant AR. It is used when the CMR is not available or feasible and in cases with equivocal echo findings.

Coronary angiography is necessary before surgery in patients with risk factors or clinical suspicion of coronary artery disease (see Chapter 15).

Therapy

Acute AR

Vasodilation with sodium nitroprusside is used as a bridge to emergency surgery. Aortic balloon counterpulsation is absolutely contraindicated. Beta blockers prolong diastole and may worsen AR.

Chronic AR

Medical therapy is aimed at reducing systolic hypertension, and thereby wall stress, and improving LV function (Table 20.5). Two randomized studies have shown improvement of LV function with hydralazine and nifedipine, respectively.[13,14] Theoretically, vasodilation with ACE/ARB should also be beneficial. Significant reduction of the regurgitant volume cannot be achieved with medical therapy because the regurgitant orifice area is fixed and the diastolic blood pressure already low. Thus, vasodilator therapy is recommended either in inoperable patients or as a bridge to surgery or in asymptomatic patients who have LV dilation but normal LVEF.

Surgery for AVR is indicated in patients with severe AR and symptoms or signs of reduced LV function (Tables 20.6 and 20.7; Figures 20.1 and 20.2).[9,15] A detailed history for detection of symptoms is therefore essential.[6] AVR should also be considered with progressive increases in LV volume or decreases in LVEF in serial studies. Mortality rates are

Table 20.5 AHA/ACC 2014 GL on valve disease. Medical therapy

Treatment of hypertension (systolic BP >140 mmHg) in chronic AR (stages B and C), preferably with dihydropyridine calcium channel blockers or ACE inhibitors/ARBs	I-B
ACE inhibitors/ARBs and beta blockers in severe AR with symptoms and/or LV dysfunction (stages C2 and D) when surgery is not performed because of co-morbidities	IIa-B

AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

Table 20.6 AHA/ACC 2014 GL on valve disease. Timing of intervention

AVR for symptomatic patients with severe AR regardless of LV systolic function (stage D)	I-B
AVR for asymptomatic patients with chronic severe AR and LVEF <50% (stage C2)	I-B
AVR for patients with severe AR (stage C or D) undergoing cardiac surgery for other indications	I-C
AVR for asymptomatic patients with severe AR with LVEF ≥50% but with severe LV dilation (LVESD >50 mm or >25 mm/m^2) (stage C2)	IIa-B
AVR in patients with moderate AR (stage B) who are undergoing other cardiac surgery	IIa-C
AVR may be considered for asymptomatic patients with severe AR and LVEF ≥50% (stage C1) but with progressive severe LV dilation (LVEDD >65 mm) if surgical risk is low	IIb-C

AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

Table 20.7 ESC 2012 GL on valve disease. AVR in AR

Severe AR	
Symptomatic patients.	I-B
Asymptomatic patients with resting LVEF ≤50%.	I-B
Patients undergoing CABG or surgery of ascending aorta or on another valve.	I-C
Asymptomatic patients with resting LVEF >50% with severe LV dilatation: End-diastolic dimension >70 mm, or	IIa-C
ESD >50 mm (or >25 mm/m^2 BSA)[1]	IIa-C
Aortic root disease (whatever the severity of AR)	
Patients who have aortic root disease with maximal aortic diameter:[2] ≥50 mm for patients with Marfan's syndrome.	I-C
≥45 mm for patients with Marfan's syndrome with risk factors.[3]	IIa-C
≥50 mm for patients with bicuspid valves with risk factors.[4]	IIa-C
≥55 mm for other patients.	IIa-C

1: Changes in sequential measurements should be taken into account.
2: Decision should take into account the shape of the different parts of the aorta. Lower thresholds can be used for combining surgery on the ascending aorta for patients who have an indication for surgery on the aortic valve.
3: Family history of aortic dissection and/or aortic size increase >2 mm/year (on repeated measurements using the same imaging technique, measured at the same aorta level with side-by-side comparison and confirmed by another technique), severe AR or mitral regurgitation, desire of pregnancy.
4: Coarctation of the aorta, systemic hypertension, family history of dissection, or increase in aortic diameter >2 mm/year (on repeated measurements using the same imaging technique, measured at the same aorta level with side-by-side comparison and confirmed by another technique).
AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.
ESC 2012 guidelines on the management of valvular heart disease. *Eur Heart J*. 2012;**33**:2451–96 with permission from Oxford University Press.

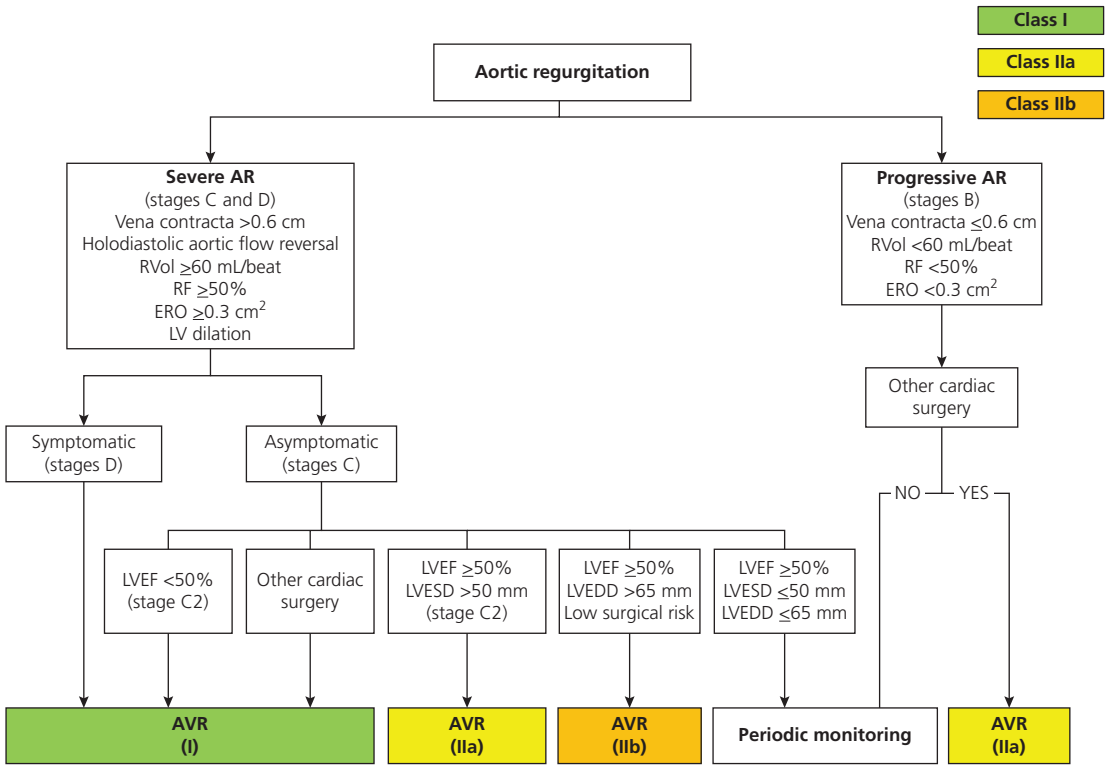

Figure 20.1 AHA/ACC 2014 GL on valve disease. Indications for AVR in chronic AR.

AR indicates aortic regurgitation; AVR, aortic valve replacement (valve repair may be appropriate in selected patients); ERO, effective regurgitant orifice; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; RF, regurgitant fraction; and RVol, regurgitant volume.

AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

presented in Table 23.1 in Chapter 23 on prosthetic heart valves. Repair of a tricuspid or bicuspid AV is also now a possibility.[17]

The choice of prosthesis is based on patient age and the risk of anticoagulation (see Chapter 23 on prosthetic valves). As with other valve diseases, optimum management of patients is hampered by the lack of definitive prospective clinical trials. TAVI may also be an option in inoperable patients, but there is a possibility of requirement of two valves and residual aortic regurgitation.[18] Indications for combined valvular and coronary interventions are provided in Chapter 16.

Non-cardiac surgery

In patients with AR, if LV dysfunction is severe (EF <30%), non-cardiac surgery should only be performed if strictly necessary, after optimization of medical therapy for HF.[15] Moderate-risk elective non-cardiac surgery can be performed with appropriate intraoperative and post-operative haemodynamic monitoring in patients with asymptomatic severe AR and a normal LVEF (AHA/ACC 2014 GL on VHD, AHA/ACC 2014 GL on VHD, and ESC 2014 GL on non-cardiac surgery, IIa-C).[9,19]

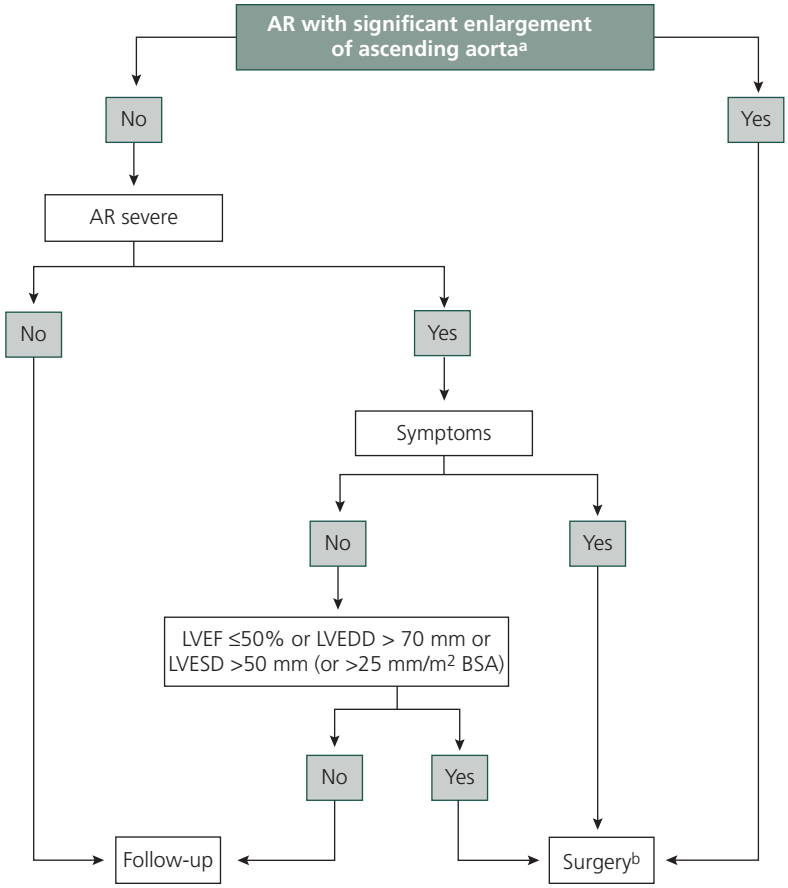

Figure 20.2 ESC GL 2012 GL on valve disease. Management of AR.

a: See Table 20.7 for definition. b: Surgery must also be considered if significant changes in LV or aortic size occur during follow-up.
ESC 2012 guidelines on the management of valvular heart disease. *Eur Heart J*. 2012;**33**:2451–96 with permission from Oxford University Press.

Pregnancy

Recommendations for pregnancy in patients with valve disease are provided in Table 16.7.

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Chapter 21

Tricuspid valve disease

Tricuspid regurgitation

Epidemiology

Tricuspid regurgitation (TR) may affect as much as 0.8% of the general population in the USA (with an estimate of 1.6% for moderate to severe MR).[1] Approximately 30% of patients with severe MR may also have severe TR, and up to 80% of patients referred for echocardiography have some degree of TR.[2]

Aetiology

TR is usually (>75% of cases) functional, i.e. secondary to other disease process, most often mitral and aortic valve disease and atrial fibrillation (Table 21.1). The main cause is pulmonary hypertension secondary to MV disease. Congenital TR is usually due to Ebstein's anomaly. Pacemaker, and especially ICD lead placement, has been reported to result in worsening of TR in up to 25% of patients.[3] However, in a recent study, device lead implantation in patients with a bioprosthetic tricuspid valve was not associated with an increased incidence of significant prosthetic TR.[4]

Pathophysiology and natural history

The tricuspid valve apparatus consists of the annulus, the anterior (largest), septal, and posterior (or inferior) leaflets, chordae, and papillary muscles. Most of the TV annulus lies on the atrioventricular junction; thus its size depends on RV volume. Tricuspid annular dilatation and reduced coaptation of the anterior (mainly) leaflet or right ventricular (RV) dilatation and papillary muscle displacement are the main mechanisms of functional TR.[5] When TR develops, there is a prolonged period of progressive RV and RA volume overload that engenders additional TR until right heart failure develops. PA pressure in functional TR is >55 mmHg. RV failure with severe TR or constrictive

Table 21.1 Causes of TV regurgitation

Functional (morphologically normal leaflets with annular dilatation)
LV dysfunction or valve disease, resulting in pulmonary hypertension Pulmonary hypertension (primary or secondary)
RV dysplasia, infarction
Idiopathic tricuspid annular dilatation Endomyocardial fibrosis
Structural
Acquired
Rheumatic heart disease Endocarditis
Traumatic
Carcinoid heart disease
Endomyocardial fibrosis
Iatrogenic (PPM/ICD lead, radiation, drugs, RV biopsy)
Congenital
Ebstein's anomaly
TV dysplasia, hypoplasia, double-orifice TV

pericarditis are possible causes of cardiac cirrhosis due to ischaemic hepatopathy. The 1-year survival of patients with severe, moderate, or no TR is 64%, 79%, and 92%, respectively.[6]

Moderate and severe TR increase mortality independently of PV pressure or RV function,[6] but in a recent study RV dysfunction, but not significant TR, was independently associated with survival late after left heart valve procedure.[7]

Presentation

Symptoms of TR are often non-specific, and patients with severe TR may be asymptomatic. Symptoms are usually of fatigue and decreased exercise tolerance as a result of low cardiac output. Elevated right atrial (RA) pressure leads to atrial arrhythmias (mainly AF), peripheral oedema, and hepatic congestion, with decreased appetite and abdominal fullness. Eventually, right heart failure with ascites and anasarca develops.

Physical findings

Elevated JVP with a prominent v wave in 35% to 75% of patients with severe TR.

Hepatomegaly is present in 90%, but pulsating liver is noted inconsistently.

The **holosystolic murmur** of TR is heard along the sternal border, increasing in intensity with inspiration as a result of increased systemic venous return (it is heard in <20% of patients with severe TR due to equalization of pressures between the RA and RV).

Investigations

Haemodynamic catheterization is rarely required to confirm the diagnosis of severe TR, and right ventriculography is not helpful because the catheter may induce TR. Echocardiography (2D or preferably 3D) is the main diagnostic tool (Tables 21.2 and 21.3).[1,8,9] Vena contracta width (indirectly reflects the effective regurgitant orifice area) >0.7 cm, large flow convergence (PISA radius >0.9 cm at Nyquist limit of 40 cm/s), and systolic flow reversal in hepatic veins are specific signs of severe TR.[10] An effective regurgitant orifice (ERO) >40 mm^2 indicates adverse clinical outcomes, even for isolated TR.[11] Additional supportive signs are a dense 'dagger-shaped', triangular, early-peaking systolic continuous wave Doppler signal, IVC dilatation and respiratory diameter variation of ≤50%, a prominent E-wave, and RA/RV dilatation. The tricuspid annulus can be measured in diastole from the apical four-chamber view; in this view, an annular diameter >40 mm (or >21 mm/m^2 body surface area) is considered to be dilated.[5] There is major respiratory variation of TR and RV shape, and echocardiographic assessment requires multiplying measurements throughout the cardiac cycle, in order to appropriately assess TR and right ventricular pressure.[11] Cardiac catheterization for pressure measurements may be necessary in case of discordant symptoms and echocardiographic findings (Table 21.4).

Table 21.2 ESC 2012 on valve disease. Echocardiographic criteria for definition of severe TR

Qualitative	
Valve morphology	Abnormal/flail/large coaptation defect
Colour flow regurgitant jet	Very large central jet or eccentric wall impinging jet[1]
CW signal of regurgitant jet	Dense/triangular with early peaking (peak <2 m/s in massive TR)
Other	–
Semi-quantitative	
Vena contracta width (mm)	≥7[a]
Upstream vein flow	Systolic hepatic vein flow reversal
Inflow	E wave dominant >1 m/s[b]
Other	PISA radius >9 mm[c]
Quantitative	
EROA (mm^2)	≥40
RVol (mL/beat)	≥45
+ enlargement of cardiac chambers/vessels	RV, RA, inferior vena cava

a: At a Nyquist limit of 50–60 cm/s.
b: In the absence of other causes of elevated left atrial pressure and of mitral stenosis.
c: Baseline Nyquist limit shift of 28 cm/s.
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Table 21.3 ACC/AHA 2014 GL on valve disease. Stages of TR

Stage	Definition	Valve anatomy	Valve haemodynamics*	Haemodynamic consequences	Symptoms
A	At risk of TR	**Primary** Mild rheumatic change Mild prolapse Other (e.g. IE with vegetation, early carcinoid deposition, radiation) Intra-annular RV pacemaker or ICD lead Post-cardiac transplant (biopsy related) **Functional** Normal Early annular dilation	No or trace TR	None	None or in relation to other left heart or pulmonary/pulmonary vascular disease
B	Progressive TR	**Primary** Progressive leaflet deterioration/destruction Moderate-to-severe prolapse, limited chordal rupture **Functional** Early annular dilation Moderate leaflet tethering	**Mild TR** Central jet area <5.0 cm^2 Vena contracta width not defined CW jet density and contour: soft and parabolic Hepatic vein flow: systolic dominance **Moderate TR** Central jet area 5–10 cm^2 Vena contracta width not defined but <0.70 cm CW jet density and contour: dense, variable contour Hepatic vein flow: systolic blunting	**Mild TR** RV/RA/IVC size normal **Moderate TR** No RV enlargement No or mild RA enlargement No or mild IVC enlargement with normal respirophasic variation Normal RA pressure	None or in relation to other left heart or pulmonary/pulmonary vascular disease
C	Asymptomatic, severe TR	**Primary** Flail or grossly distorted leaflets **Functional** Severe annular dilation (>40 mm or 21 mm/m^2) Marked leaflet tethering	Central jet area <10.0 cm^2 Vena contracta width >0.7 cm CW jet density and contour: dense, triangular with early peak Hepatic vein flow: systolic reversal	RV/RA/IVC dilated with decreased IVC respirophasic variation Elevated RA pressure with 'c-V' wave Diastolic interventricular septal flattening may be present	None, or in relation to other left heart or pulmonary/pulmonary vascular disease
D	Symptomatic, severe TR	**Primary** Flail or grossly distorted leaflets **Functional** Severe annular dilation (>40 mm or 21 mm/m^2) Marked leaflet tethering	Central jet area <10.0 cm^2 Vena contracta width >0.7 cm CW jet density and contour: dense, triangular with early peak Hepatic vein flow: systolic reversal	RV/RA/IVC dilated with decreased IVC respirophasic variation Elevated RA pressure with 'c-V' wave Diastolic interventricular septal flattening Reduced RV systolic function in late phase	Fatigue, palpitations, dyspnoea, abdominal bloating, anorexia, oedema

* Several valve haemodynamic criteria are provided for assessment of severity of TR, but not all criteria for each category will necessarily be present in every patient.

Categorization of severity of TR as mild, moderate, or severe also depends on image quality and integration of these parameters with clinical findings.

CW indicates continuous wave; ICD, implantable cardioverter–defibrillator; IE, infective endocarditis; IVC, inferior vena cava; RA, right atrium; RV, right ventricle; and TR, tricuspid regurgitation.

AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

Table 21.4 AHA/ACC 2014 GL on valve disease. Diagnosis of TR

Transthoracic echocardiography (TTE) to evaluate severity of TR, determine aetiology, measure sizes of right-sided chambers and inferior vena cava, assess RV systolic function, estimate pulmonary artery systolic pressure, and characterize any associated left-sided heart disease	I-C
Invasive measurement of pulmonary artery pressures and pulmonary vascular resistance when clinical and noninvasive data are discordant	IIa-C
Cardiac magnetic resonance (CMR) or real-time 3D echocardiography for assessment of RV systolic function and systolic and diastolic volumes in patients with severe TR (stages C and D) and suboptimal 2D echocardiograms	IIb-C
Exercise testing for the assessment of exercise capacity in patients with severe TR with no or minimal symptoms (stage C)	IIb-C

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Therapy

Diuretics is the only proven therapy for symptomatic relief but, when excessive, may decrease cardiac output (Table 21.5).

Indications for TV surgery in patients with severe TR are (Tables 21.5 and 21.6, and Figure 21.1):[10,13]

- Symptomatic RV failure
- Progressive RV enlargement
- Surgery for MV or other valve disease (even with moderate TR)
- Traumatic TV flail (early surgery is recommended)
- Carcinoid heart disease (high-risk group).

Patients with ERO <40 mm^2 in the context of isolated TR can be treated conservatively.[11] Functional TR with an annular diameter <40 mm can also be treated medically. When the diameter exceeds 40 mm, tricuspid annuloplasty with or without leaflet augmentation is recommended.[5]

Table 21.5 AHA/ACC 2014 GL on valve disease. Management of TR

Medical therapy	
Diuretics for severe TR and signs of right-sided HF (stage D)	IIa-C
Medical therapies to reduce elevated pulmonary artery pressures and/or pulmonary vascular resistance in severe functional TR (stages C and D)	IIb-C
Intervention	
Tricuspid valve surgery for patients with severe TR (stages C and D) undergoing left-sided valve surgery	I-C
Tricuspid valve repair for mild, moderate, or greater functional TR (stage B) at the time of left-sided valve surgery with either 1) tricuspid annular dilation or 2) prior evidence of right HF	IIa-B
Tricuspid valve surgery for symptomatic severe primary TR unresponsive to medical therapy (stage D)	IIa-C
Tricuspid valve repair for moderate functional TR (stage B) and pulmonary artery hypertension at the time of left-sided valve surgery	IIb-C
Tricuspid valve surgery for asymptomatic or minimally symptomatic severe primary TR (stage C) and progressive degrees of moderate or greater RV dilation and/or systolic dysfunction	IIb-C
Reoperation for isolated tricuspid valve repair or replacement for persistent symptoms due to severe TR (stage D) in patients who have undergone previous left-sided valve surgery and who do not have severe pulmonary hypertension or significant RV systolic dysfunction	IIb-C

AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

Table 21.6 ESC 2012 GL on valve disease. Indications for tricuspid valve surgery

Symptomatic patients with severe TS.[a]	I-C
Severe TS undergoing left-sided valve intervention.[b]	I-C
Severe primary or secondary TR undergoing left-sided valve surgery.	I-C
Symptomatic patients with severe isolated primary TR without severe RV dysfunction.	I-C
Moderate primary TR undergoing left-sided valve surgery.	IIa-C
Mild or moderate secondary TR with dilated annulus (≥40 mm or >21 mm/m^2) undergoing left-sided valve surgery.	IIa-C

(*continued*)

Table 21.6 Continued

Asymptomatic or mildly symptomatic patients with severe isolated primary TR and progressive RV dilatation or deterioration of RV function.	IIa-C
After left-sided valve surgery, surgery should be considered in patients with severe TR who are symptomatic or have progressive RV dilatation/dysfunction, in the absence of left-sided valve dysfunction, severe RV or LV dysfunction, and severe pulmonary vascular disease.	IIa-C

a: Percutaneous balloon valvuloplasty can be attempted as a first approach if TS is isolated.
b: Percutaneous balloon valvuloplasty can be attempted if PMC can be performed on the mitral valve.
ESC 2012 guidelines on the management of valvular heart disease. *Eur Heart J*. 2012;**33**:2451–96 with permission from Oxford University Press.

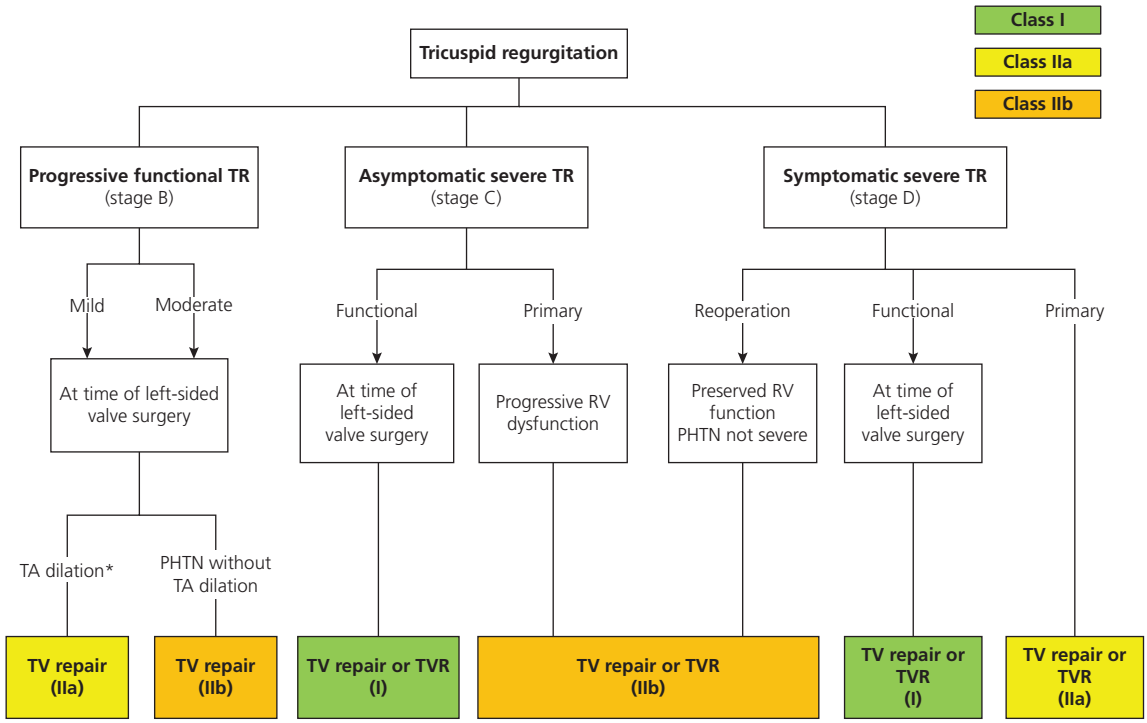

Figure 21.1 AHA/ACC 2014 GL on valve disease. Indications for surgery in TR.

TA dilation is defined by >40 mm on TTE (>21 mm/m^2) or >70 mm on direct intraoperative measurement.
LV indicates left ventricular; PHTN, pulmonary hypertension; RV, right ventricular; TA, tricuspid annular; TR, tricuspid regurgitation; TTE, transthoracic echocardiogram; TV, tricuspid valve; and TVR, tricuspid valve replacement.
AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

TV repair or replacement is the only effective treatment for symptomatic TR, and recently there has been evidence in favour of a more aggressive surgical approach to secondary (functional) TR.[14] Remodelling annuloplasty of the tricuspid valve based on tricuspid dilation (tricuspid annular diameter was greater than twice the normal size (≥ 70 mm) improves functional status of patients undergoing mitral valve repair irrespective of the grade of TR.[15]

Operative mortality for concomitant TV surgery is doubled (up to 4.5%) compared to that for isolated MV surgery but avoids the usual post-operative deterioration of existing TR and results in better mid-term survival. Patients who undergo tricuspid annuloplasty during left-sided heart valve surgery have a poor postoperative clinical outcome, and 10-year survival is limited to 50% to 66%. The presence of either >3.2 cm right ventricular mid-cavity diameter or >0.85 cm^2 tricuspid valve tethering area is associated with adverse events at 1 year after tricuspid annuloplasty.[16]

In patients with both primary and functional TV disease, **TV repair** is associated with better survival than TV replacement. Ring annuloplasty is preferable to

Table 21.7 AHA/ACC 2014 GL on valve disease. Stages of severe TS

Stage	Definition	Valve anatomy	Valve haemodynamics	Haemodynamic consequences	Symptoms
C, D	Severe TS	Thickened, distorted, calcified leaflets	T½ ≥190 ms Valve area ≤1.0cm²	RA/IVC enlargement	None or variable and dependent on severity of associated valve disease and degree of obstruction

The transtricuspid diastolic gradient is highly variable and is affected by heart rate, forward flow, and phases of the respiratory cycle. However, severe TS usually has mean pressure gradients >5 to 10 mmHg at heart rate 70. IVC indicates inferior vena cava; RA, right atrium; T½, pressure half-time; and TS, tricuspid stenosis. AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

Table 21.8 AHA/ACC 2014 GL on valve disease

Intervention in TS	
Tricuspid valve surgery for severe TS at the time of operation for left-sided valve disease	I-C
Tricuspid valve surgery for isolated, symptomatic severe TS	I-C
Percutaneous balloon tricuspid commissurotomy in patients with isolated, symptomatic severe TS without accompanying TR	IIb-C

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purse-string annuloplasty (De Vega).[1,2] Transcatheter TV repair with the Mitralign system has also been tried.[17]

TV replacement is indicated for patients whose valves are not amenable to repair. No difference has been found in survival among patients with mechanical versus biological TV prostheses, but a bioprosthesis is preferred due to the low incidence of thromboembolic complications. Right-sided bioprostheses have superior durability compared with left-sided bioprostheses. Pericardial bioprostheses are generally avoided in the tricuspid position because of leaflet stiffness and risk of obstruction.[8]

Transcatheter TV implantation using various valves is also a new option as an alternative to surgery for high-risk patients or for failing bioprostheses.[17,18]

When severe symptomatic TR is secondary to leaflet perforation or lead impingement from a **pacemaker lead**, removal or repositioning of the lead may decrease the degree of TR. Recently, however, it was shown that lead implantation in patients with a bioprosthetic tricuspid valve was not associated with an increased incidence of significant prosthetic TR.[4]

Asymptomatic patients with severe **carcinoid heart disease** may require valve replacement, enabling partial hepatic resection or liver transplantation. Carcinoid heart disease patients represent a high-risk surgical subgroup primarily because of perioperative haemodynamic lability (carcinoid crisis), characterized by peripheral vasodilatation and hypotension that requires IV octreotide administration.[8]

In patients with **pulmonary hypertension** and severe TR secondary to pulmonary thromboembolic disease, pulmonary thromboendarterectomy alone has been shown to reduce pulmonary hypertension and usually reduces TR severity without the need for concomitant tricuspid annuloplasty. TR secondary to severe primary pulmonary hypertension is usually treated with pulmonary vasodilator and diuretic therapy alone because of the risk of cardiac surgical intervention and overall poor prognosis.

Although **percutaneous balloon mitral valvuloplasty** may result in less TR, TV repair, combined with mitral valve replacement, is better than mitral balloon valvuloplasty alone in patients with severe functional TR, especially if atrial fibrillation or RV enlargement is present.[1]

Recommendations on **pregnancy** are presented in Table 16.7.

Tricuspid stenosis

Epidemiology and aetiology

Tricuspid stenosis (TS) is a very rare condition in developed countries. It is mainly due to rheumatic disease, but only 3% to 5% with rheumatic mitral valve disease have concurrent TS. Other causes are congenital TS, carcinoid, endomyocardial fibrosis, and right atrial tumours.[1,10]

Physical findings and diagnosis

Due to the usual coexistence of mitral valve disease, it is difficult to separate symptoms and signs specific to TS:

SOBOE and **peripheral oedema.**

Elevated JVP with a prominent a wave and slow y descent.

Opening snap, followed by a **diastolic rumbling murmur** at the right sternal border that varies with respiration.

As with TR, physical findings may be subtle and the murmur often inaudible.

Diagnosis is made by echocardiography. TS is considered severe when the valve area is <1.0 cm^2 (Table 21.7), but the accuracy of echocardiography is less than with MS. The 2012 ESC Guideline on valve disease defines severe TS as a valve with mean gradient ≥5 mmHg.[10] TTE is essential in patients with TS to assess the anatomy of the valve complex, evaluate severity of stenosis, and characterize any associated regurgitation and/or left-sided valve disease (AHA/ACC 2014 GL on valve disease, I-C). Invasive haemodynamic assessment may be considered in symptomatic patients when clinical and noninvasive data are discordant (AHA/ACC 2014 GL on valve disease, IIb-C).

Therapy

Valve replacement is usually the only treatment (Tables 21.5 and 21.8). The choice of prosthesis should be individualized. Tricuspid balloon valvotomy might also be considered, but it may result in severe TR. Management in pregnancy is described in Table 16.7.

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Chapter 22

Pulmonary valve disease

Pulmonary valve regurgitation

Aetiology

Mild pulmonary regurgitation (PR) may be a normal finding on Doppler echocardiography. The most common causes of pathologic PR in adults are prior interventions for congenital heart disease, such as tetralogy of Fallot repair or surgical valvotomy for congenital pulmonary stenosis. Other rare causes of PR are congenital pulmonary annular dilation, pulmonary hypertension, rheumatic or carcinoid heart disease, endocarditis, and trauma.[1,2]

Table 22.1 AHA/ACC 2014 GL on valve disease. Stages of severe pulmonic regurgitation

Stage	Definition	Valve anatomy	Valve haemodynamics	Haemodynamic consequences	Symptoms
C, D	Severe PR	Distorted or absent leaflets, annular dilation	Colour jet fills RVOT CW jet intensity and contour: dense laminar flow with steep deceleration slope; may terminate abruptly	Paradoxical septal motion (volume overload pattern) RV enlargement	None or variable and dependent on cause of PR and RV function

CW indicates continuoues wave; PR, pulmonic stenosis; RA, right atrium; RV, right ventricle; RVOT, right ventricular outflow tract.
AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

Table 22.2 AHA 2015 statement on congenital heart disease in the older adult. Published Indications for Pulmonary Valve Replacement

Clinical symptoms
Exercise intolerance
Exertional dyspnea
Arrhythmia
Echocardiographic criteria
RV hypokinesia
Isolated severe pulmonary valve regurgitation
Pulmonary valve regurgitation associated with tricuspid valve regurgitation, pulmonary artery stenosis, or residual VSD
Preoperative RV ejection fraction ≥0.40
Progressive RV dilation
Severe RV dilation
RV end-diastolic volume >170 mL/m^2
RV end-systolic volume >85 mL/m^2
Severe RV dilation and RV dysfunction
Moderate to severe RVOT obstruction (peak Doppler gradient >50 mm Hg)
Electrocardiographic criteria
QRS duration ≥180 ms
Increased QRS duration rate of change (>3.5 ms/y)
Recurrent or sustained arrhythmia
Other
Elapsed time interval from repair >2 y

RV indicates right ventricular; RVOT, right ventricular outflow tract; and VSD, ventricular septal defect.

American Heart Association Council on Clinical Cardiology. Congenital heart disease in the older adult: a scientific statement from the American Heart Association. *Circulation*. 2015;**131**:1884–931 with permission from Wolters Kluwer.

Pathophysiology

Long-standing severe PR results in progressive RV dilation and reduced RV function. RV dilatation is reflected on QRS duration and is associated with ventricular arrhythmias and sudden death. This mechanical-electrical association has been described in patients with repaired tetralogy of Fallot. Significant PR is the main predictor of sudden death in these patients (see Chapter 9).

Physical examination

RV parasternal heave in severe PR with enlarged RV

Systolic ejection murmur increased by inspiration

Soft, **diastolic, decrescendo murmur** best heard in the left upper sternal border. An increase in intensity of the murmur may be noted during inspiration.

ECG findings are non-specific or reflect RV enlargement.

Chest radiography may demonstrate cardiomegaly and pulmonary artery enlargement.

The diagnosis is made by **echocardiography**. Severe PR is indicated by a colour jet filling the outflow tract and a dense continuous wave Doppler signal with a steep deceleration slope (Table 22.1). **Cardiac magnetic resonance** is the imaging modality of choice to assess RV size and function in asymptomatic patients and guide therapy.

Therapy

Medical therapy is not effective in reducing the degree of PR or affecting the impact of PR on the RV. PV replacement is recommended in symptomatic patients (NYHA II or III) and severe PR. The management of asymptomatic patients is controversial. Most would agree that PVR is indicated in: decreased RV systolic function (ejection fraction <40% by cardiac magnetic resonance imaging),

Table 22.3 AHA/ACC 2014 GL on valve disease. Stages of severe pulmonic stenosis

Stage	Definition	Valve anatomy	Valve haemodynamics	Haemodynamic consequences	Symptoms
C, D	Severe PS	Thickened, distorted, possibly calcified leaflets with systolic doming and/or reduced excursion Other anatomic abnormalities may be present, such as narrowed RVOT	V_{max} >4 m/s; peak instantaneous gradient >64 mmHg	RVH Possible RV, RA enlargement Post-stenotic enlargement of main PA	None or variable and dependent on severity of obstruction

PA indicates pulmonary artery; PS, pulmonic stenosis; RA, right atrium; RV, right ventricle; RVH, right ventricular hypertrophy; RVOT, right ventricular outflow; and V_{max}, maximal pulmonic valve jet velocity.
AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

progressive RV dilation (cardiac magnetic resonance imaging RV end-diastolic volume 160 mL/m^2 or 82 mL/m for RV end-systolic volume) or TR related to progressive annular dilatation, severe PR in a patient requiring another cardiac operation, and QRS duration 180 ms or QRS duration increase >3.5 ms/y.[1] Table 22.2 presents published indications as summarized by the AHA 2015 statement on congenital heart disease in the adult.[3] Transcatheter therapeutic options are also emerging.[4]

Pregnancy

Recommendations are presented in Table 16.7.

Pulmonary valve stenosis

Carcinoid syndrome and rheumatic valve disease may cause pulmonary stenosis but essentially always occur in conjunction with other valve disease. Table 22.3 presents the stages of severe PS. The majority (>95%) of pulmonary stenosis cases are related to congenital or genetic disorders and are discussed in Chapter 6.

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Chapter 23

Prosthetic heart valves

Risk stratification for surgery

Surgical risk can be estimated by online risk calculators from the Society of Thoracic Surgeons (http://www.sts.org/quality-research-patient- safety/quality/risk-calculator-and-models/risk-calculator) or the European System for Cardiac Operative Risk Evaluation (EuroSCORE; http://www.euroscore.org). Current risk scores (including EuroSCORE, STS, and Ambler score) are useful but may not always provide a reliable estimate of operative mortality regardless of other patient characteristics.[1] The STS score tends to underestimate risk for AVR, whereas the logistic EuroSCORE overestimates risk for isolated valve surgery.[2] Table 23.1 presents the surgical risk assessment of patients with VHD. Table 23.2 presents reported mortality in valve disease surgery.

Prosthetic heart valves (PHV) are either mechanical or bioprostheses (tissue valves). Tissue engineering is also employed for the creation of tissues analogous to a native human heart valve.[3]

Table 23.1 AHA/ACC 2014 GL on valve disease. Risk assessment combining STS risk estimate, frailty, major organ system dysfunction, and procedure-specific impediments

	Low risk (must meet ALL criteria in this column)	Intermediate risk (any 1 criterion in this column)	High risk (any 1 criterion in this column)	Prohibitive risk (any 1 criterion in this column)
STS PROM[a]	<4% AND	4–8% OR	>8% OR	Predicted risk with surgery of death or major morbidity (all-cause) >50% at 1 y OR
Frailty[b]	None AND	1 index (mild) OR	≥2 indices (moderate to severe) OR	Predicted risk with surgery of death or major morbidity (all-cause) >50% at 1 y OR
Major organ system compromise not to be improved post-operatively[c]	None AND	1 organ system OR	No more than 2 organ systems OR	≥3 organ systems OR
Procedure-specific impediment[d]	None	Possible procedure-specific impediment	Possible procedure-specific impediment	Severe procedure-specific impediment

[a] Use of the STS PROM to predict risk in a given institution with reasonable reliability is appropriate only if institutional outcomes are within 1 standard deviation of STS average observed/expected ratio for the procedure in question.
[b] Seven frailty indices: Katz Activities of Daily Living (independence in feeding, bathing, dressing, transferring, toileting, and urinary continence) and independence in ambulation (no walking aid or assist required or 5-meter walk in <6 s). Other scoring systems can be applied to calculate no, mild, or moderate to severe frailty.
[c] Examples of major organ system compromise: cardiac—severe LV systolic or diastolic dysfunction or RV dysfunction, fixed pulmonary hypertension; CKD stage 3 or worse; pulmonary dysfunction with FEV_1 <50% or $DLCO_2$ <50% of predicted; CNS dysfunction (dementia, Alzheimer's disease, Parkinson's disease, CVA with persistent physical limitation); GI dysfunction—Crohn's disease, ulcerative colitis, nutritional impairment, or serum albumin <3.0; cancer—active malignancy; and liver—any history of cirrhosis, variceal bleeding, or elevated INR in the absence of VKA therapy.
[d] Examples: tracheostomy present, heavily calcified ascending aorta, chest malformation, arterial coronary graft adherent to posterior chest wall, or radiation damage.
CKD, indicates chronic kidney disease; CNS, central nervous system; CVA, stroke; $DLCO_2$, diffusion capacity for carbon dioxide; FEV_1, forced expiratory volume in 1 s; GI, gastrointestinal; INR, international normalized ratio; LV, left ventricular; PROM, predicted risk of mortality; RV, right ventricular; STS, Society of Thoracic Surgeons; and VKA, vitamin K antagonist.
AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

Table 23.2 ESC 2012 GL on valve disease. Operative mortality after surgery for valvular heart disease

	EACTS (2010)	STS (2010)	UK (2004–2008)	Germany (2009)
Aortic valve replacement, no CABG (%)	2.9 (40 662)	3.7 (25 515)	2.8 (17 636)	2.9 (11 981)
Aortic valve replacement + CABG (%)	5.5 (24 890)	4.5 (18 227)	5.3 (12 491)	6.1 (9113)
Mitral valve repair, no CABG (%)	2.1 (3231)	1.6 (7293)	2 (3283)	2 (3335)
Mitral valve replacement, no CABG (%)	4.3 (6838)	6.0 (5448)	6.1 (3614)	7.8 (1855)
Mitral valve repair/replacement + CABG (%)	6.8/11.4 (2515/1612)	4.6/11.1 (4721/2427)	8.3/11.1 (2021/1337)	6.5/14.5 (1785/837)

(in brackets): number of patients; EACTS: European Association for Cardiothoracic Surgery;
STS: Society of Thoracic Surgeons (USA). Mortality for STS includes first and redo interventions.
ESC 2012 guidelines on the management of valvular heart disease. *Eur Heart J*. 2012;**33**:2451–96 with permission from Oxford University Press.

Mechanical valves

Ball-cage (Starr–Edwards)

Tilting disc (Medtronic-Hall, Omniscience, and the old Lillihei–Kaster and Bjork–Shiley valves)

Bileaflet (St Jude and CarboMedics).

Randomized and observational long-term studies have shown good and comparable outcomes with FDA-approved mechanical valves, such as the Starr–Edwards valve, the Medtronic-Hall valve, and the St Jude Medical valve for AVR and MVR.[4] However, the bileaflet valves are the most commonly implanted due to low bulk and better haemodynamics and lower thrombogenicity in the mitral position. The Starr–Edwards, although the most durable valve, has a higher risk of haemolysis and thrombogenicity and is not suitable for MVR.

Tissue valves (bioprostheses)

Porcine stented xenografts (heterografts) (Hancock, Carpentier–Edwards Perimount, Medtronic Intact).

Porcine stentless xenografts (Medtronic Freestyle, Edwards Prima, St Jude) are recently developed and are supposed to offer better haemodynamics.

Pericardial bovine xenografts are fabricated valves (Carpentier–Edwards PERIMOUNT Magna/Magna Ease; Sorin Pericarbon, Sorin Mitroflow).

Table 23.3 ESC 2012 GL on valve disease. Choice of the aortic/mitral prosthesis

In favour of a mechanical prosthesis	
Desire of the informed patient and no contraindications for long-term anticoagulation.[1]	I-C
Patients at risk of accelerated structural valve deterioration.[2]	I-C
Patients already on anticoagulation due to a mechanical prosthesis in another valve position.	I-C
Patients aged <60 years for prostheses in the aortic position and <65 years for prostheses in the mitral position.[3]	IIa-C
Patients with a reasonable life expectancy[4] for whom future redo valve surgery would be at high risk.	IIa-C
Patients already on long-term anticoagulation due to high risk of thromboembolism.[5]	IIb-C
In favour of a bioprosthesis	
Desire of the informed patient.	I-C
Good quality anticoagulation is unlikely (compliance problems; not readily available) or contraindicated because of high bleeding risk (prior major bleed; co-morbidities; unwillingness; compliance problems; lifestyle; occupation).	I-C
For reoperation for mechanical valve thrombosis despite good long-term anticoagulant control.	I-C
Patients for whom future redo valve surgery would be at low risk.	IIa-C
Young women contemplating pregnancy.	IIa-C
Patients aged >65 years for prosthesis in aortic position or >70 years in mitral position or those with life expectancy[6] lower than the presumed durability of the bioprosthesis.[7]	IIa-C

1: Increased bleeding risk because of co-morbidities, compliance concerns, geographic, lifestyle, and occupational conditions.
2: Young age (<40 years), hyperparathyroidism.
3: In patients aged 60–65 years who should receive an aortic prosthesis and those between 65 and 70 years in the case of mitral prosthesis, both valves are acceptable and the choice requires careful analysis of other factors than age.
4: Life expectancy should be estimated >10 years, according to age, gender, co-morbidities, and country-specific life expectancy.
5: Risk factors for thromboembolism are atrial fibrillation, previous thromboembolism, hypercoagulable state, severe left ventricular systolic dysfunction.
6: Life expectancy should be estimated according to age, gender, co-morbidities, and country-specific life expectancy.
7: In patients aged 60–65 years who should receive an aortic prosthesis and those 65–70 years in the case of mitral prosthesis, both valves are acceptable and the choice requires careful analysis of factors other than age.
ESC 2012 guidelines on the management of valvular heart disease. *Eur Heart J*. 2012;**33**:2451–96 with permission from Oxford University Press.

Table 23.4 ACC/AHA 2014 GL on valve disease

Recommendations for prosthetic valve choice	
Choice of valve intervention and prosthetic valve type should be a shared decision-making process	I-C
A bioprosthesis in patients of any age for whom anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired	I-C
A mechanical prosthesis for AVR or MVR in patients <60 years who do not have a contraindication to anticoagulation	IIa-B
A bioprosthesis in patients more than 70 years of age	IIa-B
Either a bioprosthetic or mechanical valve in patients between 60–70 years	IIa-B
Replacement of the aortic valve by a pulmonary autograft (the Ross procedure), when performed by an experienced surgeon, in young patients when VKA anticoagulation is contraindicated or undesirable	IIb-C

AVR indicates aortic valve replacement; MVR, mitral valve replacement; and VKA, vitamin K antagonist.
AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

Homograft (allograft) aortic valves harvested from cadavers.

Autograft aortic valves. Fabricated from the patients' own pericardium or pulmonary autografts (Ross principle).

Three randomized trials have compared mechanical with bioprosthetic valves. In the old VA and Edinburgh randomized trials that were conducted in the 1970s, mechanical valves showed better survival (especially in the aortic position) and less reoperation but a higher rate of bleeding.[5,6] In the third RCT that was conducted with modern valves in the 1990s, mechanical valves had a similar survival rate, thromboembolism, bleeding, and endocarditis with bioprosthetic ones, but a significantly lower risk of valve failure and reoperation for aortic valve replacement.[7]

Recent reports from the STS National and New York State Databases showed that among AVR and MVR patients, long-term mortality rates were similar for bioprosthetic versus mechanical valve patients. Bioprostheses were associated with a higher long-term risk of reoperation and endocarditis, but a lower risk of stroke and haemorrhage.[8–10] In general, the risk of need

Table 23.5 ACC/AHA 2014 GL on valve disease

Follow-up of prosthetic valve choice	
An initial TTE study after prosthetic valve implantation for evaluation of valve haemodynamics	I-B
Repeat TTE if there is a change in clinical symptoms or signs suggesting valve dysfunction	I-C
TEE when clinical symptoms or signs suggest prosthetic valve dysfunction	I-C
Annual TTE after the first 10 years, even in the absence of a change in clinical status	IIa-C

AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

for reoperation with a bioprosthetic valve is inversely related to the patient's age at the time of implantation, with a rate of structural deterioration 15 to 20 years after implantation of only 10% in patients 70 years of age at the time of implantation compared with 90% in those 20 years of age at the time of implantation.[11] Mechanical valves are durable in patients of any age with a low risk of reoperation. Thus, mechanical valves appear to have less structural deterioration beyond 10 years, and especially in the young, but require anticoagulation for life and patients are at an increased risk of haemorrhagic complications. They are preferred in patients <60 years of age for AVR and 65 years for MVR and in surgery for infective endocarditis, as well as in patients in need of anticoagulation for AF (Tables 23.3 and 23.4).[4,11,12] An exception is women at childbearing age, given the risk of anticoagulation and thromboembolism during pregnancy. A mechanical valve is also recommended in patients on chronic haemodialysis, based on the concern of accelerated calcification of bioprosthetic valves in patients with end-stage renal disease, but no significant difference in survival of dialysis patients after cardiac valve replacement with tissue versus mechanical valves has been demonstrated.[13,14]

Continuous evolution of valve technology, especially with bioprostheses, as well as patient preferences should be taken into account for PHV selection in the current era. Glutaraldehyde-preserved bioprostheses without antimineralization treatment are at high risk of calcification, and recently a high rate of valve deterioration was reported for Sorin Mitroflow bioprostheses implanted in the aortic position of young patients.[15,16] In addition, the possibility of a valve-in-valve approach with TAVI in patients with failed surgical bioprostheses may result in implantation of bioprostheses in younger patients.[17]

The Ross procedure is performed for aortic valve disease. The patient's own PV and adjacent main pulmonary artery are removed and used to replace the AV and, if necessary, the aortic root with reimplantation of the coronary arteries into the graft. A human pulmonary or aortic homograft is inserted in the pulmonary position. However, reoperations after the Ross procedure, when required, may be complex, frequently involving multiple structures, and carry significant morbidity.[18] The value of this approach, particularly in adults with rheumatic heart disease or AR, is questionable. Table 23.5 presents a guide for follow-up of operated patients.

Anticoagulation

Target INR for mechanical prostheses is presented in Tables 23.6 and 23.7, and Figure 23.1. As a general rule, for mechanical prostheses in aortic position, an INR of 2–3 is indicated for bileaflet and Medtronic-Hall valves and 2.5–3.5 for the others. For MVR, an INR of 2.5–3.5 is targeted. Bioprostheses (and MV repair) require anticoagulation for 3 months post-operatively according to current guidelines; however, continuation of warfarin for up to 6 months resulted in reduced cardiovascular mortality in a recent large registry.[19] Low-dose aspirin is recommended in all patients receiving warfarin for a mechanical

Table 23.6 ESC GL 2012 GL on valve disease

Target INR in patients with mechanical prosthetic valves		
Prosthesis thrombogenicity[a]	**Patient-related risk factors[b]**	
	No risk factor	**Risk factor ≥1**
Low	2.5	3.0
Medium	3.0	3.5
High	3.5	4.0

a: Prosthesis thrombogenicity:
Low: Carbomedics, Medtronic-Hall, St Jude Medical, ON-X
Medium: other bileaflet valves
High: Lillehei–Kaster, Omniscience, Starr–Edwards, Bjork–Shiley, and other tilting-disc valves.
b: Patient-related risk factors: mitral or tricuspid valve replacement; previous thromboembolism; atrial fibrillation; left atrial diameter >50 mm; mitral stenosis of any degree, LVEF <35%.
ESC 2012 guidelines on the management of valvular heart disease. *Eur Heart J*. 2012;**33**:2451–96 with permission from Oxford University Press.

Table 23.7 Antithrombotic therapy with prosthetic valves

ACC/AHA 2014 GL on valve disease	
Anticoagulation with a VKA and INR monitoring in patients with a mechanical prosthetic valve	I-A
Anticoagulation with a VKA to achieve an INR of 3.0 in patients with a mechanical AVR and additional risk factors for thromboembolic events (AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions) or an older-generation mechanical AVR (such as ball-in-cage)	I-B
Anticoagulation with a VKA to achieve an INR of 3.0 in patients with a mechanical MVR	I-B
Aspirin 75–100 mg daily in addition to anticoagulation with a VKA in patients with a mechanical valve prosthesis	I-A
Aspirin 75–100 mg per day in all patients with a bioprosthetic aortic or mitral valve	IIa-B
Anticoagulation with a VKA for the first 3 months after bioprosthetic MVR or repair to achieve an INR of 2.5	IIa-C
Anticoagulation, with a VKA, to achieve an INR of 2.5 for the first 3 months after bioprosthetic AVR	IIb-B
Clopidogrel 75 mg daily for the first 6 months after TAVR in addition to lifelong aspirin 75 mg to 100 mg daily	IIb-C
Anticoagulant therapy with oral direct thrombin inhibitors or anti-Xa agents should not be used in patients with mechanical valve prostheses	III-B (harm)
ESC 2012 GL on valve disease. Indications for antithrombotic therapy after valvular surgery	
Lifelong oral anticoagulation for all patients with a mechanical prosthesis.	I-B
Lifelong oral anticoagulation patients with bioprostheses who have other indications for anticoagulation.[1]	I-C
Addition of low-dose aspirin in patients with a mechanical prosthesis and concomitant atherosclerotic disease.	IIa-C
Addition of low-dose aspirin should in patients with a mechanical prosthesis after thromboembolism despite adequate INR.	IIa-C
Oral anticoagulation for the first 3 months after implantation of a mitral or tricuspid bioprosthesis.	IIa-C
Oral anticoagulation for the first 3 months after mitral valve repair.	IIa-C
Low-dose aspirin for the first 3 months after implantation of an aortic bioprosthesis.	IIa-C
Oral anticoagulation for the first 3 months after implantation of an aortic bioprosthesis.	IIb-C

1: Atrial fibrillation, venous thromboembolism, hypercoagulable state, or, with a lesser degree of evidence, severely impaired left ventricular dysfunction (ejection fraction <35%).
AHA/ACC 2014 guideline for the management of patients with valvular heart disease. J Am Coll Cardiol. 2014;63:e57–185.
ESC 2012 guidelines on the management of valvular heart disease. *Eur Heart J.* 2012;**33**:2451–96 with permission from Oxford University Press.

prosthesis. If INR >5, warfarin is withheld, and the INR is determined after 24 h. The American College of Chest Physicians (ACCP) guidelines recommend oral vitamin K (phytomenadione, 1–2.5 mg) only when INR is >10 in the absence of bleeding.[20] Intravenous vitamin K (1–2 mg) may also be given, although, at 24h, oral vitamin K produces similar results. Oral dose is 2.5 mg or 1–2 mg of the IV preparation in a cup of orange juice. Pharmacogenetic testing for guiding doses, by means of genotyping for variants CYP2C9 and VKORG1 that are associated with reduced clearance and thus a decrease in warfarin requirement, is not clinically useful.[21,22,23] Dabigatran should not be used for anticoagulation in the presence of mechanical prosthetic valves (FDA alert December 2012). The RE-ALIGN trial was prematurely stopped due to increased incidence of thrombotic events with dabigatran compared to warfarin.[24] No data exist for bioprosthetic valves in this respect. In patients with a history of stroke before prosthetic valve insertion, the addition of aspirin (75–100 mg od) to anticoagulation is recommended.[25] If the patient has a stroke despite adequate anticoagulation, addition of aspirin 325 mg od or an increased INR target are needed.[25] The development of portable anticoagulation monitors has enabled self-testing and self-adjustment of anticoagulation therapy.[26]

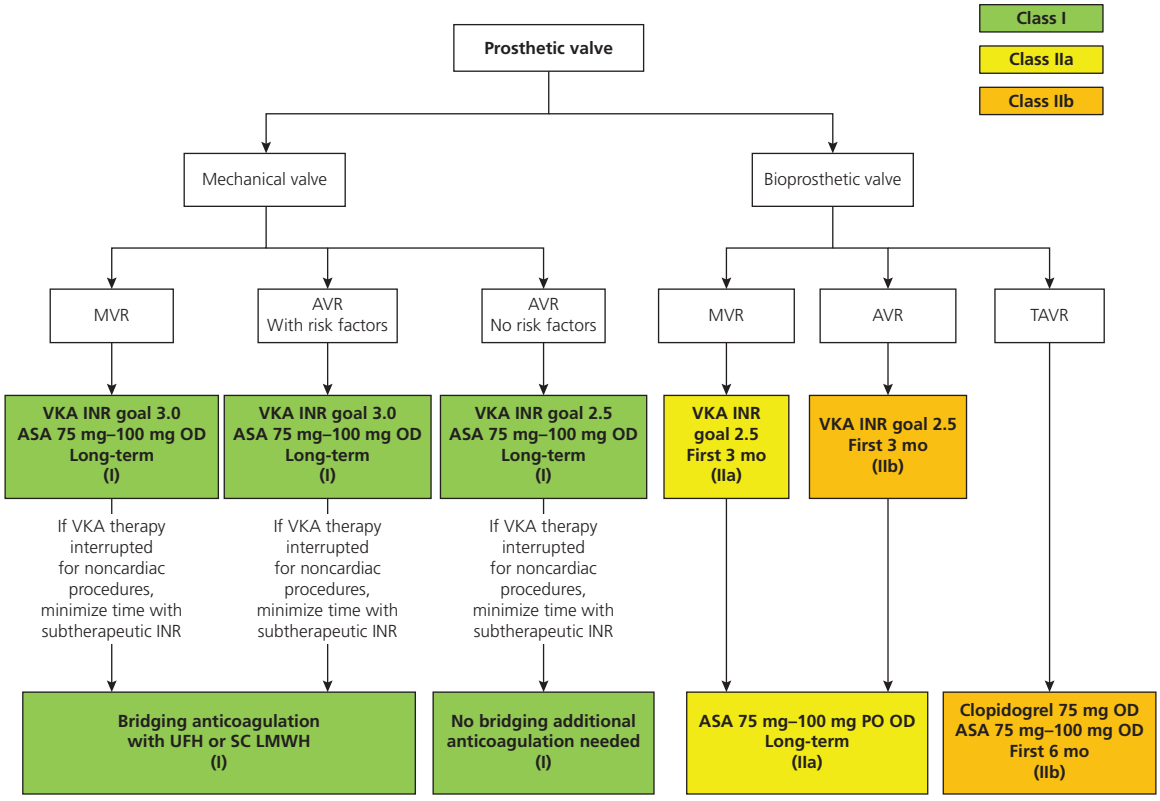

Figure 23.1 AHA/ACC 2014 GL on valve disease. Anticoagulation for prosthetic valves

Risk factors include AF, previous thromboembolism, LV dysfunction, hypercoagulable condition, and older-generation mechanical AVR.
AF indicates atrial fibrillation; ASA, aspirin; AVR, aortic valve replacement; INR, international normalized ratio; LMWH, low-molecular-weight heparin; MVR, mitral valve replacement; PO, by mouth; OD, every day; SC, subcutaneous; TAVR, transcatheter aortic valve replacement; UFH, unfractionated heparin; and VKA, vitamin K antagonist.
AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

Bridging to non-cardiac surgery

The risk of thromboembolism without anticoagulation in the presence of a mechanical prosthesis is 0.03 to 0.05 per day. For major surgical procedures the AHA/ACC 2014 guidelines are presented in Table 23.8. However, the optimal periprocedural anticoagulation is not established. In a recent meta-analysis, heparin bridging in patients receiving vitamin K antagonists for AF, PHV, or VTE conferred a >5-fold increased risk for bleeding, whereas the risk of thromboembolic events was not significantly different between bridged

Table 23.8 AHA/ACC 2014 GL on valve disease

Bridging therapy and management of excessive anticoagulation and bleeding	
Continuation of VKA anticoagulation with a therapeutic INR in patients undergoing minor procedures (such as dental extractions or cataract removal) where bleeding is easily controlled	I-C
Temporary interruption of VKA anticoagulation, without bridging agents while the INR is subtherapeutic, in patients with a bileaflet mechanical AVR and no other risk factors for thrombosis who are undergoing invasive or surgical procedures	I-C
Bridging anticoagulation with either intravenous UFH or subcutaneous LMWH during the time interval when the INR is subtherapeutic preoperatively in: 1) mechanical AVR and any thromboembolic risk factor, 2) older-generation mechanical AVR, or 3) mechanical MVR	I-C
Administration of fresh frozen plasma or prothrombin complex concentrate for emergency noncardiac surgery or invasive procedures	IIa-C
Administration of fresh frozen plasma or prothrombin complex concentrate in patients with mechanical valves and uncontrollable bleeding who require reversal of anticoagulation	IIa-B

AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

and non-bridged patients. The use of therapeutic dose LMWH was associated with an increased risk of bleeding compared with prophylactic or intermediate dose.[27] Minor procedures, such as dental extraction, do not require interruption of anticoagulation. Alternatively, warfarin may be stopped 2–3 days before the procedure or a prohaemostatic agent (i.e. tranexamic acid as a 5 mL oral dose, 5–10 min before the dental procedure, and 3–4 times daily for 1–2 days after the procedure) may be given with continuation of warfarin.[28] Patients with bileaflet mechanical aortic valves in sinus rhythm and no previous thromboembolism are low risk, and no bridging is required for interruption of warfarin.[29] Implantation of pacemakers or defibrillators in patients with moderate to high thromboembolic risk does not necessitate interruption of warfarin (INR 2–3.5) since heparin use is associated with more pocket haematomas.[30] When bridging is required, SC LMWH is convenient, but, in patients with stage IV renal failure, anti-Xa monitoring is required while, in stage V, IV UFH is recommended.[29] The management of patients on warfarin who present with an ACS is discussed in the Chapter 52 on AF.

Haemorrhage

In major bleeding four-factor prothrombin complex concentrate is preferred to fresh frozen plasma since >1500 mL of fresh frozen plasma are needed to achieve a meaningful increase in coagulation factor levels.[31,32] In the case of intracerebral haemorrhage, reversal of anticoagulation with IV vitamin K (1-2 mg to achieve an INR <1.3) is needed. Intensive treatment to lower the blood pressure with a target systolic level of <180 mmHg is recommended,[33] but there has been evidence that values <160-140 mmHg may reduce haematoma enlargement and improve functional outcomes.[34,35] After documentation of cessation of bleeding low-dose heparin may be started 1-4 days from onset.[33]

Thrombosis of prosthetic valves

Prosthetic valve thrombosis in the current era has a reported incidence of 0.03 to 0.13% per patient-year,[5] although it used to be up to 8% with the initial mechanical valves. The major contributing factors are inadequate anticoagulant therapy and mitral location of the prosthesis. Obstruction of prosthetic valves may be caused by thrombus formation, pannus ingrowth, or both. If the prosthesis is obstructed by pannus, the valve needs to be replaced. Transthoracic echocardiography can assess haemodynamic severity and follow resolution of valve dusfunction, and transoesophageal echocardiography is indicated to assess thrombus size and valve motion (AHA/ACC 2014 GL on VHD, I-B). Fluoroscopy or CT may also be used for assessing valve motion (AHA/ACC 2014 GL on VHD, IIa-C). Emergency surgery is recommended for a thrombosed left-sided prosthetic valve and NYHA III–IV symptoms or a large clot (>10 mm) or peripheral embolism (Table 23.9, and Figures 23.2–23.4). Surgery is associated with a mortality of 15%, but most of reported patients are NYHA class III/IV.[36] Fibrinolytic therapy for a left-sided prosthetic valve obstructed by thrombus may be considered for small thrombi <10 mm as determined by transoesophageal echocardiography in stable or inoperable patients. Complete success of thrombolysis is achieved in 70% of cases. Fibrinolysis should be also considered in critically ill patients unlikely to survive surgery, situations in which surgery is not immediately available, and in thrombosis of **tricuspid** or **pulmonary valve** replacements, because of the higher success rate and low risk of systemic embolism.[12] It is recommended as the first-line treatment for obstructive valve thrombosis, independent of NYHA class and thrombus size if there are no contraindications, by the Society for Heart Valve Disease.[37] Fibrinolysis is less likely to be successful in ***mitral*** prostheses, in chronic thrombosis, or in the presence of pannus that may be difficult to distinguish from thrombus. In case of haemodynamic instability a short protocol is recommended, using either intravenous recombinant tissue plasminogen activator 10 mg bolus + 90 mg in 90 minutes with UFH, or streptokinase 1 500 000 U in 60 minutes without UFH. Longer durations of infusions can be used in stable patients.[12] If fibrinolytic therapy is successful, it should be followed by intravenous UFH until warfarin achieves an INR of 3.5 for aortic and 4 for mitral prosthetic valves. Low-dose aspirin is also given. Fibrinolysis is associated with a mortality of 8%,[36] and risk of cerebral embolism 12–15% depending on the size of the clot (odds ratio of 2.41 per 1 cm^2 increment).[38]

Table 23.9 AHA/ACC 2014 GL on valve disease

Thrombosis of prosthetic heart valves	
Medical therapy	
Fibrinolytic therapy for a thrombosed left-sided prosthetic heart valve,fibrinolytic therapy for a thrombosed left-sided prosthetic heart valve, recent onset (<14 days) of NYHA class I to II symptoms, and a small thrombus (<0.8 cm^2)	IIa-B
Fibrinolytic therapy for thrombosed right-sided prosthetic heart valves	IIa-B
Intervention	
Emergency surgery for a thrombosed left-sided prosthetic heart valve with NYHA class III to IV symptoms	I-B
Emergency surgery for a thrombosed left-sided prosthetic heart valve with a mobile or large thrombus (>0.8 cm^2)	IIa-C

AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

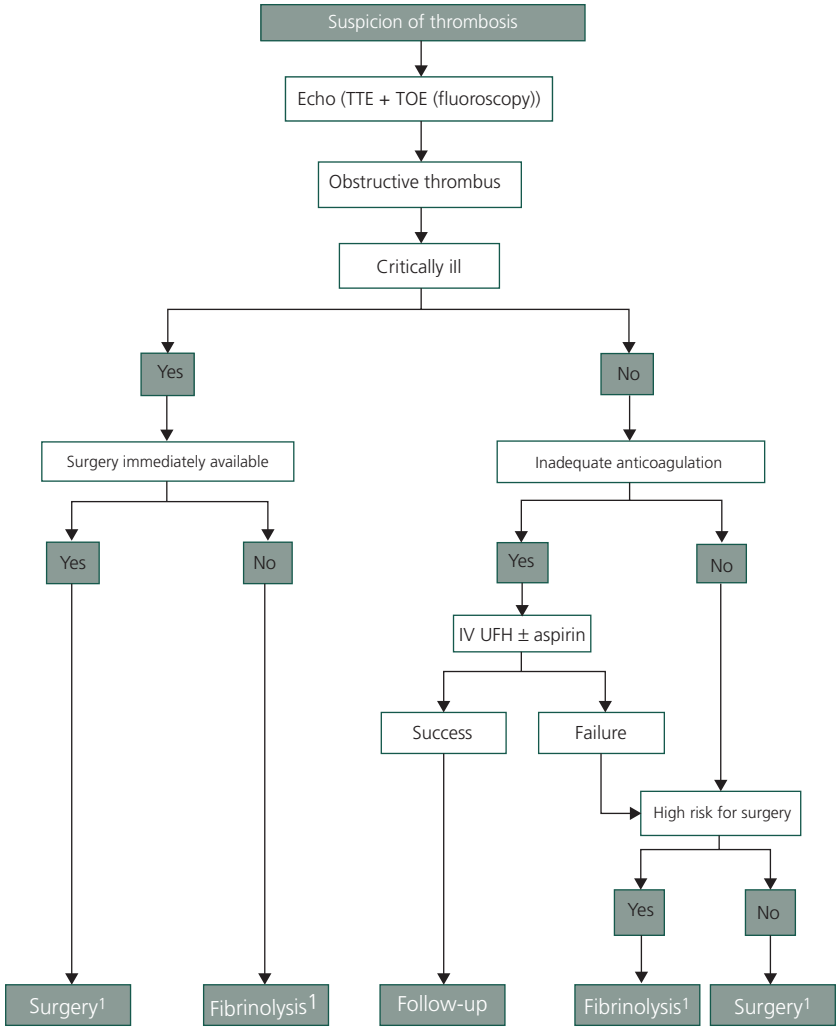

Figure 23.2 ESC 2012 on VD. Management of left-sided obstructive prosthetic thrombosis.

IV UFH, intravenous unfractionated heparin; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography. a: Risk and benefits of both treatments should be individualized. The presence of a first-generation prosthesis is an incentive to surgery.
ESC 2012 guidelines on the management of valvular heart disease. *Eur Heart J.* 2012;**33**:2451–96 with permission from Oxford University Press.

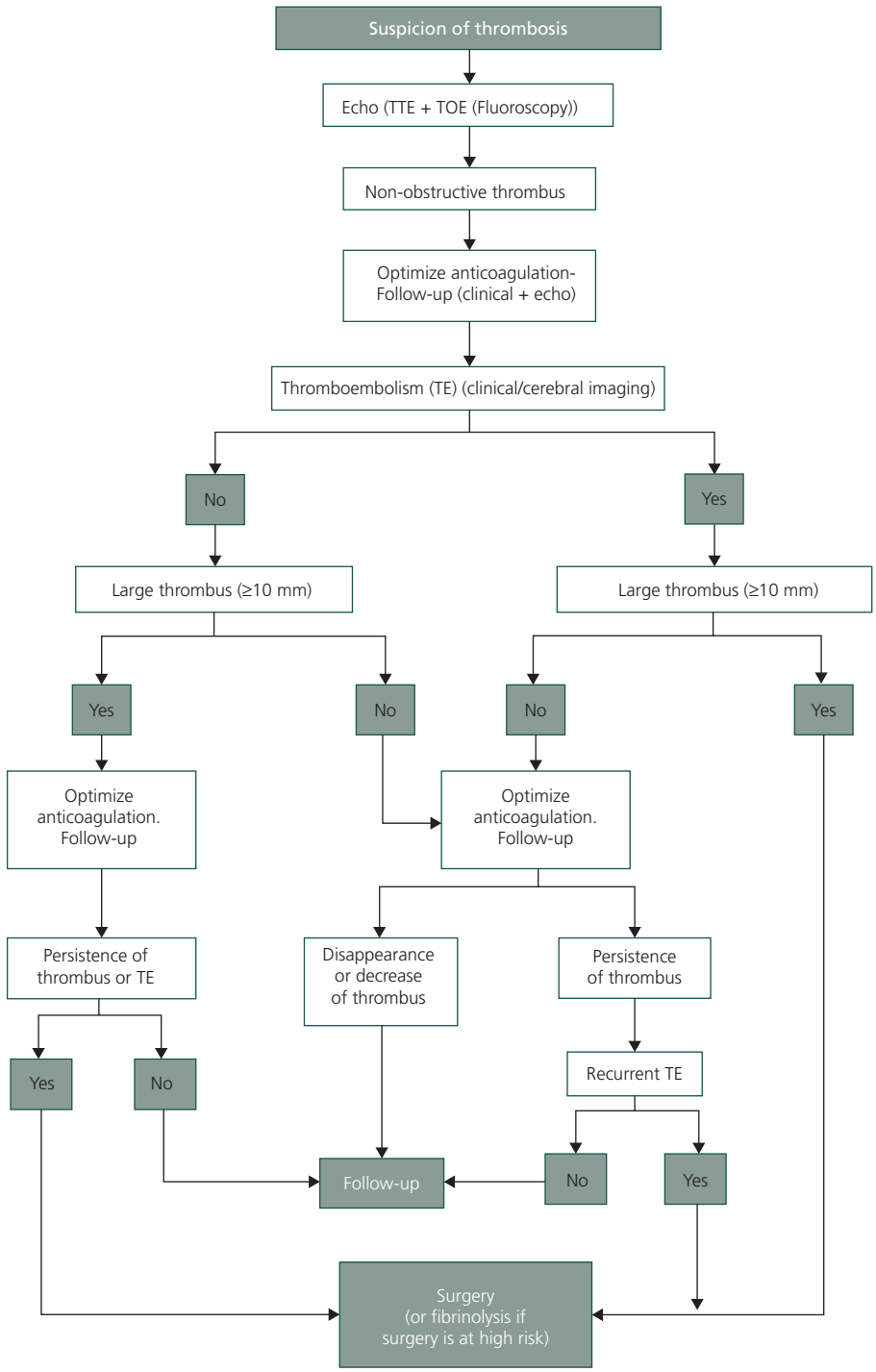

Figure 23.3 ESC 2012 on VD. Management of left-sided non-obstructive prosthetic thrombosis.

ESC 2012 guidelines on the management of valvular heart disease. *Eur Heart J.* 2012;**33**:2451–96 with permission from Oxford University Press.

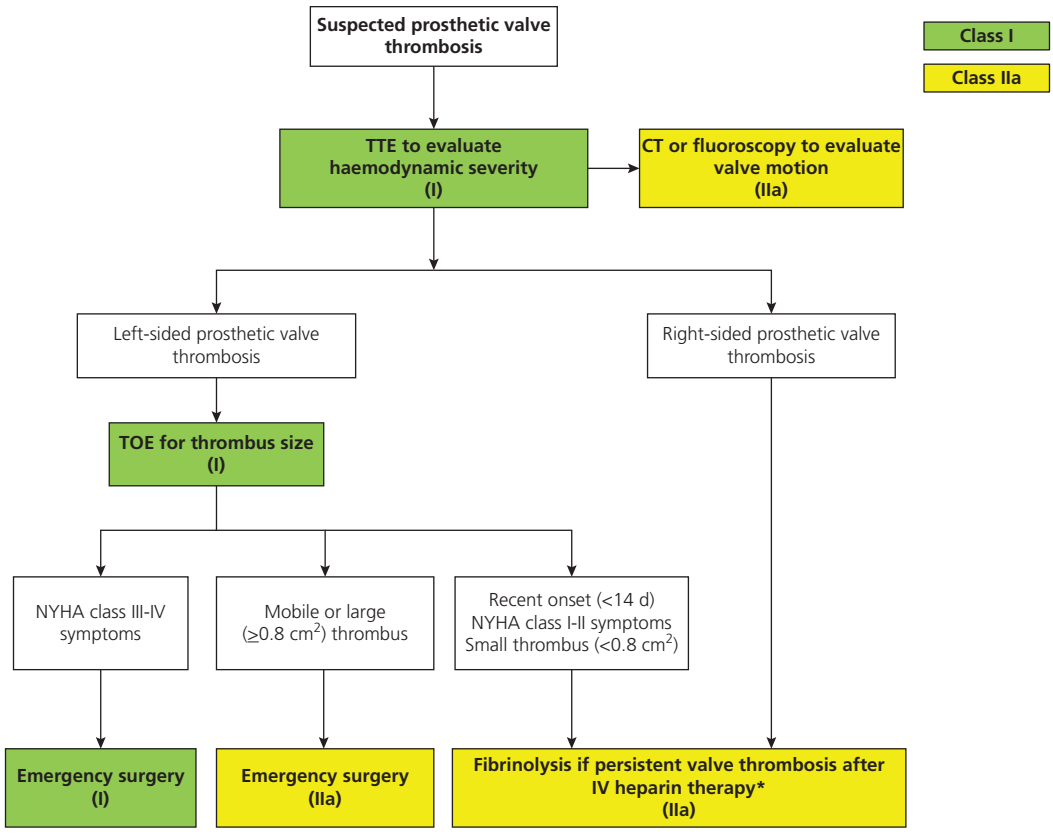

Figure 23.4 AHA/ACC 2014 GL on valve disease. Evaluation and management of suspected prosthetic valve thrombosis

*See text for dosage recommendations.
AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

Haemolysis

Subclinical intravascular haemolysis is noted in most patients with a normally functioning mechanical prosthetic valve; severe haemolytic anaemia is uncommon and suggests paravalvular leakage due to partial dehiscence of the valve or infection. Diagnosis of valve-induced haemolysis is made by increased serum lactate dehydrogenase concentrations, decreased serum haptoglobin concentrations, and reticulocytosis.[39]

Prosthetic valve stenosis and regurgitation

Mechanical valve stenosis is rare and typically due to valve thrombosis or pannus formation. Paravalvular regurgitation affects 5–17% of all surgically implanted prosthetic heart valves and mainly the mitral valve. Patients may be asymptomatic or present with haemolysis or heart failure. Reoperation is associated with increased morbidity and is not always successful because of underlying tissue friability, inflammation, or calcification. Percutaneous closure should be considered for closure of clinically symptomatic paravalvular leaks, and, in experienced centres, it is successful in up to 90% of the cases, with <10% complications rate (obstruction of the tilting valve leaflet, embolization of the device, coronary artery obstruction, or stroke).[40] Table 23.10 presents the AHA/ACC recommendations.

Table 23.10 AHA/ACC 2014 GL on valve disease. Intervention for prosthetic heart valve stenosis and regurgitation

Repeat valve replacement for severe symptomatic prosthetic valve stenosis	I-C
Surgery for operable patients with mechanical heart valves with intractable haemolysis or HF due to severe prosthetic or paraprosthetic regurgitation	I-B
Surgery for operable patients with severe symptomatic or asymptomatic bioprosthetic regurgitation	IIa-C
Percutaneous repair of paravalvular regurgitation in patients with intractable haemolysis or NYHA class III/IV HF who are at high risk for surgery and have anatomic features suitable for catheter-based therapy when performed in centres with expertise in the procedure	IIa-B

AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

MRI

Magnetic resonance imaging can be performed safely in patients with prosthetic heart valves, except those with a Pre 6000 Starr–Edwards caged-ball prosthesis.[41]

Pregnancy

Maternal mortality is estimated to be between 1% and 4%. Women with a mechanical heart valve have a 4.7% risk of valve thrombosis and only a 58% chance of experiencing an uncomplicated pregnancy with a live birth.[42]

In pregnant women with mechanical valves, anticoagulation management is not established, although the option of warfarin between weeks 6 and 12, provided that the necessary dose is <5 mg/day, is now available.[43]

The AHA/ACC 2014 GL on VHD and the ESC 2011 guidelines on pregnancy recommendations are provided in Tables 23.11 and 23.12, and Figure. 23.5.

Table 23.11 AHA/ACC 2014 GL on valve disease. Prosthetic valves in pregnancy

Diagnosis and follow-up	
Clinical evaluation and baseline TTE before pregnancy	I-C
Pre-pregnancy counselling by a cardiologist with expertise in managing patients with VHD during pregnancy	I-C
TTE in all pregnant patients with a prosthetic valve if not done before pregnancy	I-C
Repeat TTE in all patients who develop symptoms	I-C
TOE in mechanical prosthetic valve with prosthetic valve obstruction or embolic event	I-C
Pregnant patients with a mechanical prosthesis should be monitored in a tertiary care centre with a dedicated Heart Valve Team of cardiologists, surgeons, anaesthesiologists, and obstetricians with expertise in the management of high-risk cardiac patients	I-C
Medical therapy	
Therapeutic anticoagulation with frequent monitoring in patients with a mechanical prosthesis	I-B
Warfarin in patients with a mechanical prosthesis to achieve a therapeutic INR in the second and third trimesters	I-B
Discontinuation of warfarin with initiation of intravenous UFH with a PTT >2 times control before planned vaginal delivery in patients with a mechanical prosthesis	I-C
Low-dose aspirin (75–100 mg) od in the second and third trimesters with either a mechanical prosthesis or bioprosthesis	I-C
Continuation of warfarin during the first trimester in patients with a mechanical prosthesis if the dose of warfarin to achieve a therapeutic INR is 5 mg per day or less after full discussion with the patient about risks and benefits	IIa-B
Dose-adjusted LMWH at least 2 times per day (with a target anti-Xa level of 0.8 U/mL to 1.2 U/mL, 4 to 6 hours postdose) during the first trimester in patients with a mechanical prosthesis if the dose of warfarin is >5 mg per day to achieve a therapeutic INR	IIa-B
Dose-adjusted continuous intravenous UFH (with an aPTT at least 2 times control) during the first trimester in patients with a mechanical prosthesis if the dose of warfarin is >5 mg per day to achieve a therapeutic INR	IIa-B
Dose-adjusted LMWH at least 2 times per day (with a target anti-Xa level of 0.8 U/mL to 1.2 U/mL, 4 to 6 hours postdose) during the first trimester in patients with a mechanical prosthesis if the dose of warfarin is ≤5 mg per day to achieve a therapeutic INR	IIb-B
Dose-adjusted continuous infusion of UFH (with aPTT at least 2 times control) during the first trimester in patients with a mechanical prosthesis if the dose of warfarin is ≤5 mg per day to achieve a therapeutic INR	IIb-B
LMWH should not be administered to pregnant patients with mechanical prostheses unless anti-Xa levels are monitored 4 to 6 hours after administration	III-B (harm)

AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

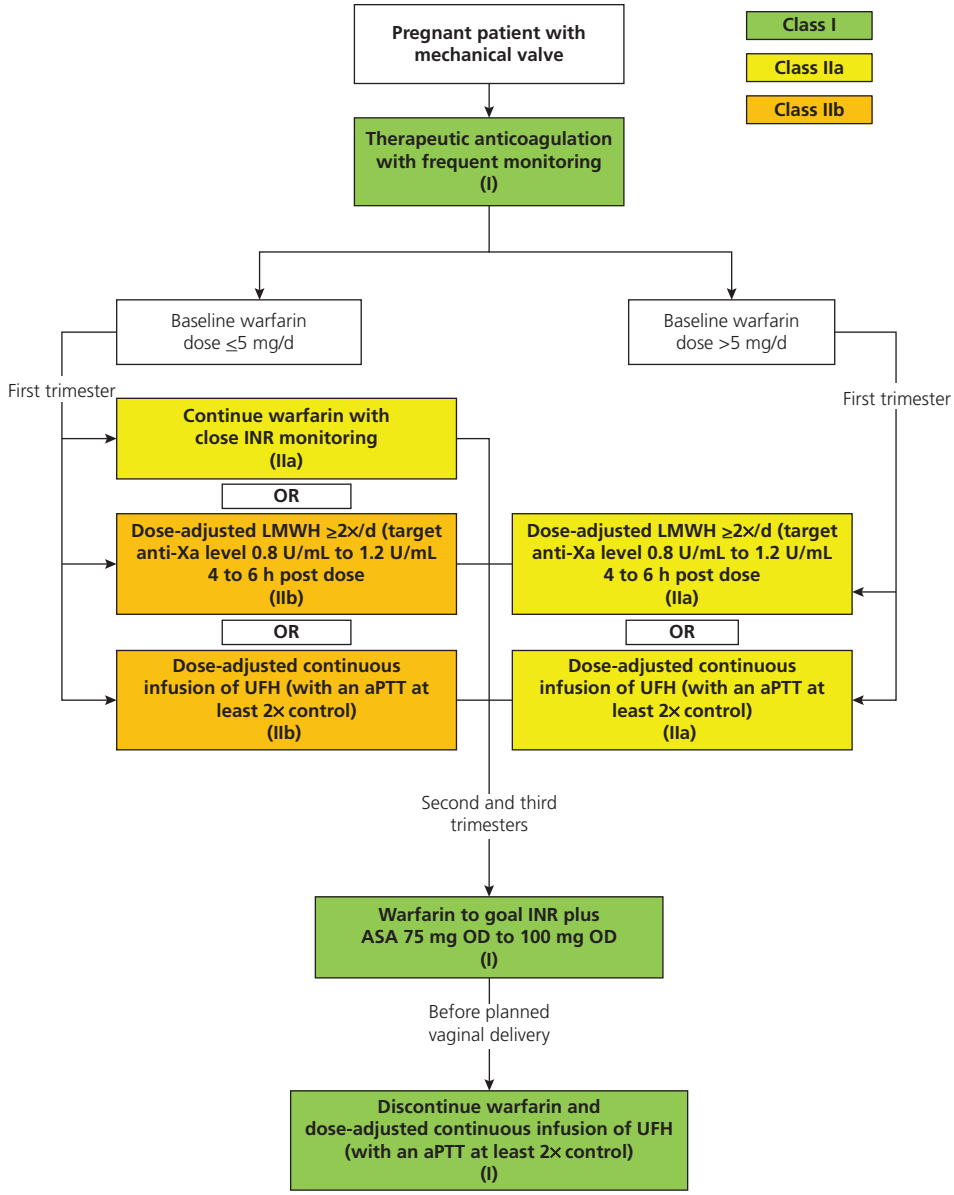

Figure 23.5 AHA/ACC 2014 GL on valve disease. Anticoagulation of pregnant patients with mechanical valves

aPTT indicates activated partial thromboplastin time; ASA, aspirin; INR, international normalized ratio; LMWH, low molecular-weight heparin; OD, once daily; and UFH, unfractionated heparin.

AHA/ACC 2014 guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:e57–185.

Table 23.12 ESC 2011 GL on pregnancy

Recommendations for the management of valvular heart disease. Mechanical valves	
OACs are recommended during the second and third trimesters until the 36th week.	I-C
Change of anticoagulation regimen during pregnancy should be implemented in hospital.	I-C
If delivery starts while on OACs, Caesarean delivery is indicated.	I-C
OAC should be discontinued and dose-adjusted UFH (aPTT ≥2 x control) or adjusted-dose LMWH (target anti-Xa level 4–6 hours post-dose 0.8–1.2 U/mL) started at the 36th week of gestation.	I-C
In pregnant women managed with LMWH, the post-dose anti-Xa level should be assessed weekly.	I-C
LMWH should be replaced by intravenous UFH at least 36 hours before planned delivery. UFH should be continued until 4–6 hours before planned delivery and restarted 4–6 hours after delivery if there are no bleeding complications.	I-C
Immediate echocardiography is indicated in women with mechanical valves presenting with dyspnoea and/or an embolic event.	I-C
Continuation of OACs should be considered during the first trimester if the warfarin dose required for therapeutic anticoagulation is <5 mg/day (or phenprocoumon <3 mg/day or acenocoumarol <2 mg/day), after patient information and consent.	IIa-C
Discontinuation of OAC between weeks 6 and 12 and replacement by adjusted-dose UFH (aPTT ≥2 x control; in high risk patients applied as intravenous infusion) or LMWH twice daily (with dose adjustment according to weight and target anti-Xa level 4–6 hours post-dose 0.8–1.2 U/mL) should be considered in patients with a warfarin dose required of >5 mg/day (or phenprocoumon >3 mg/day or acenocoumarol >2mg/day).	IIa-C
Discontinuation of OACs between weeks 6 and 12 and replacement by UFH or LMWH under strict dose control (as described above) may be considered on an individual basis in patients with warfarin dose required for therapeutic anticoagulation <5 mg/day (or phenprocoumon <3 mg/day or acenocoumarol <2 mg/day).	IIb-C
Continuation of OACs may be considered between weeks 6 and 12 in patients with a warfarin dose required for therapeutic anticoagulation >5 mg/day (or phenprocoumon >3 mg/day or acenocoumarol >2 mg/day).	IIb-C
LMWH should be avoided, unless anti-Xa levels are monitored.	III-C

OACs, oral anticoagulants.
ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J.* 2011;**32**: 3147–97 with permission from Oxford University Press.

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Part III

Systemic hypertension

Relevant guidelines

ESH/ESC 2013 Guidelines on hypertension

2013 ESH/ESC Guidelines for the management of arterial hypertension. *Eur Heart J*. 2013;**34**:2159–219.

AHA 2005 Recommendations for blood pressure measurements

Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans. *Circulation*. 2005;**111**:697–716.

AHA/ACC/ASH 2015 Statement on treatment of hypertension in ischemic heart disease

Treatment of hypertension in patients with coronary artery disease. *JACC*. 2015; **65**:1998–2038.

ACCF/AHA 2011 Expert consensus document on hypertension in the elderly

ACCF/AHA 2011 Expert consensus document on hypertension in the elderly. *J Am Coll Cardiol*. 2011;**57**:2037–114.

ACCF/AHA 2013 Guidelines on peripheral artery disease

Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations). *J Am Coll Cardiol*. 2013;**61**:1555–7.

AHA/ACC 2013 Guideline on lifestyle management

2013 AHA/ACC Guideline on lifestyle management to reduce cardiovascular risk. *J Am Coll Cardiol*. 2014;**63**:2960–84.

AHA/ACC/CDC 2013 Science Advisory on high blood pressure control

An effective approach to high blood pressure control. *J Am Coll Cardiol*. 2014;**63**:1230–8.

AHA 2013 Scientific statement on CVD prevention in older adults

Secondary prevention of atherosclerotic cardiovascular disease in older adults. *Circulation*. 2013;**128**:2422–46.

JNC 8 Guideline 2014

2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;**311**:507–20.

ESC 2012 Guidelines on cardiovascular disease prevention

European guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2012;**33**:1635–701.

ESC 2011 Guidelines on pregnancy

ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**:3147–97.

Chapter 24

Classification and pathophysiology of hypertension

Definition

Hypertension in adults aged 18 or older is defined as blood pressure (BP) ≥140/90 mmHg, based on the average of ≥2 seated blood pressure measurements, properly measured with well-maintained equipment, at each of ≥2 visits to the office or clinic.[1,2] Hypertension has been divided into stages, as shown in Table 24.1. Home blood pressures are consistently lower than clinic pressures in most hypertensive patients, and 135/85 mmHg is considered the upper limit of normal for home blood pressure.[1,3] Threshold values for office and home normal values, as well as for ambulatory blood pressure measurements, are presented in Table 24.2.

Table 24.1 Classification of hypertension schemes

Definitions and classification of blood pressure levels (mmHg)*		
ESH/ESC 2013 GL on hypertension		
Category	**Systolic**	**Diastolic**
Optimal	<120, and	<80
Normal	120–129, and/or	80–84
High normal	130–139, and/or	85–89
Grade 1 hypertension	140–159, and/or	90–99
Grade 2 hypertension	160–179, and/or	100–109
Grade 3 hypertension	≥180, and/or	≥110
Isolated systolic hypertension	≥140, and	<90

*: The blood pressure (BP) category is defined by the highest level of BP, whether systolic or diastolic. Isolated systolic hypertension should be graded 1, 2, or 3, according to systolic BP values in the ranges indicated.
ESH/ESC 2013 Guidelines for the management of arterial hypertension. *Eur Heart J*. 2013;**34**:2159–219 with permission from Oxford University Press.

Table 24.2 Normal values

ESH/ESC 2013 GL on hypertension. Definitions of hypertension by office and out-of-office blood pressure levels			
Category	**Systolic BP (mmHg)**		**Diastolic BP (mmHg)**
Office blood pressure	≥140	and/or	≥90
Ambulatory blood pressure			
Daytime (or awake)	≥135	and/or	≥85
Night-time (or asleep)	≥120	and/or	≥70
24-h	≥130	and/or	≥80
Home blood pressure	≥135	and/or	≥85
Diagnostic thresholds for ambulatory blood pressure measurements (mmHg)			
	24-hour	**Daytime**	**Night-time**
Optimal	<115/75	<120/80	<100/65
Normal	<125/75	<130/85	<110/70
Ambulatory hypertension	≥130/80	≥140/85	≥120/70

ESH/ESC 2013 Guidelines for the management of arterial hypertension. *Eur Heart J*. 2013;**34**:2159–219 with permission from Oxford University Press.

Epidemiology

Hypertension is an increasingly important public health issue, affecting approximately 25% of the overall population.[4] Based on 2009 to 2012 data, 32.6% of US adults ≥20 years of age have hypertension. African American adults have among the highest prevalence of hypertension in the world. Among non-Hispanic black men and women, the age-adjusted prevalence of hypertension was 44.9% and 46.1%, respectively.[5] According to data from the Framingham Heart Study, the lifetime risk of hypertension is approximately 90% for men and women who were not hypertensive at 55 or 65 years old and survived to age 80–85. Even after adjusting for competing mortality, the remaining lifetime risks of hypertension were 86–90% in women and 81–83% in men.[6] Suboptimal BP control is the most common attributable risk for death worldwide, being responsible for 62% of cerebrovascular disease and 49% of ischaemic heart disease, as well as an estimated 7.1 million deaths a year.[7] In most cases (>90%), no underlying pathology can be identified (primary or essential hypertension).

Aetiology

Established causes of hypertension are discussed in Chapter 26 on secondary hypertension. In primary hypertension, no cause can be identified, but certain behaviours contribute to the elevated BP. Excessive consumption of calories, salt and alcohol are among the most important behavioural determinants of hypertension. Visceral adiposity, a feature of metabolic syndrome is related to hypertension. Although systolic blood pressure temporarily rises after coffee, chronic caffeine consumption is not associated with increased risk of hypertension.[8] There is also no strong evidence for causal associations between uric acid and blood pressure or ischaemic heart disease.[9] Smoking increases BP by 10–20 mm Hg with each cigarette, thus increasing the risk of hypertension with habitual smoking. Non-steroidal anti-inflammatory agents are the main cause of drug-induced hypertension, but paracetamol use also increases blood pressure in patients with coronary artery disease.[10] Acute exposure to high altitude initially results in a reduction in BP, probably related to hypoxia-induced compensatory vasodilation from metabolites released from skeletal muscle and red blood cells which causes a 'functional sympatholysis' similar to that observed during exercise. Sympathetic nervous system activity increases immediately and continues to rise throughout the period of exposure to high altitude. As oxygen content is restored by acclimatization, hypoxic vasodilation is abolished, leaving unopposed sympathetic vasoconstrictor tone and contributing to increasing BP.[11] The previously reported association with vitamin D deficiency does not appear to be causal.[12] Recreational drugs such as amphetamines, LSD, cocaine, or ecstasy may cause resistant hypertension or hypertensive crisis.[13] Mean systolic BP is higher in winter than in summer, and this may be related to an observed substantial increase in cardiovascular mortality.[14]

Blood pressure is a complex genetic trait, with heritability estimates of 30–50%, but the intrinsic origin of essential hypertension remains obscure.[15] Certain genes can cause mendelian forms of hypertension,[16] and single-nucleotide polymorphisms have also been identified as risk factors for hypertension and coronary artery disease.[17] Genetic disorders affecting blood pressure regulation are Liddle syndrome, glucocorticoid remediable aldosteronism, Bartter syndrome, Gitelman syndrome, and pseudohypoaldosteronism.[18]

Pathophysiology

Systolic pressure within the aorta is a composite of two items: (1) the outgoing pressure wave, generated by ventricular contraction; and (2) pressure wave reflection from the periphery. Since the pulse wave is amplified in transit from the heart to the brachial artery, central aortic systolic pressure is usually lower than brachial pressure. The magnitude of amplification is greatest in people with healthy compliant arteries and diminishes with age.

Established hypertension exposes the arterial tree to increased pulsatile stress, but paradoxically major complications are thrombotic, rather than haemorrhagic, referred to as the so-called thrombotic paradox of hypertension. Blood flow abnormalities, endothelial damage or dysfunction, and a hypercoagulable state are consequences of long-standing hypertension.[19] The prothrombotic state could be the result of chronic low-grade inflammation and damage and remodelling of the vascular endothelium due to elevated shear stress. The mechanisms leading to endothelial dysfunction are multifactorial and include decreased activity of vasodilator agents and increased activity (or sensitivity) to vasoconstrictor agents. Enhanced activity of the renin–angiotensin system and kallikrein–kinin system has opposite effects, resulting in vasoconstriction and vasodilation, respectively, but both cause a hypercoagulable state.[20] Thus, hypertension not only confers a hypercoagulable state (vulnerable blood) but also gives rise to left ventricular hypertrophy, ventricular and atrial arrhythmias, increased aortic stiffness, and impaired coronary reserve (vulnerable myocardium), thereby fulfilling all criteria for a vulnerable patient. In enhancing the coagulation fibrinolysis balance, antihypertensive treatment can decrease the frequency of thrombotic events, independent of blood pressure.

Target organ disease due to essential hypertension comprises damage of the heart, brain, and kidneys. Left ventricular hypertrophy, coronary artery disease, atrial fibrillation, and ventricular arrhythmias are consequences of long-standing hypertension. Hypertension is the most common cause of atrial fibrillation and congestive heart

failure. Typically, hypertension leads to LV hypertrophy that progresses to dilated cardiac failure. However, patients with hypertension may progress directly to dilated cardiac failure in the absence of myocardial infarction or antecedent concentric hypertrophy.[21] Microalbuminuria, proteinuria and elevated creatinine levels, and reduced glomerular filtration rate are signs of progressive renal impairment. Retinopathy, Binswanger lesions (subcortical vascular dementia), transient ischaemic attacks, and, eventually, stroke and dementia are manifestations of brain damage.

Subtypes of hypertension

High normal blood pressure and prehypertension

The terms high blood pressure (systolic BP 130–139 mmHg and/or diastolic BP 85–89 mmHg)[1] and prehypertension (systolic BP 120–139 mmHg, diastolic BP 80–89 mmHg)[13] reflect the fact that health risks attributable to increasing blood pressure in adults are continuous, beginning at 115/75 mmHg.[22] These patients may develop established hypertension later, and blockade of the renin–angiotensin axis has been found to decrease this risk.[23,24] However, drug therapy for this population is not established.[25] Lifestyle modification by means of low salt diet, weight loss, exercise, and alcohol restriction are the best way for treating these patients.[26–28]

Isolated systolic hypertension

With increasing age, systolic blood pressure, unlike diastolic blood pressure, tends to rise in response to increasing arterial stiffness and losses in arterial compliance, particularly after the age of 40. Isolated systolic hypertension is a common condition in individuals aged older than 60 years[3] and represents a predominant risk factor for coronary events in this group.[29] In the young, isolated systolic hypertension has been thought to result from an amplification of the pressure wave between the aorta and the brachial artery, due to very elastic arteries in the context of normal aortic systolic pressure. Isolated systolic hypertension in the young is a heterogeneous condition and may result from an increased stroke volume and/or aortic stiffness, whereas the major haemodynamic abnormality underlying essential hypertension is an increased peripheral vascular resistance.[30] The prevalence of isolated systolic hypertension has nearly doubled among young adults during the last decade and is associated with obesity, smoking, and low socioeconomic status.[27] In adults aged 18 to 49 years, isolated systolic hypertension is associated with higher risk for cardiovascular disease mortality compared with normal blood pressure.[31]

Isolated diastolic hypertension

Some prospective studies of isolated diastolic hypertension have indicated that the prognosis may be relatively benign. Although the topic is controversial,[3] isolated diastolic hypertension appears to be a predictor of coronary risk in patients younger than 50 years (IDACO data).[29]

Pulse pressure

In older hypertensive patients, increased pulse pressure (systolic-diastolic) is the major determinant of cardiovascular risk.[32]

White coat hypertension

Differences between office and home measurements are present in the majority of hypertensive patients. White coat, or isolated office, hypertension is defined as a persistently elevated average office blood pressure of >140/90 and an average awake ambulatory reading of <135/85 mmHg,[3] or as at least three separate measurements of >140/90 mmHg at the doctor's office and at least two non-office-based measurements of <140/90 mmHg. Whether subjects with white coat hypertension have a higher cardiovascular risk than normotensive individuals is an issue still under debate, with both affirmative and negative results having been reported, but it seems that probably the condition is associated with a higher risk of incident cardiovascular events.[26,28,33,34] However, the value of therapy is not proven in patients without established hypertension,[34] and ambulatory blood pressure or repeated (>5) pressure measurements at home are superior to office blood pressure measurements in predicting treatment-induced regression of left ventricular hypertrophy.[35] Patients with white coat hypertension are very likely to develop sustained hypertension later in life and life style and dietary changes should be recommended.

Masked hypertension

Normal blood pressure measurements at the office, but elevated values elsewhere, may be due to alcohol abuse or smoking. Target organ damage (as LV hypertrophy or renal impairment) is related to the more prolonged elevation in pressure, and its presence can assist the diagnosis. There is evidence that such patients are at increased risk.[34] Masked hypertension may also occur with severe peripheral arterial disease. Masked uncontrolled hypertension is diagnosed if, despite controlled clinic BP, the mean 24-h ambulatory blood pressure monitoring average remains elevated (24-h systolic BP ≥ 130 mmHg and/or 24-h diastolic BP ≥ 80 mmHg).[37]

Pseudohypertension

May be seen with stiff, calcified vessels, in the elderly and patients with long-standing diabetes or chronic renal failure, that are difficult to compress. The Osler manoeuvre (palpable radial pulse despite occlusive cuff pressure) is not a sensitive, or specific, sign of pseudohypertension. Intra-arterial radial pressure measurement may be necessary for correct diagnosis.

Orthostatic hypotension

It is defined by a fall >20 mmHg systolic and/or >10 mmHg diastolic in response to standing from the supine position within 3 minutes or during head-up tilt at 60 degrees. It is usually a sign of dysautonomic syndromes, diabetes, Parkinson's disease, multiple myeloma, or multiple system atrophy but may also be seen in patients with vasovagal syncope. The major therapeutic problem is inability to control the level of blood pressure in patients with orthostatic hypotension who concomitantly have supine hypertension.

Blood pressure during exercise

BP increases during dynamic and static exercise, and the increase is more pronounced for systolic than for diastolic BP. There is currently no consensus on normal BP response during dynamic exercise testing. A SBP of ≥210 mmHg for men and ≥190 mmHg for women has been termed 'exercise hypertension'.[1] The results on the independent relationships of the blood pressure response to physical and mental stressors, future hypertension, and target organ damage are not consistent, and exercise testing to predict future hypertension is not recommended.[1] However, an exercise test may provide some additional prognostic information, at least in subjects with mild blood pressure elevation. The 21-year follow-up study of 1999 apparently healthy men disclosed independently predictive information on cardiovascular death of both supine systolic BP and 6-minute exercise systolic BP taken at an early moderate workload but not of maximal systolic BP during exercise.[38]

Blood pressure differential

At the first visit, BP should be checked in both arms. Differences between the two arms >15 mmHg may be seen in up to 12–15% of patients with hypertension and is an independent predictor of cardiovascular disease and death.[39] These patients may deserve further investigations for peripheral and coronary artery disease. Differences >20 mmHg may be seen in subclavian artery stenosis, severe supravalvular AS, coarctation, Ao dissection, or as a normal variant.

High-altitude hypertension

BP increase at high altitude appears to depend primarily on chemoreflex-induced increase in sympathetic activity. Ambulatory blood pressure increases progressively with increasing altitude, remaining elevated after 3 weeks. Angiotensin receptor blockade maintains blood pressure-lowering efficacy at 3400 m but not at 5400 m.[11,40]

Blood pressure measurement

Measured with the patient seated with the back supported or supine and the arm at heart level. The patient should have refrained from smoking or drinking coffee for at least 30 min and allowed to sit for 3–5 min (Table 24.3).

Patient position

Diastolic pressure measured while sitting is higher than when measured supine (by 5 mmHg), although there is less agreement about systolic pressure. When the arm position is adjusted so that the cuff is at the level of the right atrium in both positions, the systolic pressure has been reported to be 8 mmHg higher in the supine than the upright position. If the back is not supported (as when the patient is seated on an examination table as opposed to a chair), the diastolic pressure may be increased by 6 mmHg. Crossing the legs may raise systolic pressure by 2–8 mmHg. In the supine position, the arm should be supported with a pillow. In the sitting position, the right atrium level is the midpoint of the sternum or the fourth intercostal space; it is preferred in diabetics due to increased possibility of postural hypotension. Systolic blood pressure measured in the ankles (eg in patients with bilateral arm fistulae), is higher by approximately 20 mmHg than in

Table 24.3 ESH/ESC 2013 GL on hypertension

Office blood pressure measurement
◆ Allow the patients to sit for 3–5 minutes before beginning BP measurements.
◆ Take at least two BP measurements, in the sitting position, spaced 1–2 min apart, and additional measurements if the first two are quite different. Consider the average BP if deemed appropriate.
◆ Take repeated measurements of BP to improve accuracy in patients with arrhythmia such as AF.
◆ Use a standard bladder (12–13 cm wide and 35 cm long), but have a larger and a smaller bladder available for large (arm circumference >32 cm) and thin arms, respectively.
◆ Have the cuff at the heart level, whatever the position of the patient.
◆ When adopting the auscultatory method, use phase I and V (disappearance) Korotkoff sounds to identify systolic and diastolic BP, respectively.
◆ Measure BP in both arms at first visit to detect possible differences. In this instance, take the arm with the higher value as the reference.
◆ Measure at the first visit BP 1 and 3 min after assumption of the standing position in elderly subjects, diabetic patients, and in other conditions in which orthostatic hypotension may be frequent or suspected.
◆ Measure, in case of conventional BP measurement, heart rate by pulse palpation (at least 30 s) after the second measurement in the sitting position.

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the arm, whereas diastolic blood pressure measurements are not significantly different.[41]

Cuff size

The cuff should be held at the heart level, whatever the position of the patient. The length and width of the cuff should be 80%/40% of the arm circumference, 1–2 cm above the antecubital fossa. Too small cuffs overestimate BP, whereas too large ones underestimate it.

The recommended cuff sizes are:[3]

- For arm circumference of 22–26 cm, the cuff should be 'small adult' size: 12 × 22 cm
- For arm circumference of 27–34 cm, the cuff should be 'adult' size: 16 × 30 cm
- For arm circumference of 35–44 cm, the cuff should be 'large adult' size: 16 × 36 cm
- For arm circumference of 45–52 cm, the cuff should be 'adult thigh' size: 16 × 42 cm.

The cuff should be deflated at 2–3 mmHg/s, with neither the patient nor the doctor talking. Traditionally, the Korotkoff sounds have been classified into five phases: phase I, appearance of clear tapping sounds, corresponding to the appearance of a palpable pulse; phase II, sounds become softer and longer; phase III, sounds become crisper and louder; phase IV, sounds become muffled and softer; and phase V, sounds disappear completely. The fifth phase is thus recorded as the last audible sound. The onset of phase I corresponds to systolic pressure but tends to underestimate the systolic pressure recorded by direct intra-arterial measurement, whereas the disappearance of sounds (phase V) corresponds to diastolic pressure but tends to occur before diastolic pressure determined by direct intra-arterial measurement.[3] Early disappearance and recurrence of sounds (**auscultatory gap**) may occur in the elderly. The auscultatory gap often can be eliminated by elevating the arm over head for 30 seconds before inflating the cuff and then bringing the arm to the usual position to continue in the measurement. This manoeuvre reduces vascular volume in the limb and improves inflow to enhance the Korotkoff sounds. In severe AR or large AV fistulas and, rarely, in pregnancy, Korotkoff sounds may be heard until complete deflation of the cuff. In these cases, the phase IV pressure should be noted.[3] At least three measurements should be taken.[36] The Korotkoff sound method tends to give values for systolic pressure that are lower than the true intra-arterial pressure, and diastolic values that are higher.

Sphygmomanometers

All devices may be inaccurate due to technical problems and need frequent calibration. Mercury sphygmomanometers are perhaps the most reliable despite concerns about mercury toxicity. **Oscillometric automated monitors** that provide read-outs of systolic and diastolic pressure should be subjected by independent investigators to formal validation protocols, such as those developed by the Association for the Advancement of Medical Instrumentation and the British Hypertension Society.[3] **Mercury sphygmomanometers** should be examined by checking that the upper curve of the meniscus of the mercury column is at 0 mmHg, that the column is free of dirt, and that it rises and falls freely during cuff inflation and deflation. **Aneroid devices** or other non-mercury devices should be checked by connecting the manometer to a mercury column or an electronic testing device with a Y-tube. The needle should rest at the zero point before the cuff is inflated and should register a reading that is within 4 mmHg of the mercury column when the cuff is inflated to pressures of 100 and 200 mmHg. The needle should return to zero after deflation.[3]

Ambulatory and home BP measurements

Ambulatory BP

Although office BP should be used as reference, ambulatory BP may improve prediction of cardiovascular risk in untreated and treated patients.[42,43] 24-hour systolic BP is associated with the progression of cerebrovascular disease and cognitive decline in the elderly much better than office measurements.[43] Ambulatory BP monitoring should also be considered when there is a marked discrepancy between BP values measured in the office and at home, resistance to drug treatment or hypotensive episodes are suspected, particularly in elderly and diabetic patients, and office BP is elevated in pregnant women and preeclampsia is suspected. A mean 24-h ambulatory systolic blood pressure monitoring ≥ 130 mmHg and/or a diastolic average ≥ 80 mmHg is considered as denoting masked hypertension.[37]

Home BP

Self-measurement of BP at home is of clinical value, and its prognostic significance is now demonstrated. These measurements should be encouraged in order to provide more information on the BP-lowering effect of treatment at trough levels and thus on therapeutic coverage throughout the dose-to-dose time interval.

Normal values are different for office, ambulatory, and home BP (Table 24.2).

Blood pressure variability

Despite initial evidence about the adverse prognostic significance of visit-to-visit blood pressure variability in the ASCOT and MRC trials,[44] only the average BP levels were found important in the recent ELSA trial.[45]

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Chapter 25

Primary (essential) hypertension

Risk stratification

Investigations in hypertensive patients are aimed at establishing risk factors, subclinical or overt organ damage, and, when suspected, diagnosis of causes of secondary hypertension. For risk stratification, the Framingham and SCORE models are mainly used.[1,2]

Risk factors

BP ≥180 mmHg systolic and/or ≥110 mmHg, diabetes mellitus, cardiovascular or renal disease, and evidence of subclinical organ damage denote high-risk subjects.[3] Factors influencing prognosis are presented in Table 25.1.

Impaired glucose tolerance (prediabetes) is defined by WHO and the American Diabetes Association (ADA) as:

- fasting blood glucose 6.1–6.9 mmol/L (110–125 mg/dL) (WHO), or
- 5.6–6.9 mmol/L (100–125 mg/dL) (ADA), or
- ≥7.8–<11.1 mmol/L (≥140–<200 mg/dL) (WHO) or 7.8–11.0 mmol/L (140–198 mg/dL) (ADA), 2 h after 75 g glucose solution (glucose tolerance test).

Diabetes is defined as (WHO and ADA) as:

- HBA1c ≥6.5% (48 mmol/mol)
- fasting blood glucose ≥7 mmol/L (126 mg/dL), or
- ≥11.1 mmol/L (200 mg/dL) 2 h after 75 g glucose solution (glucose tolerance test).

Values above these define clinical diabetes.

Metabolic syndrome is defined as the occurrence of, at least, three out of the following five risk factors: abdominal obesity, BP >130/85 mmHg, borderline or abnormal fasting glucose, low HDL, and high triglycerides. Increased body mass index [body weight (kg)/height (m)^2] is overweight ≥25 kg/m^2 and obesity ≥30 kg/m^2.

Abdominal obesity (waist circumference: men >102 cm, women >88 cm). However, in patients with hypertension and coronary artery disease, overweight and obesity are associated with a decreased mortality risk compared with normal weight (obesity paradox).[4]

Family history of premature cardiovascular disease (men <55 years, women <65 years).

Absence of a family history of hypertension suggests secondary hypertension.

Age (men >55 years, women >65 years).

Physical examination

History and physical examination should enquire about cardiovascular risk, organ damage, and secondary hypertension (Table 25.2).

Investigations

Laboratory tests recommended by the ESC are presented in Table 25.3.

Table 25.1 ESH/ESC 2013 GL on hypertension

Factors—other than office BP—influencing prognosis	
Risk factors	
Male sex	
Age (men ≥55 years; women ≥65 years)	
Smoking	
Dyslipidaemia	
Total cholesterol >4.9 mmol/L (190 mg/dL), and/or	
Low-density lipoprotein cholesterol >3.0 mmol/L (115 mg/dL), and/or	
High-density lipoprotein cholesterol: men <1.0 mmol/L (40 mg/dL), women <1.2 mmol/L (46 mg/dL), and/or Triglycerides >1.7 mmol/L (150 mg/dL)	
Fasting plasma glucose 5.6–6.9 mmol/L (102–125 mg/dL)	
Abnormal glucose tolerance test	
Obesity [BMI ≥30 kg/m^2 (height^2)]	
Abdominal obesity (waist circumference: men ≥102 cm; women ≥88 cm) (in Caucasians)	
Family history of premature CVD (men aged <55 years; women aged <65 years)	
Asymptomatic organ damage	
Pulse pressure (in the elderly) ≥60 mmHg	
Electrocardiographic LVH (Sokolow–Lyon index >3.5 mV; RaVL >1.1 mV; Cornell voltage duration product >244 mV*ms), or	
Electrocardiographic LVH [LVM index: men >115 g/m^2; women >95 g/m^2 (BSA)][a]	
Carotid wall thickening (IMT >0.9 mm) or plaque	
Carotid-femoral PWV >10 m/s	
Ankle-brachial index <0.9	
CKD with eGFR 30–60 mL/min/1.73 m^2 (BSA)	
Microalbuminuria (30–300 mg/24 h), or albumin–creatinine ratio (30–300 mg/g; 3.4–34 mg/mmol) (preferentially on morning spot urine)	
Diabetes mellitus	
Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) on two repeated measurements, and/or	
HBA_{1c} >7% (53 mmol/mol), and/or	
Post-load plasma glucose >11.0 mmol/L (198 mg/dL)	
Established CV or renal disease	
Cerebrovascular disease: ischaemic stroke; cerebral haemorrhage; transient ischaemic attack	
CHD: myocardial infarction; angina; myocardial revascularization with PCI or CABG	
Heart failure, including heart failure with preserved EF	
Symptomatic lower extremities peripheral artery disease	
CKD with eGFR <30 mL/min/1.73m^2 (BSA); proteinuria (>300 mg/24 h)	
Advanced retinopathy: haemorrhages or exudates, papilloedema	
Total cardiovascular risk assessment	
In asymptomatic subjects with hypertension but free of CVD, CKD, and diabetes, using the SCORE model is recommended as a minimal requirement.	I-B
OD predicts CV death independently of SCORE, and search for OD should be considered, particularly in individuals at moderate risk.	IIa-B
Decisions on treatment strategies should depend on the initial level of total CV risk.	I-B

BMI: body mass index; BP: blood pressure; BSA: body surface area; CABG: coronary artery bypass graft; CHD: coronary heart disease; CKD: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; EF: ejection fraction; eGFR: estimated glomerular filtration rate; HbA1c: glycated haemoglobin; IMT: intima–media thickness; LVH: left ventricular hypertrophy; LVM: left ventricular mass; PCI: percutaneous coronary intervention; PWV: pulse wave velocity; OD, organ damage; SCORE, Systematic Coronary Risk Evaluation.
a: Risk maximal for concentric LVH: increased LVM index with a wall thickness/radius ratio of >0.42
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Table 25.2 ESH/ESC 2013 GL on hypertension

Blood pressure measurement, history, and physical examination	
Comprehensive medical history and physical examination to verify the diagnosis, detect causes of secondary hypertension, record CV risk factors, and identify OD and other CVDs.	I-C
Family history to investigate familial predisposition to hypertension and CVDs.	I-B
Office BP for screening and diagnosis of hypertension.	I-B
The diagnosis of hypertension should be based on at least two BP measurements per visit and on at least two visits	I-C
All hypertensive patients should undergo palpation of the pulse at rest to determine heart rate and to search for arrhythmias, especially atrial fibrillation	I-B
Out-of-office BP to confirm the diagnosis of hypertension, identify the type of hypertension, detect hypotensive episodes, and maximize prediction of CV risk	IIa-B
For out-of-office BP measurements, ABPM or HBPM may be considered, depending on indication, availability, ease, cost of use, and, if appropriate, patient preference	IIb-C
Physical examination for secondary hypertension, organ damage, and obesity	
Signs suggesting secondary hypertension	
Features of Cushing syndrome	
Skin stigmata of neurofibromatosis (phaeochromocytoma)	
Palpation of enlarged kidneys (polycystic kidney)	
Auscultation of abdominal murmurs (renovascular hypertension)	
Auscultation of precordial or chest murmurs (aortic coarctation; aortic disease; upper extremity artery disease)	
Diminished and delayed femoral pulses and reduced femoral blood pressure compared to simultaneous arm BP (aortic coarctation; aortic disease; lower extremity artery disease)	
Left–right arm BP difference (aortic coarctation; subclavian artery stenosis)	
Signs of organ damage	
Brain: motor or sensory defects	
Retina: fundoscopic abnormalities	
Heart: heart rate, 3rd or 4th heart sound, heart murmurs, arrhythmias, location of apical impulse, pulmonary rales, peripheral oedema	
Peripheral arteries: absence, reduction, or asymmetry of pulses, cold extremities, ischaemic skin lesions	
Carotid arteries: systolic murmurs	
Evidence of obesity	
Weight and height, calculate BMI: body weight/height^2 (kg/m^2)	
Waist circumference measured in the standing position, at a level midway between the lower border of the costal margin (the lowest rib) and uppermost border of the iliac crest	

ABPM: ambulatory blood pressure monitoring; BP: blood pressure; CV: cardiovascular; CVD: cardiovascular disease; HBPM: home blood pressure monitoring; OD: organ damage.
BMI: body mass index
ESH/ESC 2013 Guidelines for the management of arterial hypertension. *Eur Heart J*. 2013;**34**:2159–219 with permission from Oxford University Press.

Table 25.3 ESH/ESC 2013 GL on hypertension

Laboratory investigations
Routine tests
Haemoglobin and/or haematocrit
Fasting plasma glucose
Serum total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol
Fasting serum triglycerides
Serum potassium and sodium
Serum uric acid
Serum creatinine (with estimation of GFR)
Urine analysis: microscopic examination; urinary protein by dipstick test; test for microalbuminuria
12-lead ECG

(*continued*)

Table 25.3 continued

Additional tests, based on history, physical examination, and findings from routine laboratory tests	
Haemoglobin A_{1c} (if fasting plasma glucose is >5.6 mmol/L (102 mg/dL) or previous diagnosis of diabetes)	
Quantitative proteinuria (if dipstick test is positive); urinary potassium and sodium concentration and their ratio	
Home and 24-h ambulatory BP monitoring	
Echocardiogram	
Holter monitoring in case of arrhythmias	
Carotid ultrasound	
Peripheral artery/abdominal ultrasound	
Pulse wave velocity	
Ankle–brachial index	
Fundoscopy	
Extended evaluation (mostly domain of the specialist)	
Further search for cerebral, cardiac, renal, and vascular damage, mandatory in resistant and complicated hypertension	
Search for secondary hypertension when suggested by history, physical examination, or routine and additional tests	
Cut-off values for parameters used in the assessment of LV remodelling and diastolic function in patients with hypertension	
Parameter	**Abnormal if**
LV mass index (g/m^2)	>95 (women) >115 (men)
Relative wall thickness (RWT)	>0.42
Diastolic function: Septal e' velocity (cm/s) Lateral e' velocity (cm/s) LA volume index (mL/m^2)	 <8 <10 ≥34
LV filling pressures: E/e' (averaged) ratio	 ≥13
Search for asymptomatic organ damage, cardiovascular disease, and chronic kidney disease	
Heart	
An ECG to detect LVH, left atrial dilatation, arrhythmias, or concomitant heart disease	I-B
A stress echo test in all patients with a history or physical examination suggestive of major arrhythmias, long-term ECG monitoring, and in case of suspected exercise-induced arrhythmias	IIa-C
An echocardiogram to refine CV risk, and confirm ECG diagnosis of LVH, left atrial dilatation or suspected concomitant heart disease, when these are suspected	IIa-B
Whenever history suggests myocardial ischaemia, a stress ECG test, and, if positive or ambiguous, an imaging stress test (stress echocardiography, stress cardiac magnetic resonance or nuclear scintigraphy)	I-C
Arteries	
Ultrasound scanning of carotid arteries to detect vascular hypertrophy or asymptomatic atherosclerosis, particularly in the elderly	IIa-B
Carotid–femoral PWV to detect large artery stiffening	IIa-B
Ankle–brachial index to detect PAD	IIa-B
Kidney	
Measurement of serum creatinine and estimation of GFR in all hypertensive patients[a]	I-B
Assessment of urinary protein in all hypertensive patients by dipstick	I-B
Assessment of microalbuminuria in spot urine and related to urine creatinine excretion	I-B

(*continued*)

Table 25.3 Continued

Fundoscopy	
Examination of the retina in difficult to control or resistant hypertensive patients to detect haemorrhages, exudates, papilloedema, which are associated with increased CV risk	IIa-C
Examination of the retina is not recommended in mild-to-moderate hypertensive patients without diabetes, except in young patients	III-C
Brain	
In hypertensive patients with cognitive decline, brain magnetic resonance imaging or computed tomography for detecting silent brain infarctions, lacunar infarctions, microbleeds, and white matter lesions	IIb-C

BP: blood pressure; ECG: electrocardiogram; GFR: glomerular filtration rate.
LA: left atrium; LV: left ventricle; RWT: relative wall thickness
CV, cardiovascular; LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging; PAD, peripheral artery disease; PWV, pulse wave velocity
a: The MDRD formula is currently recommended, but new methods, such as the CKD-EPI method, aim to improve the accuracy of the measurement.
ESH/ESC 2013 Guidelines for the management of arterial hypertension. *Eur Heart J*. 2013;**34**:2159–219 with permission from Oxford University Press.

Therapy

General principles

- **Low-salt diet** (<100 mmol/day, i.e. 2.4 g Na or 6 g NaCl, and ideally <1.5 g Na), weight loss, exercise (3–4 sessions up to 40 min per week), and alcohol restriction (up to two drinks a day, i.e. 1 oz, or 28 g of alcohol for men and one drink for women) are the best way for small, but significant, blood pressure reductions[5–9] and are recommended in all hypertensive patients, regardless of drug therapy (Table 25.4 and Figures 25.1, 25.2, 25.3). Although systolic blood pressure temporarily rises after coffee, chronic caffeine consumption is not associated with increased risk of hypertension.[10] **Smoking** increases BP by 10–20 mmHg with each cigarette, thus increasing the risk of hypertension with habitual smoking. High-risk patients with hypertension should also receive a **statin and low-dose aspirin**.[11] Drug-induced hypertension should be considered. **Non-steroidal anti-inflammatory** agents are the main cause, but **paracetamol** use also increases blood pressure in patients with coronary artery disease.[12] Recommendations for initiation of drug therapy are presented in Table 25.5.
- **Target values** in the general population aged ≥18 years are <140/90 mmHg in patients <60 years (JNC 8-2014)[13] or <80 years (ESC-2013[3], ACC/AHA 2011[14]), (Table 25.6). The usefulness of aiming at diastolic BP values <90 mmHg is debatable.[13,15] The **J-curve phenomenon** refers to increase in cardiac events, but not stroke, with very low diastolic blood pressures achieved by therapy.[16] A probable association of a diastolic BP ≤70 mmHg with cerebral atrophy has been reported,[17] and these low values should be avoided, especially in the presence of concomitant coronary heart disease,[18,19] and in elderly patients.[20] It seems, however, that therapy should target patients at greatest cardiovascular risk, not just those with the highest blood pressure levels.[21] The BP lowering effect should last 24 hours, and drugs which exert their antihypertensive effect over 24 hours with a once-a-day administration should be preferred.
- In patients with diabetes mellitus, recommended target values are 140/85mmHg (ESC), and 140/90 mmHg (JNC 8). In high risk patients, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of major cardiovascular events, but strokes were significantly lower in the intensive therapy group."[23] In patients with **type 2 diabetes**, an angiotensin enzyme converting (ACE) inhibitor or angiotensin receptor blocker (ARB) is necessary, particularly in diabetic nephropathy with proteinuria. In a recent meta-analysis, ACE inhibitors were associated with a 13% to 17% risk reduction in all-cause mortality, cardiovascular mortality, and major cardiovascular events, while ARBs did not show a similar benefit, with the exception of heart failure.[23] An ARB combined with a calcium channel blocker (CCB) slows progression of nephropathy to a greater extent than when combined with a thiazide.[24] ACE inhibitors should also be ideally combined with calcium channel blockers in diabetics.[25] Thiazides are associated with increased risk for new-onset diabetes,[26,27,28] but their use is not precluded since they are usually necessary in combination therapies for control of hypertension in diabetics. Treatment strategies should consider an intervention against all cardiovascular risk factors, including a statin. Because of the greater chance of postural hypotension, blood pressure should also be measured in the erect posture. In patients with the **metabolic syndrome**, drug treatment should start with a blocker of the renin–angiotensin system, followed, if needed, by the addition of a calcium antagonist or a low-dose thiazide diuretic. Statins should be given to all diabetics with hypertension above the age of 40 years, according to American Diabetes Association recommendations.[29] The ESC guidelines on diabetes recommend statins for high risk patients only.[30] Recently, the Canadian Diabetes Association recommended that all

diabetics should take statins when >40 years, and antihypertensive drugs when >55 years even in the absence of hypertension or other risk factors.[31] Recommendations of the ESC for patients with diabetes or metabolic syndrome are presented in Table 25.7.

- In patients with **renal impairment**, JNC 8 recommends target values of <140/90 mmHg, and AHA values <130/80 mmHg. The ESC recommends a systolic BP <130 mmHg if proteinuria is present. In patients with proteinuria (>3 g/24h), a BP <130/80 results in lower decline of renal function.[32] An angiotensin receptor blocker or an ACE inhibitor (but not the combination of both), often with loop diuretics are required (Table 25.8). All antihypertensive drugs, except diuretics, can be used in the haemodialysis patients, with doses determined by the haemodynamic instability and the ability of the drug to be dialysed.[3] An integrated therapeutic intervention (antihypertensive, statin, and antiplatelet therapy) has to be considered in patients with renal damage. When NSAIDs are prescribed, concomitant administration of an ACE (or ARB) and a diuretic may be associated with increased risk of kidney injury.[33]
- Hypertension is a major risk factor for **coronary artery disease**. Recommendations for patients with coronary artery disease and heart failure are presented in Table 25.9.
- In patients with a history of **stroke or TIAs**, antihypertensive treatment has markedly reduced the incidence of stroke recurrence in almost all large RCTs, using different drug regimens. Although target values <130/80 mmHg have been recommended, hard evidence on this issue is lacking, and diastolic values <70 mmHg should be probably avoided.[18] Calcium channel blockers may have a slightly greater efficacy in stroke prevention (see below), but in clinical practice, all regimens are acceptable for stroke prevention.[3] Recommendations for patients with cerebrovascular disease and atherosclerotic disease in general are provided in Table 25.10.
- Reduction of blood pressure produces benefits in the **elderly**, and, probably, there is no age threshold beyond which hypertension treatment cannot be justified,[34,35] although no data exist for patients beyond the age of 90 years.[36] Hypertension raises the risk for dementia, and antihypertensive therapy reduces the risk of dementia of both the vascular and Alzheimer's type,[37] although aggressive lowering may have opposite effects in the elderly due to cerebral hypoperfusion.[38,39] The JNC 8,[13] in patients ≥60 years without diabetes or chronic kidney disease recommends a goal BP <150/90 mmHg, but a minority report from five of the authors has argued in favour of keeping the target to 140 mmHg,[40] and probably this is the case for those patients with concomitant coronary artery disease.[41] The ESC recommends therapy in patients >80 years if the systolic BP is ≥160 mmHg, with a target SBP of 140–150 mmHg (Table 25.5).[3] The ACC/AHA[14] have previously recommended a systolic BP <145 in patients ≥80 years, but recently a target <150 mmHg was deemed reasonable for this age group.[19] (Table 25.11). A diastolic BP <70 mmHg is better avoided in elderly patients.[17,20] ARBs, calcium channel blockers, and thiazides reduce the risk of stroke more than other antihypertensive drugs,[42,43] and ARBs, ACE inhibitors, and calcium channel blockers are the drugs that have been associated with a beneficial effect on cognitive function beyond blood pressure reduction.[44] However, for patients older than age 55 years, as well as in blacks, thiazides or calcium channel blockers are more effective than ACE inhibitors and ARBs in achieving desirable blood pressure reduction (low renin group).[45] Octogenarians should be seen frequently with the medical history updated at each visit. Standing BP should always be checked for excessive orthostatic decline. BP values below which vital organ perfusion is impaired in octogenarians are not known, and according to ACC/AHA (2011), systolic BP <130 and diastolic BP <65 mm Hg should be avoided.[14] In patients treated with calcium channel blockers, concurrent use of CYP3A4 inhibitors, such as clarithromycin, should be considered with care to avoid hypotension and acute kidney injury.[46] In patients receiving ACE inhibitors or ARBs, co-trimoxazole is also associated with an increased risk of sudden death probably due to unrecognized severe hyperkalaemia.[47] In addition, antihypertensive medications have been associated with an increased risk of serious fall injuries in the elderly, particularly among those with previous fall injuries. This should be taken into account when treating older adults with multiple chronic conditions.[48]
- In **young patients** BP should be reduced to <140/90 mmHg. The case may be different for young individuals with isolated systolic hypertension (diastolic BP<90 mmHg). These individuals may have a normal central systolic BP, and can be followed with lifestyle measures only.[3] The JNC 8 gives a weak recommendation for pharmacological therapy to lower diastolic BP to <80 mmHg in people 18–29 years.[13] Compared with older antihypertensive drugs, newer agents (ARBs, ACE inhibitors, calcium antagonists, and vasodilating beta blockers) have neutral or even beneficial effects on **erectile function**.[3] Phospho-diesterase-5 inhibitors may be safely administered to hypertensives, even those on multiple drug regimens (with the possible exception of alpha-blockers and in the absence of nitrate administration, see Chapter 87).[3]
- In the general **black** population, including those with diabetes, initial therapy should include a thiazide or calcium channel blocker.
- Use of oral contraceptives is associated with some small, but significant, increases in BP. Recommendations

for therapy of hypertension in **women** as well as during pregnancy are discussed later (Hypertension in pregnancy).

- The management of '**white coat**' hypertension depends on the underlying cardiovascular risk of the patient (Table 25.12).
- Obstructive ***sleep apnoea*** is one of the most common causes of secondary hypertension (see Chapter 26).[49]
- A satisfactory blood pressure response is rarely reached with **monotherapy** alone. Useful combinations are: ACE inhibitor or ARB with a diuretic or a CCB, and a beta blocker with a diuretic or a dihydropyridine.[50] A subanalysis of the ACCOMPLISH trial suggested that diuretic-based regimens are beneficial in **obese patients** in whom there is usually an excess volume. In lean patients, calcium channel blockers may be preferable.[51]

Table 25.4 Lifestyle changes

AHA/ACC/CDC 2013 Science Advisory on blood pressure control lifestyle modifications		
Modification	**Recommendation**	**Approximate systolic BP reduction, range****
Reduce weight	Maintain normal body weight (BMI 18.5–24.9 kg/m^2)	5–20 mmHg/10 kg
Adopt DASH* eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8–14 mmHg
Lower sodium intake	a. Consume no more than 2400 mg of sodium/day; b. Further reduction of sodium intake to 1500 mg/day is associated with even greater reduction in BP; c. Reduce intake by at least 1000 mg/day, even if the desired daily sodium intake is not achieved	2–8 mmHg
Physical activity	Engage in regular aerobic physical activity, such as brisk walking (at least 30 min/day, most days of the week)	4–9 mmHg
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks/day (e.g. 24 oz beer, 10 oz wine, or 3 oz 80-proof whisky) in most men and no more than 1 drink/day in women and lighter weight persons	2–4 mmHg
ESH/ESC 2013 GL on hypertension		
Adoption of lifestyle changes		
Salt restriction to 5–6 g per day		I-A/B
Alcohol consumption ≤ 20–30 g of ethanol per day in men and ≤ 10–20 g of ethanol per day in women		I-A/B
Increased consumption of vegetables, fruits, and low-fat dairy products		I-A/B
Reduction of weight to BMI of 25 kg/m^2 and of waist circumference to <102 cm in men and <88 cm in women, unless contraindicated		I-A/B
Regular exercise, i.e. at least 30 min of moderate dynamic exercise on 5–7 days per week		I-A/B
Give all smokers advice to quit smoking and offer assistance		I-A/B
Summary of recommendations on treatment of risk factors associated with hypertension		
Statins in hypertensive patients:		
at moderate to high CV risk, targeting a low-density lipoprotein cholesterol value <3.0 mmol/L (115 mg/dL)		I-A
when overt CHD is present, targeting low-density lipoprotein cholesterol levels <1.8 mmol/L (70 mg/dL)		I-A
Antiplatelet therapy, in particular low-dose aspirin, in hypertensive patients with previous CV events		I-A
Aspirin in hypertensive patients with reduced renal function or a high CV risk, provided that BP is well controlled		IIa-B
Aspirin is not recommended in low–moderate risk hypertensive patients, in whom absolute benefit and harm are equivalent		III-A
In hypertensive patients with diabetes, a HbA1c target of <7.0% with antidiabetic treatment		I-B
HbA1c target of <7.5–8.0% in more fragile elderly patients with a longer diabetes duration, more co-morbidities and at high risk		IIa-C

BP, blood pressure; CHD, coronary heart disease; CV, cardiovascular; HbA1c, glycated haemoglobin

* DASH, dietary approaches to stop hypertension (Sacks FM, *et al*. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med*. 2001;**344**:3–10.

** The effects of implementing these modifications are dose- and time-dependent and could be greater for some individuals.

Go AS, *et al*. An effective approach to high blood pressure control: a science advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention. *J Am Coll Cardiol*. 2014;**63**:1230–8 with permission from Elsevier.

ESH/ESC 2013 Guidelines for the management of arterial hypertension. *Eur Heart J*. 2013;**34**:2159–219 with permission from Oxford University Press.

Table 25.5 Drug therapy of hypertension

JNC 8 guideline 2014. Recommendations for management of hypertension	
Recommendation 1	
In the general population aged ≥60 years, pharmacologic treatment to a goal SBP <150 mm Hg and DBP <90 mm Hg. (Strong Recommendation)	
Corollary recommendation	
In the general population aged ≥60 years, if pharmacologic treatment results in lower achieved SBP (e.g. <140 mmHg) and is well tolerated and without adverse effects on health or quality of life, treatment does not need to be adjusted. (Expert Opinion)	
Recommendation 2	
In the general population <60 years, pharmacologic treatment to a goal DBP <90 mm Hg. (For ages 30–59 years, Strong Recommendation; for ages 18–29 years, Expert Opinion)	
Recommendation 3	
In the general population <60 years, pharmacologic treatment to a goal SBP <140 mmHg. (Expert Opinion)	
Recommendation 4	
In the population aged ≥18 years with CKD, pharmacologic treatment to goal SBP <140 mmHg and DBP <90 mmHg. (Expert Opinion)	
Recommendation 5	
In the population aged ≥18 years with diabetes, pharmacologic treatment to goal SBP <140 mmHg and DBP <90 mmHg. (Expert Opinion)	
Recommendation 6	
In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, CCB, ACEI, or ARB. (Moderate Recommendation)	
Recommendation 7	
In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. (For general black population: Moderate Recommendation; for black patients with diabetes: Weak Recommendation)	
Recommendation 8	
In the population aged ≥18 years with CKD, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. This applies to all CKD patients with hypertension regardless of race or diabetes status. (Moderate Recommendation)	
Recommendation 9	
If goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug from one of the classes in recommendation 6 (thiazide-type diuretic, CCB, ACEI, or ARB). The clinician should continue to assess BP and adjust the treatment regimen until goal BP is reached. If goal BP cannot be reached with two drugs, add and titrate a third drug from the list provided. Do not use an ACEI and an ARB together in the same patient. If goal BP cannot be reached using only the drugs in recommendation 6 because of a contraindication or the need to use more than three drugs to reach goal BP, antihypertensive drugs from other classes can be used. Referral to a hypertension specialist may be indicated for patients in whom goal BP cannot be attained using the above strategy or for the management of complicated patients for whom additional clinical consultation is needed. (Expert Opinion)	
Initiation of antihypertensive drug treatment	
Prompt initiation of drug treatment in individuals with grade 2 and 3 hypertension with any level of CV risk, a few weeks after or simultaneously with initiation of lifestyle changes	I-A
Lowering BP with drugs when total CV risk is high because of OD, diabetes, CVD or CKD, even when hypertension is in the grade I range	I-B
Initiation of antihypertensive drug treatment in grade I hypertensive patients at low to moderate risk, when BP is within this range at several repeated visits or elevated by ambulatory BP criteria, and remains within this range despite a reasonable period of time with lifestyle measures	IIa-B
In elderly hypertensive patients drug treatment when SBP is ≥160 mmHg	I-A
Antihypertensive drug treatment in the elderly (at least when younger than 80 years) when SBP is in the 140–159 mmHg range, provided that antihypertensive treatment is well tolerated	IIb-C
Unless the necessary evidence is obtained, do not initiate antihypertensive drug therapy at high normal BP	III-A
Lack of evidence does not allow antihypertensive drug therapy in young individuals with isolated elevation of brachial SBP, but these individuals should be followed closely with lifestyle recommendations	III-A

(*continued*)

Table 25.5 Continued

Treatment strategies and choice of drugs	
Diuretics (thiazides, chlorthalidone and indapamide), beta blockers, calcium antagonists, ACE inhibitors, and angiotensin receptor blockers are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations with each other	I-A
Some agents are the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of OD	IIa-C
Initiation of antihypertensive therapy with a two-drug combination in patients with markedly high baseline BP or at high CV risk	IIb-C
The combination of two antagonists of the RAS should be discouraged	III-A
Other drug combinations should be considered and probably are beneficial in proportion to the extent of BP reduction. However, combinations that have been successfully used in trials may be preferable	IIa-C
Combinations of two antihypertensive drugs at fixed doses in a single tablet, because reducing the number of daily pills improves adherence, which is low in patients with hypertension	IIb-B

AHA/ACC/CDC 2013 Science Advisory on blood pressure control
Suggested medications for treatment of hypertension in presence of certain medical conditions
Coronary artery disease/post MI: BB, ACEI
Systolic heart failure: ACEI or ARB, BB, ALDO ANTAG, thiazide
Diastolic heart failure: ACEI or ARB, BB, thiazide
Diabetes: ACEI or ARB, thiazide, BB, CCB
Kidney disease: ACEI or ARB
Stroke or TIA: thiazide, ACEI

AHA Scientific Statement on secondary prevention in older adults.
Selection of antihypertensive therapy for older adults based on co-morbidities

Compelling indication	**Initial therapeutic choice**
Heart failure	Thiazide, β-blocker, ACE inhibitor, angiotensin receptor antagonist, calcium channel blocker, aldosterone antagonist
Previous myocardial infarction	β-blocker, ACE inhibitor, aldosterone antagonist, angiotensin receptor antagonist
CHD or high-risk CVD	Thiazide, β-blocker, ACE inhibitor, calcium channel blocker
Angina pectoris	β-blocker, calcium channel blocker
Aortopathy/aortic aneurysm	β-blocker, angiotensin receptor antagonist, ACE inhibitor, thiazide, calcium channel blocker
Diabetes mellitus	ACE inhibitor, angiotensin receptor antagonist, calcium channel blocker, thiazide, β-blocker
Chronic kidney disease	ACE inhibitor, angiotensin receptor antagonist
Recurrent stroke prevention	Thiazide, ACE inhibitor, angiotensin receptor antagonist, calcium channel blocker
Early dementia	Blood pressure control
Most patients will require combination therapy.	

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic BP; OD, organ damage; RAS, renin-angiotensin system; SBP, systolic blood pressure.
James P, *et al*. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;**311**:507–20 with permission from the American Medical Association.
Go AS, *et al*. An effective approach to high blood pressure control: a science advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention. *J Am Coll Cardiol*. 2014;**63**:1230–8 with permission from Elsevier.
Secondary prevention of atherosclerotic cardiovascular disease in older adults: A scientific statement from the American Heart Association. *Circulation*. 2013;**128**:2422–46.

Table 25.6 Blood pressure targets

Eighth Joint National Committee Guideline (JNC 8) 2014		
Target values in the general population regardless of diabetes or chronic kidney disease		
<60 years		<140/90
≥60 years		<150/90
AHA/ACC/ASH 2015 Scientific statement on hypertension in CAD		
BP Goal, mm Hg	**Condition**	**Class/ Level of Evidence**
<150/90	Age >80 y	IIa-B
<140/90	CAD	I-A*
	ACS	IIa-C
	HF	IIa-B
<130/80	CAD	IIb-C
	Post-myocardial infarction, stroke or TIA, carotid artery disease, PAD, AAA	IIb-C
ESH/ESC 2013 GL on hypertension. Blood pressure goals in hypertensive patients (<80 years)		
A SBP goal <140 mmHg:		
a) in patients at low–moderate CV risk;		I-B
b) in patients with diabetes;		I-A
c) in patients with previous stroke or TIA;		IIa-B
d) in patients with CHD;		IIa-B
e) in patients with diabetic or non-diabetic CKD.		IIa-B
In elderly hypertensives less than 80 years old with SBP ≥160 mmHg there is solid evidence for reducing SBP to between 150 and 140 mmHg		I-A
In fit elderly patients less than 80 years old, SBP values <140 mmHg may be considered, whereas in the fragile elderly population, SBP goals should be adapted to individual tolerability		IIb-C
In individuals older than 80 years and with initial SBP ≥160 mmHg, reduce SBP to between 150 and 140 mmHg provided they are in good physical and mental conditions		I-B
A DBP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended. It should be considered that DBP values between 80 and 85 mmHg are safe and well tolerated		I-A

* CAD risk equivalents include diabetes mellitus, peripheral arterial disease, carotid arterial disease, and abdominal aortic aneurysm.
* Both I-A and IIa-B indicated in the text of the statement.
AAA indicates abdominal aortic aneurysm; ACS, acute coronary syndrome; BP, blood pressure; CAD, coronary artery disease; HF, heart failure; PAD, peripheral arterial disease; and TIA, transient ischemic attack.
James P, *et al*. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;**311**:507–20 with permission from the American Medical Association.
Treatment of hypertension in patients with coronary artery disease: a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension. *J Am Coll Cardiol*. 2015;**65**:1998–2038 with permission from Elsevier.
ESH/ESC 2013 Guidelines for the management of arterial hypertension. *Eur Heart J*. 2013;**34**:2159–219 with permission from Oxford University Press.

Table 25.7 ESH/ESC 2013 GL on hypertension

Treatment strategies in patients with diabetes	
While initiation of antihypertensive drug treatment in diabetic patients whose SBP is ≥160 mmHg is mandatory, start drug treatment also when SBP is ≥140 mmHg	I-A
A SBP goal <140 mmHg in patients with diabetes	I-A
The DBP target in patients with diabetes is recommended to be <85 mmHg	I-A
All classes of antihypertensive agents can be used in patients with diabetes; RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria	I-A
Individual drug choice should take co-morbidities into account	I-C
Simultaneous administration of two blockers of the RAS should be avoided in patients with diabetes	III-B
Treatment strategies in hypertensive patients with metabolic syndrome	
Lifestyle changes, particularly weight loss and physical exercise, for all individuals with the metabolic syndrome. These interventions improve not only BP, but the metabolic components of the syndrome and delay diabetes onset	I-B
As the metabolic syndrome can be considered a 'pre-diabetic' state, antihypertensive agents potentially improving or at least not worsening insulin sensitivity, such as RAS blockers and calcium antagonists, are preferred drugs. Beta blockers (with the exception of vasodilating beta blockers) and diuretics only as additional drugs, preferably in association with a potassium-sparing agent	IIa-C
Prescribe antihypertensive drugs with particular care in hypertensive patients with metabolic disturbances when BP is ≥140/90 mmHg after a suitable period of lifestyle changes, and to maintain BP <140/90 mmHg	I-B
BP lowering drugs are not recommended in individuals with metabolic syndrome and high normal BP	III-A

DBP, diastolic blood pressure; RAS, renin–angiotensin system; SBP, systolic blood pressure
BP, blood pressure; RAS, renin–angiotensin system.
ESH/ESC 2013 Guidelines for the management of arterial hypertension. *Eur Heart J*. 2013;**34**:2159–219 with permission from Oxford University Press.

Table 25.8 ESH/ESC 2013 GL on hypertension

Therapeutic strategies in hypertensive patients with nephropathy	
Lowering SBP to <140 mmHg	IIa-B
When overt proteinuria is present, SBP values <130 mmHg, provided that changes in eGFR are monitored	IIb-B
RAS blockers are more effective in reducing albuminuria than other antihypertensive agents, in hypertensive patients in the presence of microalbuminuria or overt proteinuria	I-A
Reaching BP goals usually requires combination therapy of RAS blockers with other antihypertensive agents	I-A
Combination of two RAS blockers, though potentially more effective in reducing proteinuria, is not recommended	III-A
Aldosterone antagonists not recommended in CKD, especially in combination with a RAS blocker, because of the risk of excessive reduction in renal function and of hyperkalaemia	III-C

BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RAS, renin–angiotensin system; SBP, systolic blood pressure.
ESH/ESC 2013 Guidelines for the management of arterial hypertension. *Eur Heart J*. 2013;**34**:2159–219 with permission from Oxford University Press.

Table 25.9 Therapy of hypertension in patients with heart disease

ESH/ESC 2013 GL on hypertension. Therapeutic strategies in hypertensive patients with heart disease	
In hypertensive patients with CHD, a SBP goal <140 mmHg	IIa-B
Beta blockers in hypertensive patients with a recent myocardial infarction. In case of other CHD all antihypertensive agents can be used, but beta blockers and calcium antagonists for symptomatic reasons (angina)	I-A
Diuretics, beta blockers, ACE inhibitors, angiotensin receptor blockers, and/or mineralocorticoid receptor antagonists in patients with heart failure or severe LV dysfunction to reduce mortality and hospitalization	I-A
In patients with heart failure and preserved EF, there is no evidence that antihypertensive therapy per se or any particular drug, is beneficial. However, in these patients, as well as in patients with hypertension and systolic dysfunction, lower SBP to around 140 mmHg. Treatment guided by relief of symptoms (congestion with diuretic, high heart rate with beta blockers, etc.)	IIa-C
ACE inhibitors and angiotensin receptor blockers (and beta blockers and mineralocorticoid receptor antagonists if heart failure coexists) as antihypertensive agents in patients at risk of new or recurrent atrial fibrillation	IIa-C

(*continued*)

Table 25.9 Continued

All patients with LVH should receive antihypertensive agents	I-B
In patients with LVH, initiation of treatment with one of the agents that have shown a greater ability to regress LVH, i.e. ACE inhibitors, angiotensin receptor blockers and calcium antagonists	IIa-B
AHA/ACC/ASH 2015 Scientific statement on hypertension in CAD	
Patients with stable CAD	
Regimen that includes: a) β-blocker in history of prior MI b) An ACE inhibitor or ARB if there is prior MI, LV systolic dysfunction, diabetes mellitus, or CKD; and c) A thiazide or thiazide-like	I-A
The above regimen in the absence of a prior MI, LV systolic dysfunction, diabetes mellitus, or proteinuric CKD	IIa-B
If β-blockers are contraindicated or produce intolerable side effects, a nondihydropyridine CCB (such as diltiazem or verapamil) if there is no LV dysfunction	IIa-B
If either the angina or the hypertension remains uncontrolled, add a long-acting dihydropyridine CCB to β-blocker, ACE inhibitor, and thiazide or thiazide-like diuretic. β-blocker and diltiazem or verapamil with caution because of the increased risk of bradyarrhythmias and HF	IIa-B
In patients with severe hypertension and antiplatelet or anticoagulant drugs, the BP should be lowered without delay to reduce the risk of haemorrhagic stroke	IIa-C
Patients with ACS	
If no contraindication, a short-acting b1-selective β-blocker without intrinsic sympathomimetic activity (metoprolol tartrate or bisoprolol) orally within 24 hours of presentation	I-A
An intravenous β-blocker (esmolol) in severe hypertension or ongoing ischaemia	IIa-B
For haemodynamically unstable patients or when decompensated HF exists, β-blockers should be delayed until stabilization has been achieved	I-A
Nitrates to lower BP or to relieve ongoing ischaemia or pulmonary congestion Avoid in patients with suspected right ventricular infarction and in those with haemodynamic instability. Sublingual or IVs nitroglycerin for initial therapy and later a longer-acting preparation if indicated	I-A
In contraindications or intolerability of β-blockers verapamil or diltiazem for ongoing ischaemia, if LV dysfunction or HF is not present. If angina or hypertension is not controlled on a β-blocker alone, add a longer-acting dihydropyridine CCB after optimal use of an ACE inhibitor	IIa-B
An ACE inhibitor or an ARB	I-A
If there is anterior MI, or hypertension persists, or LV dysfunction or HF, or diabetes mellitus. For lower risk ACS patients with preserved LVEF and no diabetes mellitus, ACE inhibitors can be considered a first-line agent	I-B IIa-A
Aldosterone antagonists added to β-blockers and ACE inhibitors after MI and LV dysfunction and either HF or diabetes mellitus. Avoid if creatinine ≥2.5 mg/dL in men, ≥2.0 mg/dL in women, or K ≥5.0 mEq/L	I-A
Loop diuretics preferred over thiazide and thiazide-type diuretics with HF (NYHA III or IV) or for CKD and a GFR <30 mL/min.	I-B
For patients with persistent hypertension not controlled with a β-blocker, an ACE inhibitor, and an aldosterone antagonist, a thiazide or thiazide-type diuretic may be added	I-B
Targets are described in Table 25.6. Avoid decreases in DBP to <60 mm Hg because this may reduce coronary perfusion and worsen ischaemia.	
Heart failure	
Risk factors management such as dyslipidaemia, obesity, diabetes mellitus, smoking, and dietary sodium and a closely monitored exercise program	I-C
Patients should be treated with ACE inhibitors (or ARBs), β-blockers (carvedilol, metoprolol succinate, bisoprolol, or nebivolol), and aldosterone receptor antagonists	I-A
Add thiazide or thiazide-type diuretics for BP control and to reverse volume overload and associated symptoms. In patients with severe HF (NYHA III and IV) or those with severe renal impairment (eGFR <30 mL/min), loop diuretics for volume control, but are less effective than thiazide or thiazide-type diuretics in lowering BP	I-C
Studies have shown equivalence of benefit of ACE inhibitors and the ARBs candesartan or valsartan in HF with reduced ejection fraction. Either class of agents is effective in lowering BP	I-A

(*continued*)

Table 25.9 Continued

Spironolactone and eplerenone should be included in the regimen if there is HF (NYHA II–IV) LVEF <40% (see above for contraindications) May be used with a thiazide or thiazide-like diuretic, particularly in patients with resistant hypertension	I-A
Hydralazine plus isosorbide dinitrate should be added to the regimen of diuretic, ACE inhibitor or ARB, and β-blocker in African American patients with NYHA III or IV HF with reduced LVEF	I-A
In hypertension and HF with preserved LVEF, control systolic and diastolic hypertension ventricular rate in AF and pulmonary congestion and peripheral oedema	I-A I-C I-C
β-blockers, ACE inhibitors, ARBs, or CCBs in HF with preserved LVEF of HF	IIb-C
In HF with reduced LVEF avoid verapamil and diltiazem, clonidine, moxonidine, and hydralazine without a nitrate	III-B harm
α-Adrenergic blockers such as doxazosin should be used only if other drugs are inadequate to control BP. NSAIDs should be used with caution	IIa-B
In older individuals with wide pulse pressures, lowering SBP may cause very low DBP values (<60 mmHg). Octogenarians should be checked for orthostatic changes with standing, and an SBP <130 mm Hg and a DBP <65 mm Hg should be avoided.	IIa-B
The therapy of acute hypertension with pulmonary oedema is as described in ACS	

BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RAS, renin–angiotensin system; SBP, systolic blood pressure.
James P, *et al*. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;**311**:507–20 with permission from the American Medical Association.
Treatment of hypertension in patients with coronary artery disease: a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension. *J Am Coll Cardiol*. 2015;**65**:1998–2038 with permission from Elsevier.
ESH/ESC 2013 Guidelines for the management of arterial hypertension. *Eur Heart J*. 2013;**34**:2159–219 with permission from Oxford University Press.

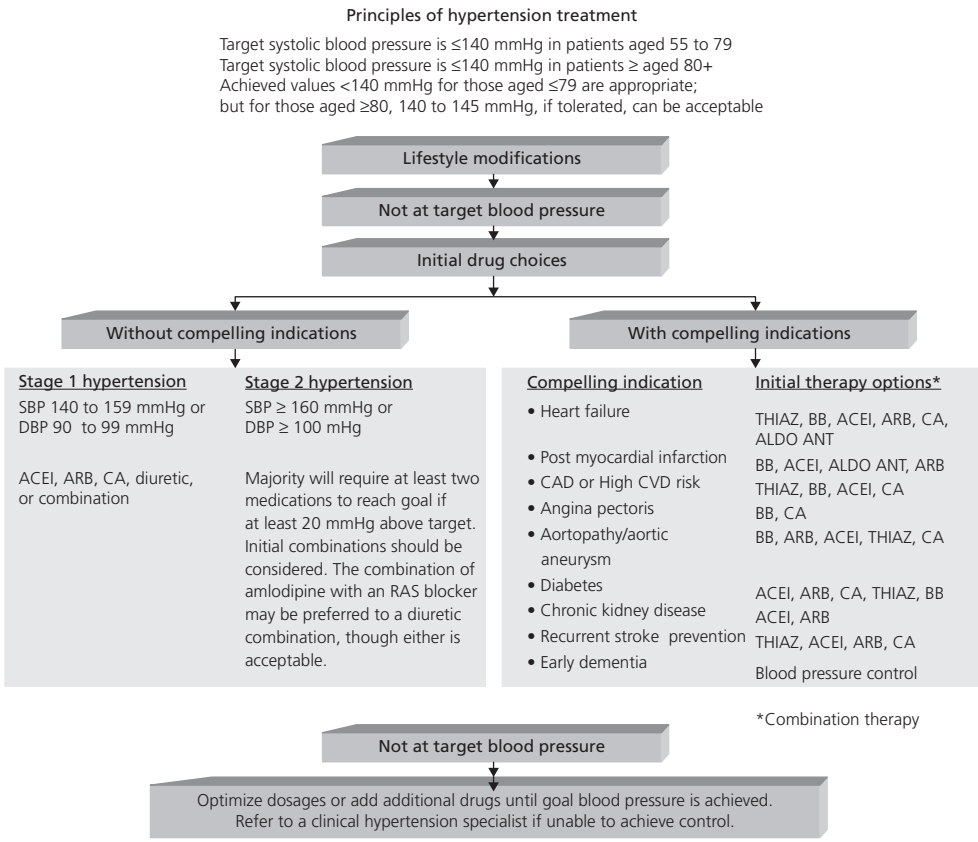
Table 25.10 ESH/ESC 2013 GL on hypertension

Therapeutic strategies in hypertensive patients with cerebrovascular disease	
Do not intervene with BP-lowering therapy during the first week after acute stroke, irrespective of BP level, although clinical judgement should be used in the face of very high SBP values	III-B
Antihypertensive treatment in hypertensive patients with a history of stroke or TIA, even when initial SBP is in the 140–159 mmHg range	I-B
In hypertensive patients with a history of stroke or TIA, a SBP goal of <140 mmHg	IIa-B
In elderly hypertensives with previous stroke or TIA, SBP values for intervention and goal somewhat higher	IIb-B
All drug regimens are recommended for stroke prevention, provided that BP is effectively reduced	I-A
Therapeutic strategies in hypertensive patients with atherosclerosis, arteriosclerosis, and peripheral artery disease	
In the presence of carotid atherosclerosis, prescription of calcium antagonists and ACE inhibitors, as these agents have shown a greater efficacy in delaying atherosclerosis progression than diuretics and beta blockers	IIa-B
In hypertensive patients with a PWV above 10 m/s all antihypertensive drugs should be considered provided that a BP reduction to <140/90 mmHg is consistently achieved	IIa-B
Antihypertensive therapy is recommended in hypertensive patients with PAD to achieve a goal of <140/90 mmHg, because of their high risk of myocardial infarction, stroke, heart failure, and CV death	I-A
Though a careful follow up is necessary, beta blockers for the treatment of arterial hypertension in patients with PAD, since their use does not appear to be associated with exacerbation of PAD symptoms	IIb-A

BP, blood pressure; SBP, systolic blood pressure; TIA, transient ischaemic attack.
ACE, angiotensin-converting enzyme; BP, blood pressure; CV, cardiovascular; PAD, peripheral artery disease; PWV, pulse wave velocity.
ESH/ESC 2013 Guidelines for the management of arterial hypertension. *Eur Heart J*. 2013;**34**:2159–219 with permission from Oxford University Press.

Table 25.11 Hypertension in the elderly

ACCF/AHA 2011 Expert consensus document on hypertension in the elderly
Treatment of hypertension in the elderly



Eighth Joint National Committee (JNC-8) 2014

In the general population aged ≥60 years, pharmacological treatment to lower BP to <150/90 mmHg	Strong recommendation
If pharmacological treatment is well tolerated and results in systolic BP <140 mmHg, it does not need to be adjusted	Expert opinion

ESH/ESC 2013 GL on hypertension
Antihypertensive treatment strategies in the elderly

In elderly hypertensives with SBP ≥160 mmHg, reduce SBP to between 150 and 140 mmHg	I-A
In fit elderly patients <80 years old, antihypertensive treatment at SBP values ≥140 mmHg, with a target SBP <140 mmHg if treatment is well tolerated	IIb-C
In individuals older than 80 years with an initial SBP ≥160 mmHg, reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions	I-B
In frail elderly patients, leave decisions on antihypertensive therapy to the treating physician, and based on monitoring of the clinical effects of treatment	I-C
Continuation of well-tolerated antihypertensive treatment when a treated individual becomes octogenarian	IIa-C
All hypertensive agents can be used in the elderly, although diuretics and calcium antagonists may be preferred in isolated systolic hypertension	I-A

ACEI indicates angiotensin-converting enzyme inhibitor; ALDO ANT, aldosterone antagonist; ARB, aldosterone receptor blocker; BB, beta blocker; CA, calcium antagonist; CAD, coronary artery disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; RAS, renin–angiotensin system; SBP, systolic blood pressure; and THIAZ, thiazide diuretic.

ACCF/AHA 2011 Expert consensus document on hypertension in the elderly. *J Am Coll Cardiol*. 2011;**57**:2037–114 with permission from Elsevier.

James P, *et al*. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;**311**:507–20 with permission from the American Medical Association.

ESH/ESC 2013 Guidelines for the management of arterial hypertension. *Eur Heart J*. 2013;**34**:2159–219 with permission from Oxford University Press.

Table 25.12 ESH/ESC 2013 GL on hypertension

Treatment strategies in white coat and masked hypertension	
In white coat hypertensives without additional risk factors, therapeutic intervention should be limited to lifestyle changes only, but this decision should be accompanied by a close follow-up	IIa-C
In white coat hypertensives with a higher CV risk because of metabolic derangements or asymptomatic OD, drug treatment addition to lifestyle changes	IIb-C
In masked hypertension, both lifestyle measures and antihypertensive drug treatment, because this type of hypertension has been consistently found to have a CV risk very close to that of in- and out-of-office hypertension	IIa-C

CV, cardiovascular; OD, organ damage.
ESH/ESC 2013 Guidelines for the management of arterial hypertension. *Eur Heart J.* 2013;**34**:2159–219 with permission from Oxford University Press.

Other risk factors, asymptomatic organ damage or disease	Blood Pressure (mmHg)			
	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other RF	• No BP intervention	• Lifestyle changes for several months • Then add BP drugs targeting <140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
1–2 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
≥3 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
OD, CKD stage 3 or diabetes	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
Symptomatic CKD, CKD stage ≥4 or diabetes with OD/RFs	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90

Figure 25.1 ESC 2013 GL on hypertension. Initiation of lifestyle changes and antihypertensive drug treatment. Targets of treatment are also indicated. Colours indicate risk, with red the highest. In patients with diabetes, the optimal DBP target is between 80 and 85 mmHg. In the high normal BP range, drug treatment should be considered in the pregnant woman with a raised out-of-office BP (masked hypertension).

RF: Risk factor (see Table 25.1).
ESH/ESC 2013 Guidelines for the management of arterial hypertension. Eur Heart J. 2013;**34**:2159–219 with permission from Oxford University Press.

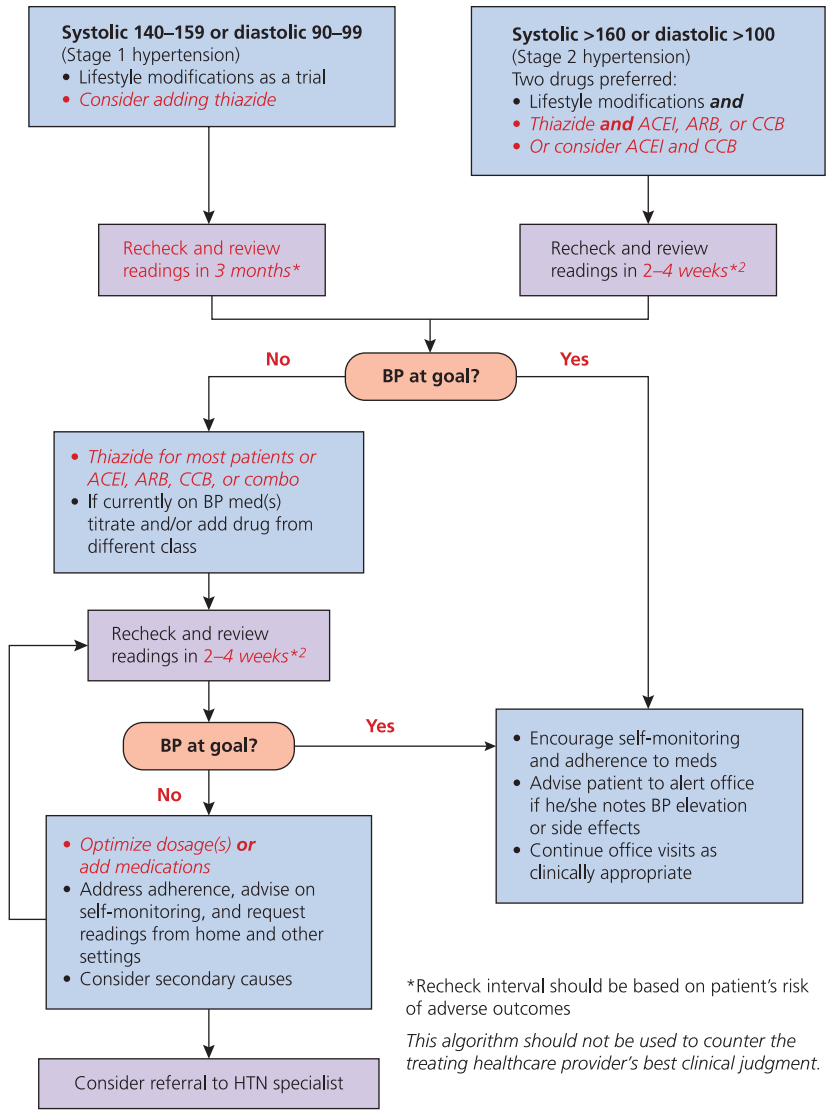


Figure 25.2 Controlling hypertension in adults.

AHA/ACC/CDC 2013 Science Advisory on high blood pressure control. An effective approach to high blood pressure control. *J Am Coll Cardiol*. 2014;**63**:1230–8 with permission from Elsevier.

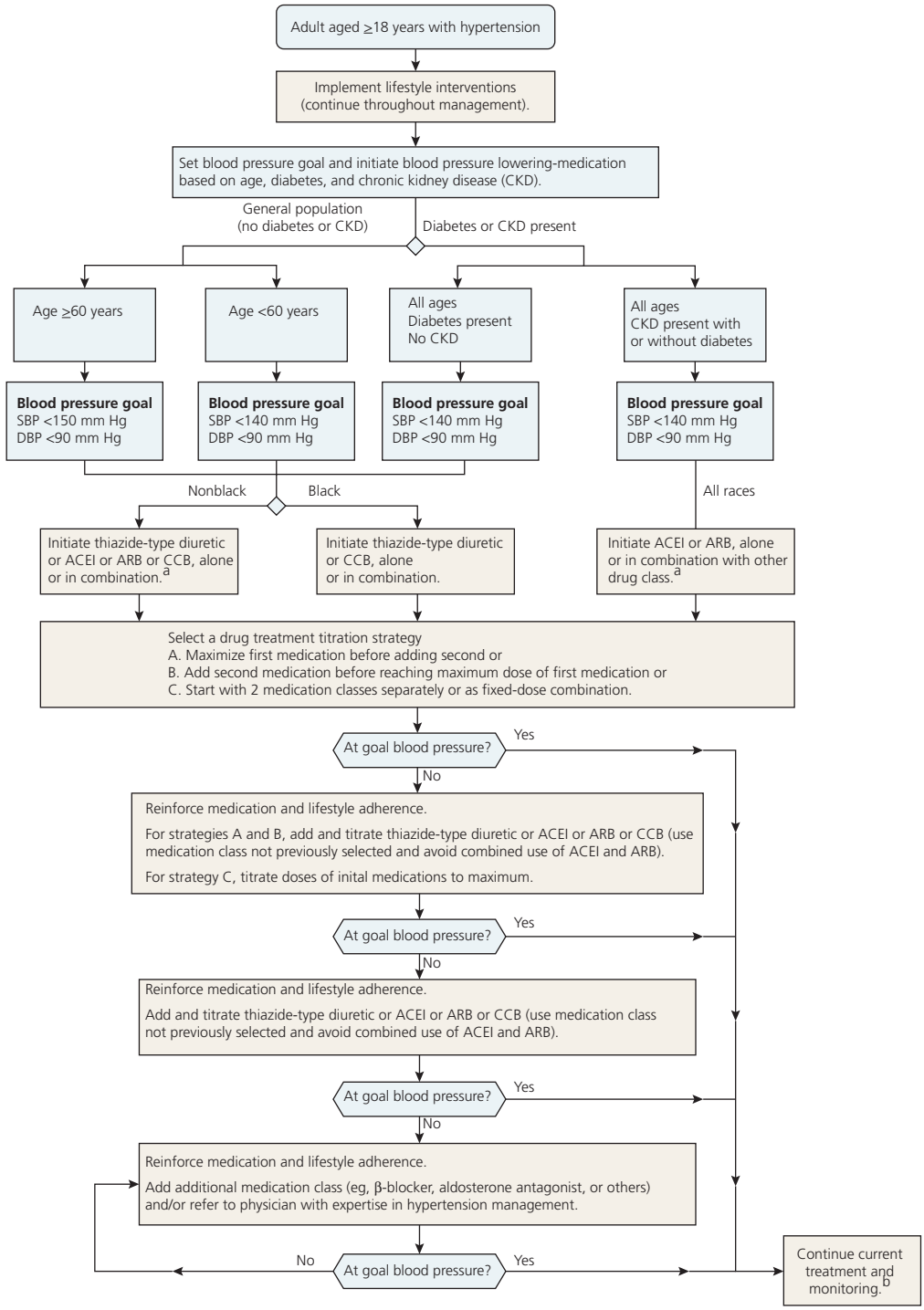


Figure 25.3 JNC 8. Hypertension guideline management algorithm.

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; ACEI, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; and CCB, calcium channel blocker.

a: ACEIs and ARBs should not be used in combination.

b: If blood pressure fails to be maintained at goal, re-enter the algorithm, where appropriate, based on the current individual therapeutic plan.

James P, *et al*. 2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;**311**:507–20 with permission from the American Medical Association.

Drugs

Specific recommendations and criteria for drug choice are in Table 25.13. Drug dosages are presented in Table 25.14.

Renin-angiotensin inhibitors

ACE inhibitors and ARBs are first-choice therapy in most instances, and especially in young people who generally have a more active renin-angiotensin system. Adherence to medication is better with ARB, followed by ACE inhibitors, CCBs, diuretics, and beta-blockers in descending order.[52]

Angioedema induced by treatment with ACE inhibitors is estimated to occur in up to 0.68% of patients, and symptoms can take years to appear. Icatibant, a selective bradykinin B2-receptor antagonist (FDA-approved for treating patients with hereditary angioedema but a very expensive drug) may resolve oedema much quicker (8 vs 27 h) than corticosteroids and antihistamines that are typically directed at mast cell-mediated angioedema.[53] ARBs also have a considerably lower incidence of **cough**.[54] They may prevent stroke and the development of dementia in hypertensives better than ACE inhibitors due to angiotensin II type 1 (AT1) receptor blockade and AT2 stimulation by increased production of angiotensin II and IV.[55] AT2 receptors reduce focal cerebral ischaemia by vasodilation and antioxidant activities. Such an advantage of ARBs over ACE inhibitors, however, has not been apparent in clinical trials.[56] In diabetics, ACE inhibitors are preferred (see 'General principles').

Initial suggestions that ARBs (such as telmisartan) are associated with a modestly increased risk of new cancer diagnosis,[57,58] were subsequently refuted.[59,60,61] In a meta-analysis of 32 trials, the FDA (2 June 2011) has also concluded that treatment with an ARB medication does not increase a patient's risk of developing cancer.[62]

The combined use of ACE inhibitors and ARBs is not recommended for the treatment of hypertension.[63,64]

Since ARBs and ACE inhibitors both increase plasma renin activity, the direct renin inhibitor **aliskiren** (150–300 mg od) has the potential to be more beneficial. It has been shown to have comparable efficacy and side effects with ARBs.[65] Combinations of aliskiren with valsartan or amlodipine have been more effective than either drug alone.[66,67] However, aliskiren should not be used with an ACE inhibitor or ARB in patients with type 2 diabetes and renal impairment. The ALTITUDE trial was stopped due to an increased incidence of non-fatal stroke, renal complications, hyperkalaemia, and hypotension with this combination.[68]

Calcium channel blockers

Both long-acting dihydropyridines and non-dihydropyridine calcium channel blockers have been studied in hypertension, and are now considered first-choice drugs together with ACE inhibitors/ARBs.

CCBs may offer protection against dementia due to a reduction of excess intracellular free calcium in neurons, which seems to happen in patients with dementia of the Alzheimer's type.[37,55] **Diltiazem** and **verapamil** cause less peripheral oedema than dihydropyridines and no tachycardia, and are better tolerated (particularly diltiazem; verapamil may cause constipation). They can be added to a scheme containing a dihydropyridine in resistant cases. They are especially useful in patients with chronic renal disease and renal transplantation,[69,70] but care is needed because diltiazem may interfere with cyclosporine levels. The combination of CCBs with renin–angiotensin system blockers reduce the risk of CCB-associated peripheral oedema, and ACE inhibitors might be more efficacious than ARBs in this respect.[71] However, there is evidence that patients with hypertension, and especially diabetics, treated with CCBs have increased incident heart failure,[72] and, as monotherapy, CCBs are inferior to ACE inhibitors, ARBs, and diuretics for reducing the risk of acute myocardial infarction, congestive heart failure, and major cardiovascular events.[73] All CCBs are contraindicated in heart failure, and diltiazem and verapamil in sick sinus syndrome, AV nodal conduction disease, and concomitant use of high doses of beta-blockers. An association of CCBs, and possibly diuretics, with chronic eczematous eruptions in patients older than 50 years has been reported.[74] In the elderly, concurrent use of clarithromycin a CYP3A4 inhibitor has been associated with increased levels of CCBs, hypotensive episodes, and a greater 30-day risk of hospitalization with acute kidney injury.[46] Third-generation CCBs, such as lercanidipine, lacidipine, and manidipine, may induce less peripheral oedema than other dihydropyridines.[75]

Table 25.13 ESH/ESC 2013 GL on hypertension. Criteria for antihypertensive drugs selection

Compelling and possible contra-indications to the use of antihypertensive drugs		
Drug	**Compelling**	**Possible**
Diuretics (thiazides)	Gout	Metabolic syndrome Glucose intolerance Pregnancy Hypercalcaemia Hypokalaemia

(*continued*)

Table 25.13 Continued

Drug	Compelling	Possible
Beta blockers	Asthma A–V block (grade 2 or 3)	Metabolic syndrome Glucose intolerance Athletes and physically active patients Chronic obstructive pulmonary disease (except for vasodilator beta blockers)
Calcium antagonists (dihydropyridines)		Tachyarrhythmia Heart failure
Calcium antagonists (verapamil, diltiazem)	A–V block (grade 2 or 3, trifascicular block) Severe LV dysfunction Heart failure	
ACE inhibitors	Pregnancy Angioneurotic oedema Hyperkalaemia Bilateral renal artery stenosis	Women with childbearing potential
Angiotensin receptor blockers	Pregnancy Hyperkalaemia Bilateral renal artery stenosis	Women with childbearing potential
Mineralocorticoid receptor antagonists	Acute or severe renal failure (eGFR <30 mL/min) Hyperkalaemia	

Drugs to be preferred in specific conditions

Condition	Drug
Asymptomatic organ damage	
LVH	ACE inhibitor, calcium antagonist, ARB
Asymptomatic atherosclerosis	Calcium antagonist, ACE inhibitor
Microalbuminuria	ACE inhibitor, ARB
Renal dysfunction	ACE inhibitor, ARB
Clinical CV event	
Previous stroke	Any agent effectively lowering BP
Previous myocardial infarction	BB, ACE inhibitor, ARB
Angina pectoris	BB, calcium antagonist
Heart failure	Diuretic, BB, ACE inhibitor, ARB, mineralocorticoid receptor antagonists
Aortic aneurysm	BB
Atrial fibrillation, prevention	Consider ARB, ACE inhibitor, BB or mineralocorticoid receptor antagonist
Atrial fibrillation, ventricular rate control	BB, non-dihydropyridine calcium antagonist
ESRD/proteinuria	ACE inhibitor, ARB
Peripheral artery disease	ACE inhibitor, calcium antagonist
Other	
ISH (elderly)	Diuretic, calcium antagonist
Metabolic syndrome	ACE inhibitor, ARB, calcium antagonist
Diabetes mellitus	ACE inhibitor, ARB
Pregnancy	Methyldopa, BB, calcium antagonist
Blacks	Diuretic, calcium antagonist

A-V, atrio-ventricular; eGFR, estimated glomerular filtration rate; LV, left ventricular.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, beta blocker; BP, blood pressure; CV, cardiovascular; ESRD, end-stage renal disease; ISH, isolated systolic hypertension; LVH, left ventricular hypertrophy.
ESH/ESC 2013 Guidelines for the management of arterial hypertension. *Eur Heart J*. 2013;**34**:2159–219 with permission from Oxford University Press.

Table 25.14 Dosages of drugs for hypertension (in mg)

ACEI	
Captopril	25–100 bd
Enalapril	2.5–10 bd
Lisinopril	10–40 od
Perindopril	4–8 od
Ramipril	2.5–10 od
Trandolapril	0.5–4 bd
ARB	
Valsartan	40–320 od
Irbesartan	75–300 od
Telmisartan	40–80 od
Candesartan	4–32 od
Losartan	25–50 bd
Eprosartan	200–400 bd
Calcium channel blockers	
Nifedipine (slow release)	30–90 od
Amlodipine	5–10 od
Felodipine	5–10 od
Lacidipine	2–6 od
Verapamil slow release	240–480 od
Diltiazem slow release	120–360 od
Aldosterone antagonists	
Eplerenone	25–50 od
Spironolactone	25–50 od
Other potassium-sparing diuretics	
Amiloride	2.5–5 od
Loop diuretics	
Furosemide	10–40 od or bd
Bumetanide	0.5–1.0 od or bd (not licensed for hypertension in the USA)
Torsemide	5–10 od
Thiazide diuretics	
Hydrochlorothiazide	25–50 od
Bendrofluazide	5–10 od
Thiazide-like	
Metolazone	2.5–5 od
Indapamide	1.25–2.5 od
Chlorthalidone	12.5–25 od
Beta blockers	
Carvedilol	6.25–25 bd
Nebivolol	2.5–10 od

Thiazide diuretics

Thiazides exert their action by reducing extracellular fluid and plasma volume, leading to decreased cardiac preload. They also reduce systemic vascular resistance, but the exact mechanisms are unclear. Secondary activation of the renin–aldosterone axis makes their combination with ACE inhibitors/ARB attractive. They are particularly indicated in **low-renin or salt-sensitive hypertension** (elderly, obese, blacks) and in **resistant hypertension**.

Thiazides effectively reduce blood pressure and the risk of cardiovascular events, but at a risk of an excess of 3–4% of new cases of diabetes over several years, compared to other antihypertensive medications.[76] Patients with hypertension have a higher risk of developing new-onset diabetes in general, and that risk, although relatively small, is higher with diuretics in patients with impaired glucose tolerance and cardiovascular risk factors.[28] However, as discussed, their use in diabetes is not precluded. The odds ratio of developing it with diuretics almost doubles, compared to ARB (odds ratio for ARB 0.57, ACE inhibitor 0.67, CCB 0.75, placebo 0.77, beta-blocker 0.90, with diuretics as reference).[26] In the ALLHAT study, the largest randomized trial performed to date, **chlorthalidone** (12.5–25 mg daily) was more effective in reducing systolic blood pressure and cardiovascular complications than lisinopril (10–40 mg daily) or amlodipine (2.5–10 mg daily), but at an increased risk of diabetes.[27] Chlorthalidone is a thiazide-like diuretic that binds to erythrocyte carbonic anhydrase and has a longer half-life than hydrochlorothiazide. It is twice as potent as hydrochlorothiazide,[77] and probably superior to hydrochlorothiazide in reducing cardiovascular events,[78] although it produces more pronounced hypokalaemia in the elderly.[79] It seems that the difference in antihypertensive efficacy of various thiazides is mainly due to their potency.[80] A meta-analysis of 14 studies has shown that hydrochlorothiazide in doses 12.5–25 mg was significantly less effective as monotherapy in reducing blood pressure, compared to ARB, ACEI, beta blockers, and calcium channel blockers.[81] Thiazides are a reasonable choice in obese patients with excess volume, but they are less protective than calcium channel blockers against cardiovascular events in lean patients.[82] **Indapamide** is a non-thiazide sulfonamide that also possesses Vaughan-Williams class III activity and may prolong the QT.

Thiazides are considered ineffective when the **glomerular filtration rate** decreases below 30–40 mL/min/1.73 m^2 of BSA, since the reduced glomerular filtration rate limits the overall filtered sodium load reaching the distal tubule, and reabsorption in the distal tubule is only modestly effective as compared with that in the thick ascending limb, although direct evidence is lacking. However, thiazides can elicit an antihypertensive response in patients with chronic kidney disease.[76]

Hypokalaemia and **hypomagnesaemia** are common, especially in the elderly and with hydrochlorothiazide or chlorthalidone doses exceeding 25 mg daily. Hydrochlorothiazide appears safer than chlorthalidone in the elderly, in this respect.[79] Hypokalaemia is managed by

salt restriction, hypomagnesaemia correction, and addition of an ARB/ACE inhibitor or a potassium-sparing diuretic (preferred to supplemental KCl). These should also be considered from the beginning of therapy if baseline potassium levels are <3.8 mmol/L. Potassium homeostasis is important in view of the evidence that hypokalaemia is implicated in thiazide-induced dysglycaemia and the development of coronary events.[83] **Dilutional hyponatraemia** may also occur, especially in the elderly and with combinations with loop diuretics. SSRIs and excessive water intake should be avoided. Hyponatraemia (serum sodium concentration <135mmol/L) is the most common disorder of body fluid and electrolyte balance encountered in clinical practice. Guidelines for its treatment have been recently published by European societies.[84] Correction of hypokalaemia may also reduce night **muscle cramps**. Alternatively, calcium channel blockers, such as diltiazem, vitamin B complex, and naftidrofuryl oxalate (a drug that may enhance utilization of oxygen and glucose in peripheral vascular disease and protection of brain parenchyma during anoxia), with or without magnesium supplements, may be tried for muscle cramps.[85] Quinine derivatives are better avoided for routine use because of the potential of toxicity.

Thiazides reduce the excretion of calcium and uric acid, and exacerbations of **gout** may require discontinuation of the thiazide during the acute attack if uric acid levels are significantly elevated. Reduced uric acid excretion is also accentuated by low-dose aspirin administration. Uricosuric prophylaxis may be needed in the long term.

Thiazides may increase **total cholesterol and LDL** by 5–7% in the first year of therapy.[76]

Concerns have also been raised about a possible association between long-term use of diuretics and **renal carcinoma**, but hypertension itself increases the risk of malignant disease.[86]

Loop diuretics, aldosterone antagonists, and potassium-sparing agents

Loop diuretics are less effective in reducing blood pressure than thiazides.[76] Usually, **furosemide** is used in diuretic tolerance (see Chapter 31 on CCF) or renal failure (glomerular filtration rate <40 mL/min/1.73 m^2 of BSA, usually, but not invariably, corresponding to a creatinine >2.5 mg/dL). **Bumetanide** and **torsemide** (longer action than furosemide) may be used in patients not responsive to furosemide.

Aldosterone antagonists. Eplerenone is a selective aldosterone antagonist that, combined with enalapril, decreases proteinuria and LVH beyond what is achieved by either drug alone.[87,88] Renal function and serum potassium levels must be closely monitored due to the risk of hyperkalaemia, especially when these agents are used together with an ACE inhibitor or ARB. **Spironolactone** is also effective but may cause painful gynaecomastia in men (antagonist of aldosterone and androgen and progesterone receptors). Aldosterone antagonists have been found particularly effective in patients who are obese or have sleep apnoea.[89] They should not be used in the presence of hyperkalaemia (K >5 mmol/L) or creatinine >2.5 mg/dL.

Potassium-sparing agents are amiloride and triamterene. **Amiloride** is an epithelial sodium channel blocker that is more effective than spironolactone in blacks with drug-resistant hypertension.[90] It is combined with thiazides for correction of hypokalaemia.

Beta blockers

In patients with uncomplicated hypertension, beta blockers exert no effect in reducing stroke, and do not have any protective effect with regard to coronary artery disease. They may increase the risk for new-onset diabetes,[91,92,93,94] although this finding is not consistent.[28] In contrast to what occurs in patients with myocardial infarction and heart failure, beta blocker-associated reduction in heart rate might increase the risk of cardiovascular events and death in hypertensive patients.[92,95] These effects have been attributed to suboptimal effect in lowering blood pressure compared to other drugs, their 'pseudoantihypertensive' efficacy (failure to lower central aortic pressure), lack of an effect on regression of left ventricular hypertrophy and endothelial dysfunction, and unfavourable metabolic effects. However, much of the unfavourable data were collected from studies involving traditional beta blockers, such as atenolol. Vasodilatory third-generation beta blockers (i.e. carvedilol and nebivolol) reduce blood pressure, in large part through reducing systemic vascular resistance rather than by decreasing cardiac output, and have less effect on metabolic and lipid parameters. **Carvedilol** is a very slightly β_1-selective beta blocker that becomes non-selective at higher doses. In addition, it possesses alpha 1-blocking (vasodilatory) and antioxidant properties.[96] **Nebivolol** is the most β_1-selective beta blocker (3-fold that of bisoprolol and more than 4-fold that of metoprolol) at doses <10 mg. It does not have sympathomimetic activity, but it is an agonist of β_2 and β_3 receptors and can cause relatively less bronchoconstriction or sexual dysfunction. It also improves endothelial dysfunction via stimulation of endothelial nitric oxide synthase and antioxidant properties.[97] According to published evidence, beta blockers, in general, are indicated in hypertensive patients with prior myocardial infarction (metoprolol), heart failure (carvedilol, metoprolol, bisoprolol, and nebivolol in the elderly), arrhythmias (propranolol, carvedilol, metoprolol, bisoprolol), patients <60 years old with increased sympathetic activity (metoprolol, bisoprolol, carvedilol, nebivolol). In phaeochromocytoma, labetalol, a beta and alpha blocker, is preferred to avoid unopposed alpha-mediated vasoconstriction.

Device-based therapy

Various methods for therapeutic modulation of the sympathetic nervous system, via radiofrequency ablation (mainly) and baroreceptor stimulation within the renal arteries, as well as central iliac arteriovenous anastomosis are under study.[98–101] Renal denervation has also been promising in cases of resistant hypertension,[102,103] although it failed to reach its primary efficacy endpoint in the SYMPLICITY HTN-3 trial.[103]

Non-cardiac surgery

Non-cardiac surgery may not be deferred with BP <180/110 mmHg (ESC 2014 GL on non-cardiac surgery, IIb-B), but large peri-operative BP fluctuations should be avoided (IIa-B).[104]

Follow-up

Titration to BP control requires regular visits, followed by 6-month follow-up after establishment of normal values. Therapy is usually needed for life, unless lifestyle modifications are successful.

Resistant hypertension

Resistant hypertension is generally defined as failure to achieve optimum blood pressure values when a patient adheres to maximum tolerated doses of 3 antihypertensive drugs including a diuretic.[3,13,105,106] There is no consensus on a uniform definition for resistant hypertension, and its exact prevalence is not known, with reported values ranging from 13 to 30%.[105,106] Refractory hypertension can be either true (Table 25.15) or apparent, i.e. pseudohypertension (see Chapter 24), due to bad measuring technique or non-adherence to treatment. According to the largest published studies so far (NHANES, ACOT, ALLHAT, ACCOMPLISH), up to one-third of hypertensive patients remain uncontrolled on two antihypertensive agents while, among patients with incident hypertension and treatment with ≥3 antihypertensive agents, 2% will develop resistant hypertension and will have an increased risk of cardiovascular events.[107] Since volume overload is the most common cause of resistant hypertension, diuretics are essential.[108] Hyperaldosteronism is also common in patients with resistant hypertension,[109,110] and a mineralocorticoid receptor antagonists may be useful in all resistant cases.

The management of resistant hypertension (Table 25.16) can be improved by evaluating whether the failure of blood pressure control results from sodium volume excess (**low plasma renin activity**), insufficiently blocked renin levels (**high plasma renin activity**), or a combination of both (**medium plasma renin activity**) and adjusting therapy accordingly.[111,112] Low plasma renin activity is an indication of a diuretic, and high plasma renin activity of an ACE inhibitor or ARB or a direct renin inhibitor, such as aliskiren, and, if this fails, addition of a vasodilating beta blocker. In patients with normal plasma renin activity who are already on triple therapy of ACE inhibitor/ARB, diuretic, and calcium channel blockers, an aldosterone antagonist, if the patient is obese or has sleep apnoea, may be beneficial. If BP control is still not achieved with full doses of a four-drug combination, the use of other agents, such as alpha blockers (**doxazosin** 4–8 mg od),[113] the imidazoline I_1-receptor agonist **moxonidine** (0.2–0.4 mg od) that has favourable effects on the insulin resistance syndrome, drugs with central action on the sympathetic system [alpha agonists, such as **methyldopa** (250–750 mg bd) and **clonidine**], or vasodilators, such as **hydralazine**, may be needed. These agents are effective for lowering BP but have poor tolerability and lack of positive outcome data. Moxonidine, clonidine, and hydralazine without a nitrate should be avoided in ischaemic heart failure.[19] Novel drugs, such as endothelin receptor antagonists (darusentan), aldosterone synthetase inhibitors, and gene therapies are under study.[114] Intensive lipid-lowering is also recommended in patients with treatment-resistant hypertension.[115]

Renal denervation is considered by the ESC (but not approved by the FDA) when the following criteria are fulfilled:[102]

- Office-based systolic BP ≥ 160 mmHg (≥150 mmHg diabetes type 2)
- ≥3 antihypertensive drugs in adequate dosage and combination (including diuretic)
- Lifestyle modification
- Exclusion of secondary hypertension
- Exclusion of pseudo-resistance using ambulatory BP monitoring (average BP > 130 mmHg or mean daytime BP > 135 mmHg)
- Preserved renal function (GFR ≥45 mL/min/1.73 m^2)
- Eligible renal arteries: no polar or accessory arteries, no renal artery stenosis, no prior revascularization

However, recently the SYMPLICITY HTN-3 trial did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after renal-artery denervation as compared with a sham

Table 25.15 True resistant hypertension

Poor adherence to therapeutic plan
Associated condition
Diabetes mellitus or metabolic syndrome
Excess alcohol intake
Obesity (visceral obesity)
Obstructive sleep apnoea
Anxiety-induced hyperventilation or panic attacks
Pain
Unsuspected secondary cause

(*continued*)

Table 25.15 Continued

Irreversible or scarcely reversible organ damage
Volume overload
Excessive dietary sodium intake
Inadequate diuretic treatment
Reduced renal function
Hyperaldosteronism
Compensatory response to vasodilatory drugs
Drug-induced
Non-steroidal anti-inflammatory drugs (including COX2 inhibitors and paracetamol)
Sympathomimetics (nasal drops, appetite suppressants)
Cocaine, amphetamines
Oral contraceptives
Glucocorticoids/mineralocorticoids
Liquorice
Herbal drugs (ginseng, yohimbin, ma huang, bitter orange)
Erythropoietin, ciclosporin, tacrolimus, carbenoxolone
Antiangiogenic and anti-vascular endothelial growth factor (VEGF) chemotherapy agents (bevacizumab, sorafenib, sunitinib, pazopanib)
Causes of spurious resistant hypertension
Isolated office (white coat) hypertension
Failure to use large cuff on large arm
Pseudohypertension

Table 25.16 ESH/ESC 2013 on hypertension

Therapeutic strategies in patients with resistant hypertension	
In resistant hypertensive patients, check whether the drugs included in the existing multiple drug regimen have any BP lowering effect, and withdraw them if their effect is absent or minimal	I-C
Mineralocorticoid receptor antagonists, amiloride, and the alpha-1-blocker doxazosin, if no contraindication exists	IIa-B
In case of ineffectiveness of drug treatment invasive procedures such as renal denervation and baroreceptor stimulation	IIb-C
Until more evidence is available on the long-term efficacy and safety of renal denervation and baroreceptor stimulation, these procedures should remain in the hands of experienced operators and diagnosis and follow-up restricted to hypertension centres	I-C
Invasive approaches are considered only for truly resistant hypertensive patients, with clinic values ≥160 mmHg SBP or ≥110 mmHg DBP and with BP elevation confirmed by ABPM	I-C

ESH/ESC 2013 Guidelines for the management of arterial hypertension. *Eur Heart J.* 2013;**34**:2159–219 with permission from Oxford University Press.

control,[116] and this was also verified by ambulatory 24-h measurements.[117]

Hypertensive emergencies

Hypertensive emergencies are defined as large elevations in BP (systolic > 180 mmHg or diastolic > 120 mmHg) associated with impending or progressive organ damage such as major neurological changes, hypertensive encephalopathy, cerebral infarction, intracranial haemorrhage, acute LV failure, acute pulmonary oedema, aortic dissection, renal failure, or eclampsia.[3,105] Severe acute arterial hypertension without obvious organ damage is usually defined as hypertensive crisis.[118] Hypertension with a diastolic BP >140 mmHg consists of an emergency. Care should be taken that extremely rapid falls in blood pressure may not be associated with complications, such as underperfusion of the brain and cerebral infarction or damage to the myocardium and kidneys. Excessive or rapid reductions in blood pressure should be avoided in acute stroke. Therapeutic schemes are presented in Table 25.17.[3,105,118]

Nitroprusside is the most effective agent, but it lowers venous return and cardiac output and may increase intracranial pressure (Table 25.17). Potential complications are nausea, vomiting, muscle twitching, sweating, thiocynate and cyanide intoxication. Fenoldopam is useful for most hypertensive emergencies but caution is required with glaucoma. Liquid or sublingual nifedipine results in ischaemic complications due to too rapid reduction of blood pressure and is no longer recommended. Treatment of pre-eclampsia and phaeochromocytoma are discussed in the relevant sections.

Table 25.17 Therapy of hypertensive crisis/emergencies

Less severe cases:	Sublingual captopril 12.5–25 mg
Urgent reduction:	nitroprusside (0.25–10 μg/kg/min IV)
LV failure:	nitroglycerine (5–100 μg/min IV) with furosemide (boluses of 20–40 mg IV)
Ischaemia and tachycardia:	esmolol (200–500 mg/kg for 4 min, then 50–300 μg/kg/min IV) or labetalol (20–80 mg IV every 10 min or 2 mg/min or infusion 2.5–30 μg/kg/min IV)
Severe hypertension with renal failure:	fenoldopam (0.2–0.5 μg/kg/min)
Acute aortic dissection:	esmolol (200–500 mg/kg for 4 min, then 50–300 μg/kg/min IV)
Phaeochromocytoma:	labetalol or phentolamine 1–3 mg boluses
Most emergencies but no heart failure:	nicardipine (5–15 mg/h IV), labetalol together with furosemide (boluses of 20–40 mg IV unless if volume depletion), esmolol

Hypertension in pregnancy

In pregnancy, hypertension is defined on absolute values >140/90 mmHg (Table 25.18).[119]

Pre-existing hypertension complicates 1–5% of pregnancies, and either precedes pregnancy or develops before 20 weeks of gestation. Hypertension usually persists >42 days post-partum. It may be associated with proteinuria. Undiagnosed hypertensive women may appear normotensive in early pregnancy because of the physiological BP fall commencing in the first trimester.

Gestational hypertension is pregnancy-induced hypertension and complicates 6–7% of pregnancies. Gestational hypertension develops after 20 weeks gestation and resolves in most cases within 42 days post-partum. Gestational hypertension needs close attention since 50% of patients will develop pre-eclampsia.

Pre-eclampsia is a pregnancy-specific syndrome that occurs after mid-gestation.[120] It has been traditionally defined by the *de novo* appearance of hypertension, accompanied by new onset of significant proteinuria (≥0.3 g/day in a 24 h urine collection or ≥30 mg/mmol urinary creatinine in a spot random urine sample), but in the recent report of the American College of Obstetricians and Gynecologists, the requirement of proteinuria for diagnosing pre-eclampsia has been abandoned (Table 25.19).[121]

Pre-eclampsia complicates 5–7% of pregnancies but increases to 25% in women with pre-existing hypertension. Pre-eclampsia occurs more frequently during the first pregnancy, in multiple fetuses, hydatidiform mole, or diabetes and is one of the most common causes of prematurity.

Symptoms and signs of severe pre-eclampsia include right upper quadrant/epigastric pain (liver oedema), headache, occipital lobe blindness, hyperflexia and convulsions (cerebral oedema), and HELLP syndrome (haemolysis, elevated liver enzymes, low platelet count). Women with no proteinuria, but who have these features and fetal compromise, are likely to have pre-eclampsia, even if proteinuria is absent.[122] Elevated blood pressure during pregnancy, regardless of type and even without known risk factors, indicates high risk of later cardiovascular disease, chronic kidney disease, and diabetes mellitus.[123]

Table 25.18 Classification of hypertension in pregnancy

Classification	Criteria met
Pre-eclampsia	After 20 wk of gestation, SBP ≥140 mmHg or DBP ≥90 mmHg in a previously normotensive woman. Proteinuria (excretion of ≥0.3 g protein in a 24-h urine collection) or with other systemic manifestations
Gestational hypertension	Elevated BP (SBP ≥140 mmHg or DBP ≥90 mmHg) after 20 wk of gestation in a previously normotensive woman
Chronic hypertension	SBP ≥140 mmHg and/or DBP ≥90 mmHg before pregnancy or before 20 wk of gestation
Chronic hypertension with superimposed pre-eclampsia	New onset of proteinuria in the setting of hypertension before 20 wk of gestation. An increase in proteinuria (if present earlier). An increase in blood pressure. Onset of HELLP syndrome.

BP, blood pressure; DBP, diastolic blood pressure; HELLP, haemolysis, elevated liver enzymes, low platelets; SBP, systolic blood pressure.
Seely EW, Ecker J. Chronic hypertension in pregnancy. *Circulation*. 2014;**129**:1254–61 with permission from Wolters Kluwer.

Table 25.19 Diagnostic criteria for pre-eclampsia

BP
≥140 mmHg systolic or ≥90 mmHg diastolic on two occasions at least 4 h apart after 20 weeks of gestation in a woman with a previously normal BP
≥160 mmHg systolic or ≥110 mmHg diastolic, hypertension can be confirmed within minutes to facilitate timely therapy, ***and***:
Proteinuria
≥300 mg/24 h urine collection (or this amount extrapolated from a timed collection), ***or***
Protein (mg/dL)/creatinine (md/dL) ratio ≥0.3
Dipstick reading +1 (only if other methods unavailable)
In the absence of proteinuria, new-onset hypertension with the new onset of any of the following:
Thrombocytopenia
<10 000/microlitre
Renal insufficiency
Creatinine >1.1 mg/dL or doubling of creatinine in the absence of other renal disease
Pulmonary oedema
Cerebral or visual symptoms

Seely EW, Ecker J. Chronic hypertension in pregnancy. *Circulation*. 2014;**129**:1254–61 with permission from Wolters Kluwer.

Table 25.20 ESH/ESC 2013 on hypertension*

Treatment strategies in hypertensive women	
Hormone therapy and selective oestrogen receptor modulators are not recommended and should not be used for primary or secondary prevention of CVD. If treatment of younger perimenopausal women is considered for severe menopausal symptoms, the benefits should be weighed against potential risks	III-A
Drug treatment of severe hypertension in pregnancy (SBP >160 mmHg or DBP >110 mmHg) is recommended	I-C
Drug treatment may also be considered in pregnant women with persistent elevation of BP ≥150/95 mmHg, and in those with BP ≥140/90 mmHg in the presence of gestational hypertension, subclinical OD or symptoms	IIb-C
In women at high risk of pre-eclampsia, provided they are at low risk of gastrointestinal haemorrhage, treatment with low dose aspirin from 12 weeks until delivery may be considered	IIb-B
In women with child-bearing potential RAS blockers are not recommended and should be avoided	III-C
Methyldopa, labetalol, and nifedipine should be considered preferential antihypertensive drugs in pregnancy. Intravenous labetalol or infusion of nitroprusside should be considered in case of emergency (pre-eclampsia)	IIa-B

* Additional recommendations by ESC are presented in Chapter 85 on Cardiovascular disease in pregnancy.
SBP ≥170 mmHg or DBP ≥110 mmHg in a pregnant woman is an emergency, and hospitalization is recommended (I-C). Induction of delivery in gestational hypertension with proteinuria with adverse conditions such as visual disturbances, coagulation abnormalities, or fetal distress (I-C).
BP, blood pressure; CVD, cardiovascular disease; DBP, diastolic blood pressure; OD, organ damage; RAS, renin–angiotensin system; SBP, systolic blood pressure.
ESH/ESC 2013 Guidelines for the management of arterial hypertension. *Eur Heart J*. 2013;**34**:2159–219 with permission from Oxford University Press.

Table 25.21 Schemes of antihypertensive medications in acute, sustained (>151), severe hypertension in pregnancy (SBP ≥160 mmHg or DBP ≥110 mmHg)

Drug	Starting dose	Repeating doses and intervals if BP is not controlled	Maximum total dose	Comments
Labetalol	20 mg IV over 2′	40 after 10′, 80 mg every 10′ for two additional doses	220 mg	Avoid in asthma, chronic obstructive airways disease, heart failure; avoid in women of Afro-Caribbean origin; associated with neonatal bradycardia and hypoglycaemia
Hydralazine	5 mg IV or 10 mg i.m.	5 or 10 mg, depending on response, every 20′; once BP control has been achieved, repeat as needed (usually ~3 h)	20 mg IV or 30 mg i.m.	Risk of sudden hypotension and maternal tachycardia; may need preloading or simultaneous loading with 500 mL of fluid infusion
Short-acting nifedipine	10 mg po	10 mg po after 30′	20 mg	Not approved by the US Food and Drug Administration for management of hypertension; should be avoided in women with coronary artery disease, aortic stenosis, long-standing diabetes mellitus, and women older than 45 years because of the risks of untoward cardiovascular events
Sodium nitroprusside	0.25 micrograms/kg/ min	Maximum dose of 5 micrograms/kg/min	Fetal cyanide poisoning may occur if used for >4 h	To be used only for extreme emergencies for the shortest time possible because of the risk of cyanide and thiocyanate toxicity for mother and infant and the risk of maternal increased intracranial pressure (ESC)
Continuous intravenous infusion of labetalol	Infusion of 20 mg/h	Titrated according to BP	160 mg/h	Second-line alternative after failure of both intermittent bolus of parental labetalol and hydralizine (ACOG)
Continuous intravenous infusion of nicardipine	Infusion of 3 mg/h	Titrated according to BP	10 mg/h	Second-line alternative after failure of both intermittent bolus of parental labetalol and hydralazine (ACOG)
Glyceryl trinitrate	IV infusion of 5 micrograms/min	Gradually increased every 3–5 min	100 micrograms/min	Drug of choice in pre-eclampsia associated with pulmonary oedema for ESC

Melchiorre K, *et al*. Cardiovascular implications in preeclampsia: an overview. *Circulation*. 2014;**130**:703–14 with permission from Wolters Kluwer.

Therapy

Low-dose aspirin (60–80 mg) beginning in the late first trimester may reduce preeclampsia in high-risk women. Bed rest and salt restriction are not recommended any more.[121] BP persistently above systolic 160 mmHg and diastolic >105 mm Hg, 120 (or >110 mm Hg) should be treated with antihypertensive drugs. In a recent RCT, tight control of mild-to-moderate nonproteinuric hypertension in pregnancy (diastolic blood-pressure targets, 100 mm Hg and 85 mm Hg, respectively) conferred no apparent benefits to the fetus and only a moderate benefit (a lower rate of progression to severe hypertension) for the mother. However, tight control, as targeted in this study, did not carry major risks for the fetus or newborn.[124] Systolic BP levels ≥170 or diastolic BP ≥110 mmHg should be considered an emergency requiring hospitalization (Tables 25.20 and 25.21). Labetalol (100–400 mg tds up to 1200 mg/day), oral nifedipine (long-acting 20–120 mg od), and oral methyldopa (250–500 mg tds up to 2000 mg/day) are drugs of choice.[120] There is some evidence that labetalol may be preferable to methyldopa in this setting.[125] Beta blockers (except atenolol) and thiazides may also be used.[126,127] ACEIs and ARBs are contraindicated, especially in the second and third trimester. No association with low weight for gestational age has been found for labetalol (started after the 6th week of gestation), as opposed to atenolol. Hydrochlorothiazide may also be used since previous concerns about increased risk are not supported by recent data.[127]

SBP ≥ 170 mmHg or DBP ≥ 110 mmHg in a pregnant woman is an emergency, and hospitalization is recommended.[119] Induction of delivery is also recommended in gestational hypertension with proteinuria with adverse conditions such as visual disturbances, coagulation abnormalities, or fetal distress.[119] In pre-eclampsia with pulmonary oedema, nitroglycerine is the drug of choice; diuretic therapy is inappropriate because plasma volume is reduced. As emergency intravenous labetalol,[126] oral methyldopa, and oral nifedipine are indicated. Intravenous infusion of sodium nitroprusside is useful in hypertensive crises, but prolonged administration should be avoided.

Calcium channel blockers, diuretics, and angiotensin-converting enzyme inhibitors pose little risk to **breastfed infants**. Beta blockers, especially those not secreted by the kidneys, may be given under supervision of the baby.[128] Untreated hypertension, late initiation of treatment and non-selective beta blockers have been associated with an increased risk of hypospadias.[129] Detailed comments on the drug use in pregnancy are presented in Appendix 3.

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Chapter 26

Secondary hypertension

Introduction

Specific causes of hypertension can be diagnosed in less than 10% of patients with established hypertension (Table 26.1). An additional very common cause is sleep apnoea. Early onset of hypertension (i.e. <30 years), resistant hypertension or severe hypertension, non-dipping or reverse dipping during 24 h ambulatory BP monitoring, and presence of target organ damage suggest secondary hypertension.[1] Up to 35% of elderly patients with secondary hypertension do not respond to specific therapy.

Obstructive sleep apnoea

Obstructive sleep apnoea is one of the most common causes of secondary hypertension (5–15%),[1] mainly associated with hypertension in patients < 60 years old.[1,2] Most patients complain of exaggerated daytime sleepiness, snoring, morning headache, lack of concentration, and irritability. Typical clinical findings are obesity, large neck, and macroglossia. Both nocturnal (non-dipping) and daytime blood pressure are increased. Patients often display significant tachycardia and/or bradycardia during nighttime, probably due to hypoxaemia-induced autonomic activity alterations. Continuous positive airways pressure (but not nocturnal oxygen supplement alone), and weight loss result in decreases of both nocturnal and daytime blood pressure.[3-5] Sleep apnoea stimulates atrial natriuretic peptide release with resultant nocturnal diuresis and sympathetic nerve activity; thus beta blockers are more efficacious than thiazides, but ACE inhibitors and ARBs have been equally effective in some studies.[2] Patients with treatment-resistant hypertension usually have a good antihypertensive response to aldosterone antagonists.[6]

Table 26.1 ESH/ESC 2013 GL on hypertension

Clinical indications and diagnostics of secondary hypertension

	Clinical indications			Diagnostics	
Common causes	**Clinical history**	**Physical examination**	**Laboratory investigations**	**First-line test(s)**	**Additional/ confirmatory test(s)**
Renal parenchymal disease	History of urinary tract infection or obstruction, haematuria, analgesic abuse; family history of polycystic kidney disease	Abdominal masses (in case of polycystic kidney disease)	Presence of protein, erythrocytes, or leucocytes in the urine, decreased GFR	Renal ultrasound	Detailed work-up for kidney disease
Renal artery stenosis	Fibromuscular dysplasia: early onset hypertension (especially in women). Atherosclerotic stenosis: hypertension of abrupt onset, worsening or increasingly difficult to treat; flash pulmonary oedema	Abdominal bruit	Difference of >1.5 cm in length between the two kidneys (renal ultrasound), rapid deterioration in renal function (spontaneous or in response to RAA blockers)	Renal Duplex Doppler ultrasonography	Magnetic resonance angiography, spiral computed tomography, intra-arterial digital subtraction angiography
Primary aldosteronism	Muscle weakness; family history of early onset hypertension and cerebrovascular events at age <40 years	Arrhythmias (in case of severe hypokalaemia)	Hypokalaemia (spontaneous or diuretic-induced); incidental discovery of adrenal masses	Aldosterone–renin ratio under standardized conditions (correction of hypokalaemia and withdrawal of drugs affecting RAA system)	Confirmatory tests (oral sodium loading, saline infusion, fludrocortisone suppression, or captopril test); adrenal CT scan; adrenal vein sampling
Uncommon causes					
Phaeochromocytoma	Paroxysmal hypertension or a crisis superimposed to sustained hypertension; headache, sweating, palpitations and pallor; positive family history of phaeochromocytoma	Skin stigmata of neurofibromatosis (café-au-lait spots, neurofibromas)	Incidental discovery of adrenal (or in some cases, extra-adrenal) masses	Measurement of urinary fractionated metanephrines or plasma-free metanephrines	CT or MRI of the abdomen and pelvis; 123 I-labelled meta-iodobenzyl-guanidine scanning; genetic scanning for pathogenic mutations
Cushing's syndrome	Rapid weight gain, polyuria, polydipsia, psychological disturbances	Typical body habitus (central obesity, moon-face, buffalo hump, red striae, hirsutism)	Hyperglycaemia	24-h urinary cortisol excretion	Dexamethasone-suppression tests

CT, computed tomography; GFR, glomerular filtration rate; MRI, magnetic resonance imaging; RAA, renin–angiotensin–aldosterone.
ESH/ESC 2013 Guidelines for the management of arterial hypertension. *Eur Heart J.* 2013;**34**:2159–219 with permission from Oxford University Press.

Renal parenchymal disease

Renal parenchymal disease (2-8%). It is due to diabetic nephropathy, hypertensive nephrosclerosis that, by itself, further increases blood pressure, polycystic kidney disease, and chronic glomerulonephritis. **Kidney ultrasound** (for kidney size, cortical thickness, urinary tract obstruction, and cysts or masses), assessment of **serum creatinine** and **electrolytes**, and **urinalysis** for red and white blood cells and proteinuria are essential initial tests in all patients with established hypertension. In haemodialysis patients (lack of renin activity), hypertension is labile and sensitive to changes in fluid volumes.

Acute renal disease, such as acute glomerulonephritis or urinary tract obstruction, may also result in hypertension.

Renovascular hypertension

This is also a relatively common cause of secondary hypertension (1-8%). However, renal artery stenosis is difficult to prove to be the cause of hypertension.[7,8] Clinical clues for such an association are:

- Resistant hypertension
- Sudden onset of hypertension before 50 years of age
- Negative family history for hypertension
- Generalized atherosclerosis
- Hypokalaemia
- Deterioration of renal function with ACEI/ARB.

A decrease in renal perfusion pressure activates the renin–angiotensin system, which leads to the release of renin and the production of angiotensin II, that has direct effects on sodium excretion, sympathetic nerve activity, intrarenal prostaglandin concentrations, and nitric oxide production, with resultant renovascular hypertension. When hypertension is sustained, plasma renin activity decreases, partially explaining the limitations of renin measurements for identifying patients with renovascular hypertension.[8]

Aetiology

Two forms of renal artery stenosis are described in adults.

Fibromuscular dysplasia is a nonatherosclerotic, noninflammatory vascular disease that may result in arterial stenosis, occlusion, aneurysm, or dissection.[9] It is primarily seen in women, and most commonly affects the renal (usually distal two thirds), carotid, and vertebral arteries but may occur in virtually every artery of the body. It is the second most frequent cause of renovascular hypertension (10–15% of cases). Renal Doppler detects dysplasia but instead of one area of stenosis, as usually happens in atherosclerosis, there are multiple areas of stenosis making the flow characteristics different. CT scanning is also useful, but the gold standard remains catheter-based angiography.[9] A cerebrovascular event, including transient ischaemic attack, stroke, and/or amaurosis fugax, occurs in 25% of patients.[10] The presence of a carotid bruit in a patient under 60 or an epigastric bruit in a patient with hypertension should alert the clinician to the possible diagnosis of the condition.

Atherosclerotic disease (85–90%), involving the proximal one-third of the main renal artery, is usually seen in elderly men. ACE inhibitors and ARBs are effective in these patients, but the loss of renal mass and reduction in transcapillary filtration pressure can produce acute or chronic renal insufficiency, especially if renal artery stenosis affects both kidneys or the sole functional kidney. Medical therapy consists of diuretics, CCBs, ACEI/ARBs (in the absence of bilateral stenosis), and statins.

Rare causes are **aortic dissection** with renal artery involvement, **acute renal artery occlusion** (thrombosis, embolism, or trauma), **Takayasu** or **giant cell arteritis**, **congenital mid-aortic syndrome**, and **antiphospholipid antibodies syndrome**.

Diagnosis

Kidney ultrasonography may show a difference of more than 1.5 cm in length between the two kidneys in 60–70% of the patients with renovascular hypertension and is diagnostic for renal artery stenosis (Table 26.1). **Doppler ultrasonography** is capable of detecting stenosis, particularly when localized proximally, but **gadolinium-enhanced MRI** is considered the diagnostic procedure of choice, but is contraindicated in the presence of GFR <30mL/min.

Significant renal artery stenosis is defined as ≥50% diameter stenosis, associated with peak translesional gradient ≥20 mmHg, or a mean gradient ≥10 mmHg.[7] However, both arteriography and Doppler measurements overestimate renal artery stenosis as defined by the detection of a distal renal to aortic pressure ratio of <0.9.[11]

Therapy

Angioplasty with stenting or surgical revascularization are not recommended any more for atherosclerotic renovascular disease.[12,13,14] Medical therapy for control of hypertension and high-intensity statins are indicated. Angioplasty or surgical revascularization has also yielded moderate benefits in patients with fibromuscular dysplasia renal artery stenosis,[15] although angioplasty without stenting appears to be the best therapeutic option.[9] The condition also responds to ACEI and ARB therapy.

Significant increase of creatinine with a small dose of ACEI/ARB suggests bilateral renal artery stenosis. Anatomically relevant renal artery stenosis >70% should be verified by functional measurements, since systolic pressure gradient is ≥21 mmHg or Pd/Pa pressure ratio <0.9.[11] The best evidence supporting intervention may be for bilateral stenosis with 'flash' pulmonary oedema unrelated to acute coronary syndrome (Pickering syndrome) (Table 26.2).[16,17]

Table 26.2 ACCF/AHA 2013 guideline on peripheral artery disease

Treatment of renovascular disease (RAS)	
Medical treatment	
ACE inhibitors for hypertension associated with unilateral RAS.	I-A
Angiotensin receptor blockers for hypertension associated with unilateral RAS.	I-B
Calcium-channel blockers for hypertension associated with unilateral RAS.	I-A
Beta blockers for hypertension associated with RAS.	I-A
Indications for revascularization	
ASYMPTOMATIC STENOSIS	
Percutaneous revascularization for treatment of an asymptomatic bilateral or solitary viable kidney with a haemodynamically significant RAS.	IIb-C
The usefulness of percutaneous revascularization of an asymptomatic unilateral haemodynamically significant RAS in a viable kidney is not well established and is presently clinically unproven.	IIb-C
HYPERTENSION	
Percutaneous revascularization for patients with haemodynamically significant RAS and accelerated hypertension, resistant hypertension, malignant hypertension, hypertension with an unexplained unilateral small kidney, and hypertension with intolerance to medication.	IIa-B
PRESERVATION OF RENAL FUNCTION	
Percutaneous revascularization for patients with RAS and progressive chronic kidney disease with bilateral RAS or a RAS to a solitary functioning kidney.	IIa-B
Percutaneous revascularization for patients with RAS and chronic renal insufficiency with unilateral RAS.	IIb-C
IMPACT OF RAS ON CONGESTIVE HEART FAILURE AND UNSTABLE ANGINA	
Percutaneous revascularization is indicated for haemodynamically significant RAS and recurrent, unexplained congestive heart failure or sudden, unexplained pulmonary oedema.	I-B
Percutaneous revascularization for haemodynamically significant RAS and unstable angina.	IIa-B
Endovascular treatment for renal artery stenosis (RAS)	
Renal stent placement is indicated for ostial atherosclerotic RAS lesions that meet the clinical criteria for intervention.	I-B
Balloon angioplasty with bailout stent placement if necessary is recommended for fibromuscular dysplasia lesions.	I-B
Surgery for RAS	
Vascular surgical reconstruction for fibromuscular dysplastic RAS with clinical indications for interventions (same as for percutaneous transluminal angioplasty), especially those exhibiting complex disease that extends into the segmental arteries and those having macroaneurysms.	I-B
Vascular surgical reconstruction for atherosclerotic RAS and clinical indications for intervention, especially those with multiple small renal arteries or early primary branching of the main renal artery.	I-B
Vascular surgical reconstruction for atherosclerotic RAS in combination with pararenal aortic reconstructions (in treatment of aortic aneurysms or severe aortoiliac occlusive disease).	I-C

Management of patients with peripheral artery disease (Compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations). *J Am Coll Cardiol*. 2013;**61**:1555–7.

Primary aldosteronism

The prevalence of primary aldosteronism in patients with hypertension varies among reported studies because of the unreliability of the renin/aldosterone ratio test; it is, most probably, approximately 5%.[18,19] Adrenal adenomas account for 30% of cases and are usually small (less than 2 cm in diameter) and benign; 70% are caused by adrenal hyperplasia (considered by some a variant of essential hypertension).[18,20] There are also rare cases of adrenal carcinoma and the autosomal dominant condition of glucocorticoid-remediable aldosteronism.

Diagnosis

The condition should be suspected in resistant hypertension and in unprovoked hypokalaemia, but only a small number of patients will have hypokalaemia at an early stage in their disease. Increased **urinary excretion of potassium** (>30 mmol/day in the presence of hypokalaemia and in the absence of extra potassium intake) points to aldosteronism. It can be confirmed by the overnight **dexamethasone (1 mg) suppression test** and measurement of aldosterone and renin under standardized conditions. The usefulness of the **aldosterone-to-renin** ratio (ARR) is controversial.[20]

Aldosterone can be high or renin low in elderly people or black patients. Also, a high ARR is seen in chronic renal disease where high potassium stimulates aldosterone release and, in the case of rare genetic mutations, leading to increased aldosterone levels.[21] For appropriate measurement of the ARR, medication should be changed to drugs that have minimal effect on ARR (calcium channel blockers, hydralazine, doxazosin), the blood should be collected in the mid-morning, at least 2 h after awakening and with the patient sitting 5-15 min.[1] **CT, magnetic resonance imaging**, or **isotopic techniques** using radiolabelled cholesterol are used for imaging of the adrenals. Adrenal venous sampling is necessary to avoid false positive results that could provoke unnecessary adrenalectomy for non-functioning tumours.[21]

Therapy

Includes medical therapy with mineralocorticoid receptor antagonists and laparoscopic adrenalectomy for patients with unilateral adenomas.

Phaeochromocytoma

It is a very rare cause of secondary hypertension (0.2–0.4%), inherited or acquired, with an estimated annual incidence of 2–8/million population.[22,23] Phaeochromocytomas are mostly benign catecholamine-producing tumours of chromaffin cells of the adrenal medulla or of a paraganglion. Typical clinical manifestations are sustained or paroxysmal hypertension, palpitations, pallor, pounding headaches, palpitations, and sweating. However, their presentation is highly variable (hypertension occurs in about 70% of all cases of phaeochromocytoma) and can mimic many other diseases. If remaining unrecognized or untreated, they can be a life-threatening condition.

Diagnosis

The test with the highest sensitivity is the measurement of **plasma free metanephrines**, together with **urinary fractionated metanephrines**. However, because measurement of plasma free metanephrines is not widely available for routine diagnosis, measurement of **24-hour urinary fractionated metanephrines** and **urinary catecholamines** remains the diagnostic test of choice.[21] Beta-blockers and diuretics should be stopped before sampling. Stimulation or suppression tests with glucagon or clonidine, respectively, are less often used nowadays. Phaeochromocytomas are localized by a **computed tomography** scan and **magnetic resonance imaging** of the adrenal glands and abdomen. Complementary ^{123}I-metaiodobenzylguanidine scintigraphy and ^{18F}-dihydroxyphenylalanine-positron emission tomography may also be useful. Because approximately 25% of phaeochromocytomas are hereditary (multiple endocrine neoplasia type 2 **(MEN2)**, von Hippel–Lindau disease **(VHL)**, neurofibromatosis type 1, and familial paragangliomas), screening for genetic alterations is important. To date, mutations in five genes have been described leading to familial disorders associated with phaeochromocytomas.[24]

Therapy

Laparoscopic and adrenal-sparing surgical intervention following preoperative alpha blockade (prazosin, phenoxybenzamine or labetalol) and fluid expansion are the treatment of choice and usually curative. In malignant phaeochromocytomas, radiotherapy and chemotherapy are palliative treatment options.

Adrenal 'incidentaloma'

An adrenal 'incidentaloma' is an adrenal mass, generally 1 cm or more in diameter, that is discovered serendipitously during a radiologic examination performed for indications other than an evaluation for adrenal disease.[25]

The majority of adrenal incidentalomas are clinically non-hypersecreting, benign adrenocortical adenomas, occurring in 4–6% in the general population and in up to 70% of patients aged > 70 years.[24] . Other diagnoses include cortisol-secreting adrenocortical adenoma (5%), phaeochromocytoma (5%), adrenocortical carcinoma (5%), metastatic carcinoma (2.5%), and aldosterone-secreting adenoma (1%). When adrenal masses occur bilaterally (15% of patients with adrenal incidentaloma), the most likely diagnoses are metastatic disease, congenital adrenal hyperplasia, bilateral cortical adenomas, and infiltrative disease of the adrenal glands. Hormone production is determined by overnight dexamethasone suppression and blood or 24-h fractionated metanephrines and catecholamines, and a CT scan is performed. Laparoscopic adrenalectomy is indicated if the adrenal mass is ≥4 cm in diameter and if the mass enlarges by 1 cm or more during a period of 4 years with 6-monthly examinations; if evidence of autonomous hormonal secretion develops, laparoscopic adrenalectomy is considered.[22,25]

Other causes of hypertension

Cushing's syndrome, **coarctation of the aorta**, **hypo- and hyperthyroidism**, **intracranial tumours**, and **drug-induced hypertension** are also causes of secondary hypertension. Although non-steroidal anti-inflammatory agents are the most common cause of drug-induced hypertension, other drugs, as described in Table 25.15 in Chapter 25 on primary hypertension, should be also considered. Antiangiogenic and anti-vascular endothelial growth factor (VEGF) chemotherapy agents that are currently used

for the treatment of various forms of cancer are a common cause of secondary hypertension.[26]

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Part IV

Coronary artery disease

Relevant guidelines

Acute coronary syndromes (NSTEMI and STEMI)

AHA/ACC 2014 Guidelines on NSTE-ACS

2014 AHA/ACC Guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary. *J Am Coll Cardiol*. 2014;**64**:e139–228.

ESC 2015 Guidelines on NSTE-ACS

2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2016;**37**:267–315

ACCF/AHA 2013 Guidelines on STEMI

2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2013;**61**:e78–140.

ESC 2012 Guidelines on STEMI

ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;**33**:2501–2.

ACC/AHA 2015 update on primary PCI

2015 ACC/AHA/SCAI focused update on primary PCI for patients with STEMI. *J Am Coll Cardiol*. 2016;**67**:1235–42.

ACC/AHA 2016 update on duration of dual antiplatelet therapy

2016 ACC/AHA Guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. *Circulation*. 2016; Mar 29. [Epub ahead of print].

ESC 2014 Guidelines on revascularization

2014 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2014;**35**:2541–619

AHA 2015 Statement on pharmacotherapy in patients with ACS and chronic kidney disease.

Pharmacotherapy in chronic kidney disease patients presenting with acute coronary syndrome: a scientific statement from the American Heart Association. *Circulation*. 2015;**131**:1123–49

ESC 2011 Guidelines on pregnancy

ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**:3147–97

2015 ESC 2015 Guidelines on ventricular arrhythmias and prevention of sudden cardiac death

2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015;**36**:2793–867

EHRA/EAPCI/ACCA/HRS/APHRS 2014 consensus document on antithrombotic therapy in AF patients presenting with ACS and/or undergoing PCI

Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions. *Eur Heart J*. 2014;**35**:3155–79

AHA/ESC 2013 Consensus document on sexual counselling

Sexual counselling for individuals with cardiovascular disease and their partners. *Eur Heart J*. 2013;**34**:3217–35.

ESC 2014 Position paper on the management of antiplatelet therapy in patients undergoing CABG

Expert position paper on the management on antiplatelet therapy in patients undergoing coronary artery bypass graft surgery. *Eur Heart J*. 2014;**35**:1510–14

Stable CAD

ACC/AHA 2012 Guideline on stable IHD

2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol*. 2012;**60**:e44–e164.

ACC/AHA 2014 Guideline update on stable IHD

2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol*. 2014;**64**:1929–49

ESC 2013 Guidelines on stable CAD

2013 ESC Guidelines on the management of stable coronary artery disease. *Eur Heart J*. 2013;**34**:2949–3003

ACCF/AHA 2011 Guideline on PCI

2011 ACCF/AHA/SCAI Guideline on percutaneous coronary intervention. *J Am Coll Cardiol*. 2011;**58**:e44–122

ACC/AHA 2016 update on duration of dual antiplatelet therapy.

2016 ACC/AHA Guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *Circulation*. 2016; Mar 29. [Epub ahead of print].

ACCF/AHA 2011 Guidelines on CABG

2011 ACCF/AHA Guideline on CABG. *Circulation*. 2011;**124**: 2610–42.

ESC 2014 Guidelines on revascularization

2014 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2014;**35**:2541–619.

ACC/AHA 2014 Guidelines on perioperative cardiovascular evaluation

2014 ACCF/AHA Guidelines on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *J Am Coll Cardiol*. 2014;**64**:e77–137

ACC/AHA 2013 Guideline on treatment of cholesterol

2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. *J Am Coll Cardiol*. 2014;**63**:2889–934.

2016 ACC statement on non-statin therapies

2016 ACC Expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk. *J Am Coll Cardiol*. 2016; Mar 28 [E-Pub ahead of print].

AHA/ACC 2013 Guideline on lifestyle management

2013 AHA/ACC Guideline on lifestyle management to reduce cardiovascular risk. *J Am Coll Cardiol*. 2014;**63**:2960–84.

AHA/ACC 2013 Guideline on risk assessment

2013 ACC/AHA Guideline on the assessment of cardiovascular risk. *J Am Coll Cardiol*. 2014;**63**:2935–59.

AHA/ACC 2013 Guideline for management of obesity

2013 AHA/ACC/TOS Guideline for the management of overweight and obesity in adults. *J Am Coll Cardiol*. 2014;**63**:2985–3023.

AHA 2015 Statement on secondary prevention after CABG

Secondary prevention after coronary artery bypass graft surgery: a scientific statement from the American Heart Association. *Circulation*. 2015;**131**:927–64

ESC 2011 Guidelines on dyslipidaemias

ESC/EAS Guidelines for the management of dyslipidaemias. *Eur Heart J*. 2011;**32**: 1769–818.

ESC 2012 Guidelines on cardiovascular disease prevention

European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). *Eur Heart J*. 2012;**33**: 1635–701.

ACC/AHA 2014 Guideline on noncardiac surgery

ACC/AHA 2014 Guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *J Am Coll Cardiol*. 2014;**64**:e77–137

ESC/ESA 2014 Guidelines on noncardiac surgery

2014 ESC/ESA Guidelines on noncardiac surgery: cardiovascular assessment and management. *Eur Heart J*. 2014;**35**:2383–431

ESC 2013 Guidelines on diabetes

ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J*. 2013;**34**:3035–87.

ESC 2011 Guidelines on pregnancy

ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**:3147–97.

AHA 2013 Scientific statement on secondary prevention in older adults

Secondary prevention of atherosclerotic cardiovascular disease in older adults: *Circulation*. 2013;**128**:2422–46

AHA 2015 Prevention of cardiovascular disease in adults with Type 2 diabetes

Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association. *Circulation*. 2015;**132**:691–718.

AHA/ESC 2013 Consensus document on sexual counselling

Sexual counselling for individuals with cardiovascular disease and their partners: a consensus document from the American Heart Association and the ESC Council on Cardiovascular Nursing and Allied Professions (CCNAP). *Eur Heart J*. 2013;**34**:3217–35

AHA/ACCF 2012 Statement on cardiac disease evaluation and management in kidney and liver transplantation candidates

Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *J Am Coll Cardiol*. 2012;**60**:434–80

Chapter 27

Epidemiology and pathophysiology of coronary artery disease

Definitions and classification

Persons with atherosclerosis of epicardial coronary arteries and/or microcirculation may be asymptomatic or present with angina pectoris on effort or develop an acute coronary syndrome (ACS). Chronic stable angina is the initial manifestation of CAD in approximately 50% of all patients with CAD. **Stable coronary artery disease** may be detected following a diagnostic ischaemia test or diagnosed after presentation with an ACS. **ACS** refers to an acute imbalance of myocardial oxygen supply and demand due to progressive or abrupt flow-limiting coronary stenosis and/or high-output or increased afterload states. ACS include myocardial infarction with ST segment elevation or new LBBB (**STEMI**), and non-ST elevation myocardial infarction (**NSTEMI**) that is diagnosed by enzyme rise. Unstable angina is diagnosed when there are new or worsening symptoms of ischaemia, and ischaemic ECG changes such as ST segment depressions and T-wave inversion, with normal biomarkers. It is now evident that a large majority of patients with clinical manifestations of myocardial ischaemia, with rest pain but without elevated troponins by a commercially available assay, and therefore considered to have UA, have an elevation of circulating troponins measured by a high-sensitivity assay and could therefore be classified as NSTEMI.[1]

The spectrum of ischaemic heart disease is presented in Figure 27.1.

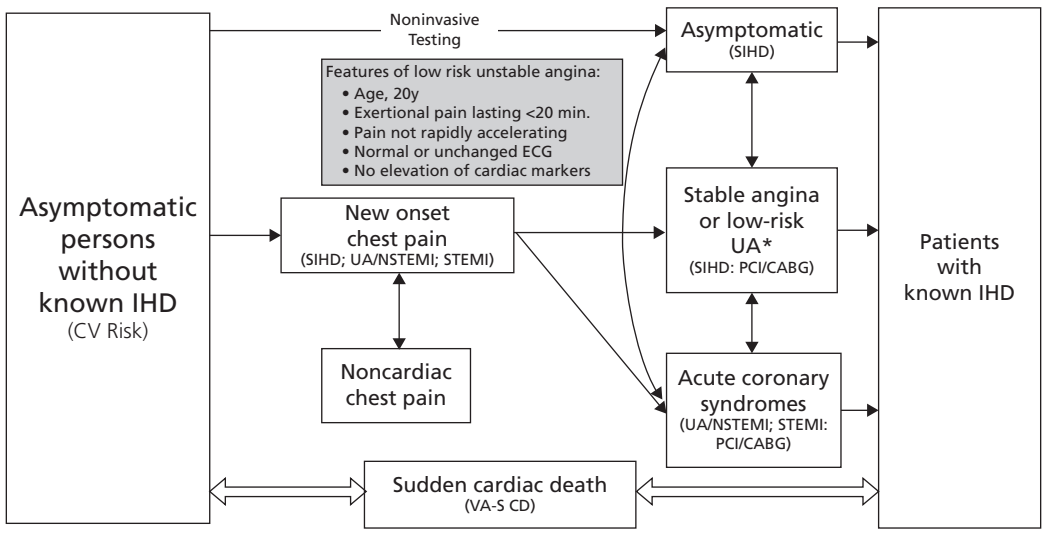


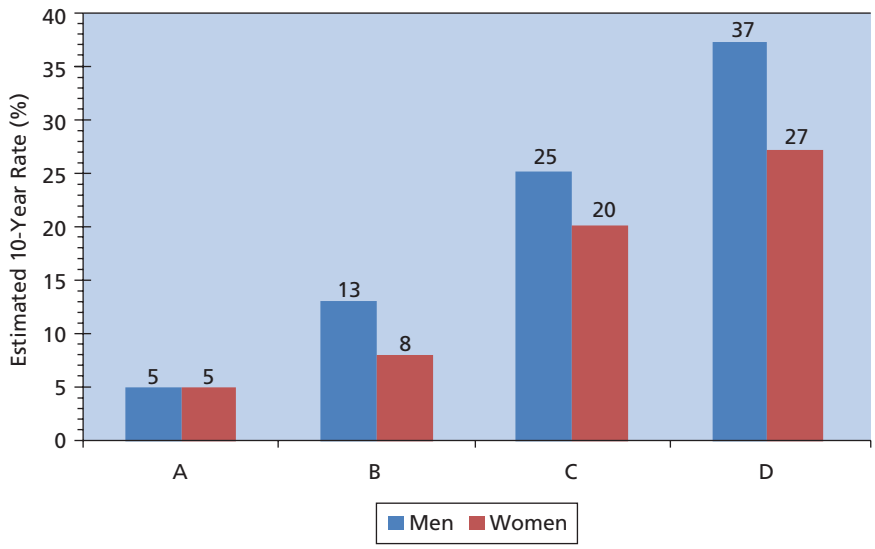
Figure 27.1 ACC/AHA 2012 on stable IHD: spectrum of IHD. Guidelines relevant to the spectrum of IHD are in parentheses.

CABG indicates coronary artery bypass graft; CV, cardiovascular; ECG, electrocardiogram; IHD, ischaemic heart disease; PCI, percutaneous coronary intervention; SCD, sudden cardiac death; SIHD, stable ischaemic heart disease; STEMI, ST elevation myocardial infarction; UA, unstable angina; UA/NSTEMI, unstable angina/non–ST elevation myocardial infarction; and VA, ventricular arrhythmia.
ACCF/AHA/ACP/AATS /PCNA/SCAI/STS 2012 Guideline for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol*. 2012;**60**:2564–603 with permission from Elsevier.

Epidemiology

Coronary artery disease (CAD) is the single most common cause of death in the developed world, responsible for about one in every six deaths.[2] In 2010, out of 52.7 million deaths worldwide, approximately 15.6 million were due to cardiovascular disease (as compared with approximately 3.8 million due to tuberculosis, human immunodeficiency virus, and malaria combined).[2] Mortality from cardiovascular disease, in general, is estimated to reach 23.4 million in 2030.[3] Coronary artery disease is responsible for about half of these cardiovascular deaths. In the USA, the 2011 overall rate of death attributable to cardiovascular disease (CVD) was 229.6 per 100 000 persons. The death rates were 275.7 for males and 192.3 for females. From 2001 to 2011, the actual number of CVD deaths per year declined by 15.5%. Yet in 2011, CVD still accounted for 31.3% (786 641) of all 2 515 458 deaths, or approximately 1 of every 3 deaths in the USA.[4] CAD alone caused approximately 1 of every 7 deaths in the USA 2011, being responsible for a total of 375 295 deaths.[4] Epidemiology data in the USA are presented in Figures 27.2, 27.3, and 27.4. More than 4 million Europeans die of CVD every year, of whom approximately half due to CAD.[5] Although the risk factor burden is lowest in low-income countries, the rates of major cardiovascular disease and death are substantially higher in low-income countries than in high-income countries, probably due to better control of risk factors and proper therapy.[6]

Worldwide, more than 3 million people each year are estimated to have a STEMI, and more than 4 million have a NSTEMI.[7] In the USA, an estimated ≈635 000 Americans have a new coronary attack (defined as first hospitalized myocardial infarction or coronary heart disease death) and approximately 300 000 have a recurrent attack each year. It is estimated that an additional 155 000 silent first myocardial infarctions occur each year. Approximately every 34 seconds, 1 American has a coronary event, and approximately every 1 minute 24 seconds, an American will die of one.[4] Hospital mortality is higher in patients with STEMI, but in the long-term mortality is higher in patients with NSTEMI.[8] Myocardial infarction that occurs in the community still carries a 25% mortality risk, whereas in-hospital mortality without fibrinolysis approaches 15%. Current pharmacological and mechanical therapeutic approaches have reduced this risk to 3–4%.[7,9] In-hospital occurring STEMI carries a higher mortality, especially in patients admitted for non-cardiac reasons.[10]



	A	B	C	D
Blood Pressure	120/80	140/90	140/90	140/90
Cholesterol	200	240	240	240
HDL-C	50	50	40	40
Diabetes	No	No	Yes	Yes
Cigarettes	No	No	No	Yes

Figure 27.2 Estimated 10-year coronary heart disease risk in adults 55 years of age according to levels of various risk factors (Framingham Heart Study). HDL-C indicates high-density lipoprotein cholesterol.

Mozaffarian D, *et al*. Heart disease and stroke statistics—2015 update: A report from the American Heart Association. *Circulation*. 2015;**131**:e29–322 with permission from Wolters Kluwer.

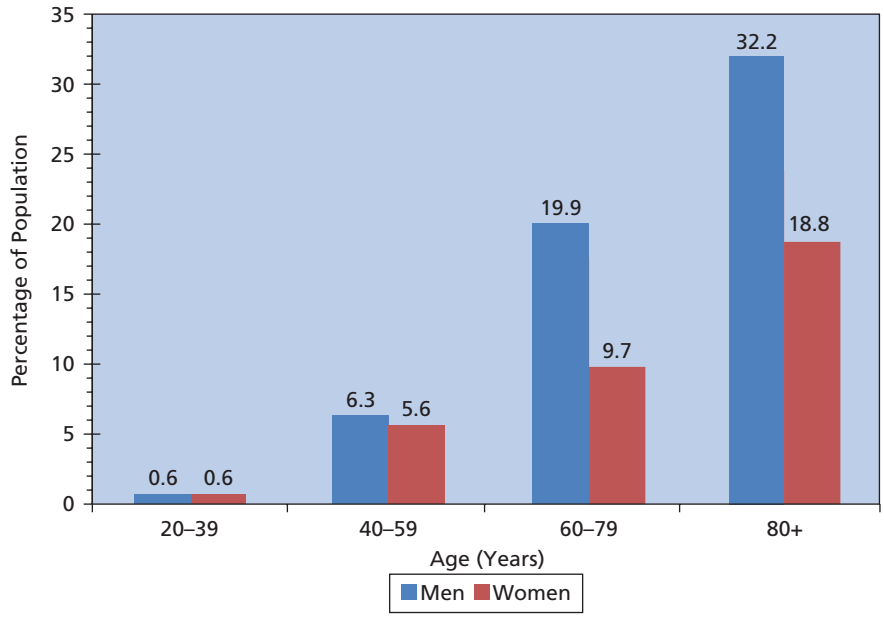


Figure 27.3 Prevalence of coronary heart disease by age and sex (National Health and Nutrition Examination Survey: 2009–2012). Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

Mozaffarian D, et al. Heart disease and stroke statistics—2015 update: A report from the American Heart Association. *Circulation*. 2015;**131**:e29–322 with permission from Wolters Kluwer.

Approximately 3.48 million people ≥40 years of age have angina pectoris per year in the USA, but only 18% of coronary attacks are preceded by long-standing stable angina.[4] In patients with stable CAD the annual mortality rate is approximately 2%, and the annual rate of major events such as death, myocardial infarction, and stroke is 4.5%.[11]

The estimated direct and indirect cost of heart disease in the USA in 2010 was $204.4 billion, with myocardial

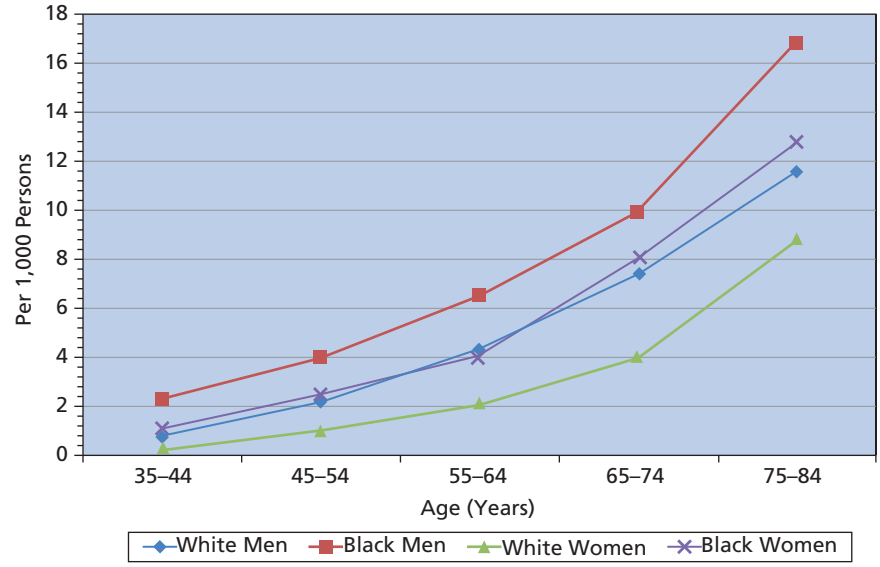


Figure 27.4 Incidence of heart attack or fatal coronary heart disease by age, sex, and race (Atherosclerosis Risk in Communities Surveillance: 2005–2011). Source: National Heart, Lung, and Blood Institute.

Mozaffarian D, *et al*. Heart disease and stroke statistics—2015 update: A report from the American Heart Association. *Circulation*. 2015;**131**:e29–322 with permission from Wolters Kluwer.

infarction ($11.5 billion) and coronary heart disease ($10.4 billion) being two of the ten most expensive hospital principal discharge diagnoses in 2011. Between 2013 and 2030, medical costs of CHD are projected to increase by ≈100%.[4]

Aetiology

More than 90% of myocardial infarctions are attributable to modifiable risk factors such as **hypertension, smoking, dyslipidaemia, diabetes, abdominal obesity, exposure to traffic air pollution (PM_{10}, $PM_{2.5}$, NO_2, and ozone) andnoise, psychosocial factors, and insomnia.**[12–18] Recent data from the Framingham and CARDIA studies provide evidence for the effectiveness of healthier lifestyle measures to prevent the development of cardiovascular disease.[19,20] Consumption of fruits and vegetables, and regular physical activity have a protective effect. The value of strenuous **exercise** is debatable. Exceeding guideline physical activity levels has been shown to produce important CHD-risk reductions.[21] However, a U-shaped association between all-cause mortality and dose of jogging has been detected with light and moderate joggers having lower mortality than sedentary non-joggers, but strenuous joggers having a mortality rate not statistically different from that of the sedentary group.[22] Moderate amounts of **alcohol**, as opposed to heavy drinking, are associated with a reduced risk of CAD and myocardial infarction (see Chapter 30).[23,24] Excess **sodium** intake is associated with an increased risk of coronary heart disease[25] Patients with **chronic kidney disease** and end-stage renal disease are at 5- to 10-fold higher risk for developing CVD than age-matched controls. Uremic toxins may be directly responsible for the pathogenesis of CVD in chronic kidney disease.[26] Patients with extreme hypercholesterolaemia have an elevated risk of ischaemic events. The **severe hypercholesterolaemia phenotype** includes all patients with low-density lipoprotein cholesterol levels >190 mg/dL, regardless of cause. Autosomal dominant hypercholesterolaemia results from mutations in genes controlling LDL levels. This includes familial hypercholesterolaemia, a common monogenic disorder caused by mutations in the LDL receptor (LDLR), the apolipoprotein B (apoB), or proprotein convertase subtilisin kexin type 9 (PCSK9) genes, as well as inherited forms of a potential polygenic origin, without defects in any of the three genes.[27] On the contrary, rare variations in a gene (APOC3) that encodes apolipoprotein C3 are associated with reduced triglyceride levels and lower risk for heart disease, thus suggesting a potential drug target.[28,29] The prevalence of molecularly defined homozygous autosomal dominant familial hypercholesterolaemia is rather high (1/300 000) and the clinical phenotype is more variable than previously assumed.[30] There is a causal effect of triglycerides on CAD risk, but a causal role for HDL-C, though possible, remains less certain.[31] **Shorter height** is associated with increased risk for coronary artery disease.[32] Both early and late menarche are associated with increased risk of CAD.[33] Women who use **oral contraceptives** containing **ethinylestradiol** are at dose-dependent increased risk for thrombotic stroke and myocardial infarction compared to women using progesterone only contraception.[34] These cardiovascular risk factors induce oxidative stress that causes endothelial inflammation and damage. **Stillbirths and miscarriages** are associated with increased rates of myocardial infarction, cerebral infarction, and renovascular hypertension.[35] This has been attributed to either shared aetiology or the initiation of pathological processes by a pregnancy loss, leading to atherosclerosis. Both androgen deprivation therapy, prescribed for prostatic cancer, and testosterone therapy have been associated with increased risk of CVD.[36,37] **Mental and substance addiction disorders**, especially when diagnosed at a young age, are associated with increased risk of cardiovascular disease.[38] **Antipsychotic drugs** use may also be associated with a transient increase in risk for acute myocardial infarction, possibly mediated by dopamine type 3 receptor blockades.[39] **Anxiety and depression** as well as outbursts of anger, and combat experience increase the risk of CAD and myocardial infarction.[40,41] Psychosocial factors in youth such as the socioeconomic and emotional environments predict development of CAD.[42] **Vitamin D deficiency** has been implicated in the pathogenesis of cardiovascular disease, but a causal relationship has not been established.[43] Platelet cyclo-oxygenase (COX)-1 activity results in the production of thromboxane A, whereas COX-2 activity results in the production of prostacyclin (PGI_2). **NSAIDs** (both non-selective and selective COX-2 inhibitors that spare COX-1 in the gut) are associated with an increased thrombotic risk (see Chapter 30).[44] **Community-acquired bacteraemia** is associated with increased short-term risk of myocardial infarction and stroke.[45] **Chemotherapeutic drugs for cancer** such as the new ABL protein kinase inhibitors ponatinib and nilotinib, that are used for the treatment of chronic myeloid leukaemia, may also cause accelerated atherosclerosis and arterial thrombotic events.[46] Premature coronary artery disease may be seen in 3% of patients with **HIV/AIDS**.[47] **Fibromuscular dysplasia** involving the coronary arteries is an uncommon but important condition that can present as acute coronary syndrome.[48] **Hodgkin lymphoma** survivors have an increased risk of cardiovascular disease for at least 40 years after diagnosis.[49] The rate of progression of cellular **ageing** in late midlife (reflected by the rate of leucocyte telomere length attrition) relates to vascular damage, independently from contribution of CV risk factor exposure.[50]

Distinct morphological characteristics such as left main or proximal disease display a high heritability,[51] and epidemiological studies have shown that **genetic predisposition** accounts for 40–60% of the risk for coronary artery disease.[52] Genome-wide association studies have led to the discovery of more than 56 loci associated with the risk of coronary artery disease.[52–57] Approximately ten of them are associated with hypertension or hyperlipidaemia, and the rest of them (including 9p21.3) mediate their risks through

unknown mechanisms. The strongest genetic effect on the risk of coronary artery disease and myocardial infarction is that of single nucleotide polymorphisms at chromosome **9p21.3**, that is also a significant risk factor for abdominal aortic aneurysm, stroke, and Alzheimer's disease.[53,55,58] The 9p21.3 risk allele is carried by 75% of the European population and confers a risk of coronary atherosclerosis in a dose-dependent way (by means of allele copies). The identification of the **ABO blood group** locus as a risk factor for myocardial infarction might provide an explanation on why blood group O offers protection from myocardial infarction compared to blood groups A and B.[59] Common genetic influences appear to affect both height and CAD risk, partly mediated by genetic effects on LDL cholesterol and triglycerides.[32] The presence of a common **Y chromosome variant, haplogroup I**, has been found to increase coronary risk by 50%.[60] This might explain the higher prevalence of CAD in men. All these genetic variants are not yet ready for routine testing.

Secondary unstable angina is due to additional conditions in the presence of coronary stenoses, such as tachycardia, fever, thyrotoxicosis, anaemia, aortic stenosis, hypertension or hypotension, and hyperviscosity states. Rare non–atherosclerotic causes of MI are presented in Table 29.2.

Pathophysiology

Originally thought to be dominantly a lipid storage disease, our current understanding of the pathogenesis of atherosclerosis implicates endothelial injury and inflammation. Following endothelial injury, smooth muscle cells and monocytes/macrophages migrate into the arterial intima in the preatherosclerotic stage and during plaque development and become foam cells by accumulating cholesterol.[61] Additional chemical and mechanical factors that may trigger endothelial injury are altered sheer stress, high oxidative stress, smoking, and insulin resistance.[62] More than half of men and women with suspected CAD have microvascular dysfunction, even with the absence of an abnormal stress test, and this is a major predictor of major adverse events.[63] Coronary microvascular disease may represent an epiphenomenon or contribute to the pathogenesis of cardiovascular disease.[64] The development of atherosclerotic disease may be an age-related asymptomatic process or lead to stable ischaemic heart disease or an acute coronary syndrome.

Stable ischaemic heart disease

The underlying mechanism of chronic CAD is the chronic limited ability to increase oxygen supply to the myocardium in the setting of increased oxygen demand, usually caused by the obstruction of at least one large epicardial coronary artery by atheromatous plaque, microvascular dysfunction, vasoconstriction at the site of dynamic stenosis, or a combination of the above.[65] Because myocytes already extract about 75% of the oxygen in coronary blood at rest, a higher demand is primarily met by increasing coronary blood flow. Myocardial ischaemia results in hypoxia that activates cellular anaerobic pathways; produced mediators such as lactate are responsible for the sensation of pain.

Acute coronary syndromes

The most frequent mechanism of an ACS is a reduction of the myocardial oxygen supply usually due to rupture or erosion of a vulnerable atherosclerotic plaque, which results in endothelial injury and associated thrombosis and dynamic vasoconstriction. Vulnerable plaques likely to rupture or erode have evidence of inflammation with macrophages, that overproduce matrix metalloproteinases (MMP) with collagenase activity, and T-cell infiltrates.[62,66] Histologically, vulnerable plaques have thin fibrous caps (<55 microns) with large lipid cores (thin-cup fibroatheroma, TCFA).[62,66–69] The detection of lipid accumulation within the coronary artery wall by near-infrared spectroscopy predicts cardiovascular outcomes.[70] Usually, atherosclerosis occurs within an environment of low shear stress, but high shear stress may promote plaque rupture. Intraplaque haemorrhage also plays an important triggering role.[71] Plaque haemorrhage may occur from plaque rupture (fissure) or from neovascularization (angiogenesis). Plaque fissure or rupture exposes the highly thrombogenic subendothelium (collagen and tissue factor) to circulating platelets and white blood cells. Platelets are also activated by vasoconstrictors, such as thromboxane A2 and adenosine diphosphate (ADP) that binds to $P2Y_{12}$ receptors, and cause increased expression of glycoprotein IIb/IIIa that binds fibrinogen or von Willebrand factor. Thus, platelet aggregation and creation of the **white clot** occur. The platelet-derived mediators, together with other potent vasoconstrictors, such as activated thrombin, oxygen-derived free radicals, and endothelin, result in dynamic vasoconstriction and transient thrombosis. The coagulation cascade may be activated, and factor X leads to the generation of thrombin that converts fibrinogen to fibrin (**red clot**).[72] If the ischaemia is prolonged and severe enough to cause limited myocardial necrosis, a NSTEMI occurs; further damage, usually due to the formation of a red thrombus that causes ST elevation, produces the clinical picture of STEMI. The term 'calcified nodule' is used for a rare type of coronary thrombosis not caused by plaque rupture, but related to disruptive nodular calcifications protruding into the lumen, usually tortuous heavily calcified arteries in older individuals.[69] It should be noted that erosion or rupture of the coronary atherosclerotic plaque is typically required for an event to happen, but only when coinciding with a prothrombotic state and subsequent thrombosis at the site of plaque rupture or

erosion does it lead to an event. In the majority of cases, plaque ruptures or erosions take place in the absence of symptoms and commonly lead to healing and progression of coronary arterial narrowing.[73] Vulnerable plaques, intact or ruptured, may be found along the coronary tree, and the true culprit lesion can be difficult to define.[74]

Rupture of vulnerable coronary plaques with subsequent thrombosis and occlusion of the coronary artery is the most common cause of **myocardial infarction**.[75,76] Angiography at the acute phase reveals an occluded coronary artery in 90% of cases, although the converse is not the case due to the possible presence of collaterals. Intracoronary thrombi are mainly composed of fibrin, platelets, erythrocytes, few cholesterol crystals, and leucocytes.[76] There is a circadian periodicity with most events, occurring between 6 a.m. and noon. Platelet hyper-reactivity and pro-coagulant states contribute to the thrombotic process that diminishes microcirculatory perfusion by reduced coronary artery flow through epicardial stenoses as well as by distal embolization of thrombus. Histochemical stains can identify **zones of necrosis** 2–3 hours after the onset of necrosis while gross pathology changes can be identified 6–12 hours following occlusion. Eight to 10 days after infarction the thickness of the affected ventricular wall is reduced as necrotic muscle is removed by mononuclear cells, and over the next 2–3 months a firm scar develops. Infarct expansion (disruption and tissue loss not explained by additional necrosis) and ventricular dilation may also occur and determine ventricular remodelling. In the modern era of primary PCI, improved LVEF is detected in 55% of patients 1 month after the event.[77] The systemic inflammatory reaction to acute myocardial infarction can aggravate inflammation in the plaque, thus resulting in recurrent thrombotic events in the aftermath of an acute coronary syndrome.[62] Following reperfusion, the course of myocardial edema is bimodal. Acute reperfusion is responsible for the initial acute oedematous reaction that dissipates at 24h. The deferred wave initiates days after infarction, peaking at 1 week, and occurs mainly because of tissue healing processes.[78]

Myocardial infarctions have been previously shown to frequently occur at sites of mild to moderate stenosis.[79–81] Post-mortem examinations, however, have also demonstrated that ruptured plaques, leading to thrombosis, more likely occur within the segment of significant (>50%) stenoses.[82–84] Angiographic data also indicate that the majority of coronary events occur in patients with complex lesions and significant stenosis.[85–88] In the PROSPECT trial on patients with acute coronary syndromes treated by coronary intervention, 3-year recurrence rates were 20%. Half of them occurred in angiographically mild (<70% stenosis), non-culprit lesions. However, predictors of recurrent events were both a luminal area ≤4 mm^2 and the presence of thin-cap fibroatheroma.[89] An analysis of the data from the COURAGE trial has shown that MIs are not more likely to occur from mild coronary lesions, compared with moderate or severe ones; the number of non-revascularized lesions ≥50% was the only angiographic predictor of an ACS.[90] In the ROMICAT trials, lesions with ≥ 50% stenosis were detected in 78% of patients with ACS.[91] Recent data from a large retrospective cohort study of US veterans undergoing elective coronary angiography also demonstrated that obstructive CAD (stenosis ≥70%) was associated with worse outcomes, such as MI and death. Patients with non-obstructive CAD were at increased risk compared to those with no apparent CAD.[92] TCFA lesions with a large plaque burden, as detected by intravascular ultrasound radiofrequency analysis, carry a higher risk than small thin-cap fibroatheroma lesions.[93] When intravascular imaging information is available, the lesions with <85 micron-thick cap and >75% cross-sectional luminal area stenosis are the most probable to rupture.[68] In a recent study, the absolute number of TCFA was three times greater in non-severe stenosis than in severe stenosis. It was, however, twice as likely for a lesion to be TCFA in cases of severe stenosis than in non-severe stenosis, and TCFA in severely stenotic areas had more features of plaque vulnerability.[94]

Additional causes of UA/NSTEMI are **coronary spasm, emboli, coronary arterial inflammation, or spontaneous dissection** of the coronary artery in the absence of occlusive atherosclerosis in 10–15% of patients with NSTEMI.[95] Pregnancy-related spontaneous **coronary artery dissection** is a rare and potentially lethal complication of pregnancy. It is estimated that one in 16 000 pregnancies is complicated by acute MIs in the USA, and up to a quarter of these are due to spontaneous coronary dissection.[96] Spontaneous coronary artery dissection, in general, affects predominantly young women with a mean age of 42 years. Postpartum status, cocaine use, Ehlers-Danlos syndrome, hormonal therapy, fibromuscular dysplasia, connective tissue disorders and vasculitis, and extreme physical exertion are conditions that have been associated with spontaneous coronary dissection.[97]

Up to 30% of women with non-ST elevation acute coronary syndromes (NSTEACS) have angiographically normal coronary arteries despite elevated troponins and myocardial infarctions detected by MRI.[98] Vasospasm and embolism without evident plaque disruption are particularly common in women in this setting.[97] **Coronary spasm** is a well-reported cause of cardiac arrest. It occurs commonly in the absence of severe coronary disease and can present with or without anginal pain. Identification of non-critical coronary disease in the absence of other causes of cardiac arrest might suggest the diagnosis, particularly in cocaine abusers, as well as in smokers.[99,100] **Coronary embolism** occurs in up to 3% of patients with STEMI, and AF is the most frequent cause.[101] Approximately 6% of all

patients with STEMI also have normal coronary arteries. They tend to be younger and female, and causes are myocarditis, Tako-tsubo cardiomyopathy, vasospastic angina, and hereditary thrombophilia disorders.[102]

Stunned myocardium refers to depressed contractility, i.e. reduced perfusion with maintained metabolism, due to ischaemic insults of short duration. ***Hibernating myocardium*** is dysfunctional and viable myocardium but with more severe cellular structural changes. Stunned myocardium is more likely to recover than hibernating myocardium.

Assessment of cardiovascular risk

Guidelines on assessment of cardiovascular risk in the adult population as well as on lifestyle management for risk reduction have been published (Tables 27.1 and 27.2).[103,104] Several objective tools to assess the risk for cardiovascular

Table 27.1 ACC/AHA 2013 GL on the assessment of cardiovascular risk. Recommendations on risk assessment

The race- and sex-specific Pooled Cohort Equations* to predict 10-year risk for a first hard atherosclerotic cardiovascular disease (ASCVD) event in non-Hispanic, white, and African Americans, 40–79 years of age.	I-B
It may be considered in other populations.	IIb-C
If quantitative risk assessment uncertain, family history, hs-CRP, CAC score, or ABI—to inform treatment decision making.**	IIb-B
The contribution of ApoB, CKD, albuminuria, or cardiorespiratory fitness is uncertain at present.	
Carotid intima media thickness (CIMT) is not recommended for routine risk assessment.	III-B
Assessing traditional ASCVD risk factors every 4–6 years in adults 20–39 years, and estimate 10-year risk every 4–6 years in adults 40–79 years.	IIa-B
Assessing 30-year ASCVD risk based on traditional risk factors*** in adults 20–59 years, who are not at high short-term risk.	IIb-C

*: A downloadable spreadsheet enabling estimation of 10-year and lifetime risk for ASCVD and a web-based calculator are available at http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/scienceand-quality/practice-guidelines-and-quality-standards/2013-prevention-guideline-tools.aspx. It is derived from pooled data from NHLBI-funded cohorts such as the ARIC study, CHS, CARDIA study, and Framingham, but not the MESSA trial. It may overestimate the risk.
**: Family history of premature CVD: 1st degree relative male <55 years, and female <65 years; high sensitivity-CRP ≥2 mg/L, CAC-coronary artery calcium score ≥300 Agatston units, and ABI—ankle brachial index <0.9.
***: Traditional ASCVD risk factors such as age, sex, total and HDL–cholesterol, systolic BP, use of antihypertensive therapy, diabetes, and current smoking.
AHA/ACC 2014 Guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:2438–88 with permission from Elsevier.

Table 27.2 ACC/AHA 2013 GL on lifestyle management to reduce cardiovascular risk. Recommendations on lifestyle management

Diet	
LDL-C—Advise adults who would benefit from LDL–C lowering to:	
Dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils and nuts; and limits intake of sweets, sugar-sweetened beverages, and red meats. Adapt this dietary pattern and achieve it by following plans such as the DASH dietary pattern, the USDA Food Pattern, or the AHA Diet.	I-A
Aim for 5–6% of calories from saturated fat.	I-A
Reduce percent of calories from saturated and trans fat.	I-A
BP—Advise adults who would benefit from BP lowering to:	
Dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils and nuts; and limits intake of sweets, sugar-sweetened beverages and red meats. Adapt this dietary pattern and achieve it by following plans such as the DASH dietary pattern, the USDA Food Pattern, or the AHA Diet.	I-A
Lower sodium intake.	I-A
No more than 2400 mg of sodium/day. Further reduction to 1500 mg/day desirable. Reduction by at least 1000 mg/day.	IIa-B
Combine the DASH dietary pattern with lower sodium intake.	I-A
Physical activity	
Lipids and BP	
Aerobic physical activity to reduce LDL-C and non-HDL-C and to lower BP, 3–4 sessions a week, 40 minutes per session, and involving moderate-to-vigorous intensity physical activity.	IIa-A

DASH, Dietary Approaches to Stop Hypertension.
2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk. *J Am Coll Cardiol*. 2014;**63**:2960–84

disease have been used to identify patients at high cardiovascular risk and candidates for preventive therapy. It should be noted that all used algorithms, including those based in the Framingham risk score as well as the new ACC/AHA algorithm, overestimate the risk.[105] Genetic risk estimate for CAD may also be used to predict sudden cardiac death.[106]

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Chapter 28

Non-ST elevation acute coronary syndromes

Definition

Non-ST elevation acute coronary syndromes refer to a spectrum of conditions due to acute ischaemia that is sufficiently severe and prolonged to cause myocardial damage that results in the release of a biomarker of myocardial necrosis into the circulation, but without causing ST elevation or new LBBB.[1–3]

Unstable angina (UA) is a clinical term that denotes rest angina (usually lasting >20 minutes), new-onset (within the past 2 months and, at least, Canadian Cardiovascular Society III in severity), and increasing angina (in severity and frequency). Its diagnostic hallmark was lack of enzyme rise, but in the era of high-sensitivity assays the term is rather obsolete[2] (see also Chapter 27). Variant angina (Prinzmetal's angina, periodic angina) denotes angina that usually occurs spontaneously and is characterized by transient ST-segment elevation that spontaneously resolves or resolves with nitrates without progression to STEMI.

Presentation

Typical symptoms are **chest pain, indigestion or 'heartburn', nausea and/or vomiting, persistent shortness of breath, or dizziness and/or loss of consciousness**, although diabetics and the elderly may have vague symptoms or no symptoms at all. Differential diagnosis of chest pain is discussed in Chapter 30. Patients at increased risk of ACS, such as those with known coronary artery disease, cerebral or peripheral vascular disease, diabetes mellitus, chronic kidney disease, or a 10-year risk greater than 20% as calculated by Framingham equations, and with symptoms suggestive of an ACS should be evaluated by trained specialists.

Patients with suspected ACS should be risk stratified based on the likelihood of ACS and adverse outcome(s), to decide on the need for hospitalization and assist in the selection of treatment options (AHA/ACC 2014 GL on NSTE-ACS, I-B). Patients with high-risk features such as continuing chest pain, severe dyspnoea, syncope/presyncope, or palpitations should be referred immediately to the emergency department and transported by emergency medical services when available (AHA/ACC 2014 GL on NSTE-ACS, I-C). Patients with less severe symptoms may be considered for referral to the emergency department, a chest pain unit, or a facility capable of performing adequate evaluation depending on clinical circumstances (AHA/ACC 2014 GL on NSTE-ACS, IIb-C). Age should be taken into account; nonagenarians have substantially higher rates of death with or without preceding rehospitalization after NSTEMI, and twice the adjusted mortality than those aged 65–79 years.[4]

Diagnosis

Immediate 12-lead ECG, and then serial ECGs in 15–30 min intervals if the initial ECG is non-diagnostic, are taken. Symptoms of ACS associated with **ST segment depression, T wave inversion, or non-specific ST-T abnormalities** suggest UA/NSTEMI. These findings are present in 30–50% of patients with an ACS. However, apart from assisting in diagnosis, they also carry adverse prognostic significance when present as new findings. New ST segment deviation, even of only 0.05 mV, is an important and specific measure of ischaemia and prognosis. T wave inversion is sensitive for ischaemia but is less specific, unless it is marked (≥0.3 mV).[5] Comparison with previous ECGs is valuable for the assessment of ST changes.

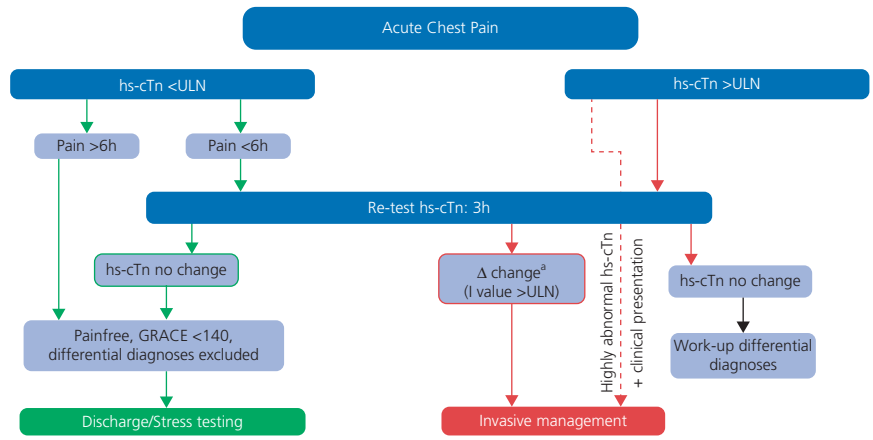
Cardiac biomarkers (preferably a cardiac-specific troponin) are measured, and, if negative within 6 h of the onset of symptoms, they are remeasured within 6–12 h after symptom onset. The degree of elevation of troponin is associated with mortality in ACS.[6,7] Biomarkers for risk stratification in patients with established diagnosis of ACS are CRP, white blood cell count, high sensitivity troponins (hs-TnT and hs-TNI), BNP or NT-pro-BNP, and GDF-15, a member of the transforming growth factor family that is released by myocytes during ischaemia and reperfusion.[8–11] In a substudy of the PLATO trial, hs-TnT, NT-proBNP, and GDF-15 were predictors of cardiovascular death, myocardial infarction, and stroke in patients with NSTE-ACS managed noninvasively, and NT-proBNP and GDF-15 also in those managed invasively.[11] Levels of high-sensitivity cardiac troponin are considered quantitative markers of cardiomyocyte damage, but elevations up to 3-fold the upper reference limit have only limited (50–60%) positive predictive value for acute MI and may be associated with several other conditions (see Chapter 29).[3] A rapid protocol (0 and 3 h) is recommended when high-sensitivity troponin assays are available (Figure 28.1). Accelerated diagnostic protocols (2 h), including TIMI score, ECG, and triple marker panels (CK-MB, myoglobin, and troponin), may identify low-risk patients that can be discharged early.[12] C-reactive protein values >3 mg/L indicate high risk by means of cardiovascular prevention, but values ≥10mg/L are more appropriate for patients with ACS.[13]

Stress testing and CT coronary angiography In patients with acute chest pain, CT angiography in an

experienced centre is faster to obtain than a stress test and improves diagnostic ability albeit at an increased radiation exposure.[14,15]

Risk stratification models, such as TIMI (Thrombolysis In Myocardial Infarction),[16] GRACE (Global Registry of Acute Coronary Event),[17] PURSUIT, or FRISC, are useful for subsequent decision-making (Tables 28.1 to 28.3 and Figure 28.1). Clinical features, ECG, and laboratory findings have been incorporated into these clinical risk scores that stratify patients into risk categories. The most simple, but less accurate, is the TIMI. Resting myocardial perfusion imaging (MPI) in patients with ongoing chest discomfort and non-diagnostic ECG or biomarker results will also identify active ischaemia. However, MPI cannot distinguish between recent and older infarcts; thus, abnormal MPI is not specific for ACS.[18] CMR can provide substantial information regarding ventricular function, ongoing ischaemia/perfusion, early and late regions of infarction, and coronary anatomy.[19] The greatest benefit of non-invasive CT angiography is to exclude CAD in patients with a low to intermediate probability of ACS.[20]

The management of patients without established ACS is presented in Table 28.4.



GRACE = Global Registry of Acute Coronary Events score; hs-cTn = high sensitivity cardiac troponin; ULN = upper limit of normal, 99th percentile of healthy controls. [a]Δ change, dependent on assay. Highly abnormal hsTn defines values beyond 5-fold the upper limit of normal.

Figure 28.1 ESC 2015 GL on NSTE-ACS. 0 h/3 h rule-out algorithm of non-ST-elevation acute coronary syndromes using high-sensitivity cardiac troponin assays.

ESC 2015 Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2016;**37**:267–315 with permission from Oxford University Press.

Table 28.1 The TIMI risk score predictor variables

1. Age ≥ 65 years
2. At least 3 risk factors for coronary artery disease, including family history, hypertension, hypercholesterolemia, diabetes, smoking
3. Prior coronary stenosis ≥ 50%
4. ST-segment deviation
5. At least 2 anginal events in prior 24 hours
6. Use of aspirin in prior 7 days
7. Elevated serum cardiac markers.

TIMI risk score	All-cause mortality, new or recurrent MI, or severe recurrent ischaemia requiring urgent revascularization through 14 days after randomization (%)
0–1	4.7
2	8.3
3	13.2

(*Continued*)

Table 28.1 Continued

4	19.9
5	26.2
6–7	40.9

The TIMI risk score is determined by the sum of the presence of seven variables at admission; 1 point is given for each of the following variables:
Age ≥65 years; At least three risk factors for coronary artery disease, including family history, hypertension, hypercholesterolaemia, diabetes, smoking; Prior coronary stenosis ≥50%; ST segment deviation; At least two anginal events in prior 24 hours; Use of aspirin in prior 7 days; Elevated serum cardiac markers.
Prior coronary stenosis of 50% or more remained relatively insensitive to missing information and remained significant predictor of events.
Antman EM, *et al*. The TIMI risk score for unstable angina/non ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA* 2000;**284**:835–42.

Table 28.2 GRACE prediction score for all-cause mortality at 6 months after an ACS

Risk calculator for 6-month postdischarge mortality after hospitalization for acute coronary syndrome

Record the points for each variable at the bottom left and sum the points to calculate the total risk score. Find the total score on the x-axis of the nanogram plot. The corresponding probability on the y-axis is the estimated probability of all-cause mortality from hospital discharge to 6 months.

Medical history

① Age in years — Points
- ≤29 — 0
- 30–39 — 0
- 40–49 — 18
- 50–59 — 36
- 60–69 — 55
- 70–79 — 73
- 80–89 — 81
- ≥90 — 100

② History of congestive heart failure — 24

③ History of myocardial infarction — 12

Findings at initial hospital presentation

④ Resting heart rate, beats/min — Points
- ≤49.9 — 1
- 50–69.9 — 3
- 70–89.9 — 9
- 90–109.9 — 14
- 110–149.9 — 23
- 150–199.9 — 35
- ≥200 — 43

⑤ Systolic blood pressure, mm Hg
- ≤79.9 — 24
- 80–99.9 — 22
- 100–119.9 — 16
- 120–139.9 — 14
- 140–159.9 — 10
- 160–199.9 — 4
- ≥200 — 0

⑥ ST-Segment depression — 11

Findings during hospitalization

⑦ Initial serum creatinine, mg/dL — Points
- 0–0.39 — 1
- 0.4–0.79 — 3
- 0.8–1.19 — 5
- 1.2–1.59 — 7
- 1.5–1.99 — 9
- 2–3.99 — 15
- ≥4 — 20

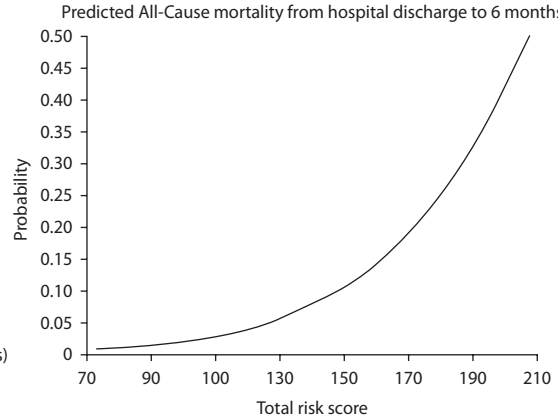
⑧ Elevated cardiac enzymes — 15

⑨ No in-hospital Percutaneous Coronary invervention — 12

Points
① _____
② _____
③ _____
④ _____
⑤ _____
⑥ _____
⑦ _____
⑧ _____
⑨ _____

Total risk score _____ (Sum of points)

Mortality risk _____ (From plot)



Eagle KA, *et al*. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA*. 2004;**291**:2727–33.

Table 28.3 Risk stratification

ESC 2015 GL on NSTE-ACS. Diagnosis, risk stratification, imaging, and rhythm monitoring	
Diagnosis and risk stratification	
Diagnosis and short-term ischaemic/bleeding risk stratification should be based on a combination of clinical history, symptoms, physical findings, ECG, and laboratory results.	I-A
A 12-lead ECG within 10 min after first medical contact and immediately read by an experienced physician. Repeat in the case of recurrence of symptoms, or diagnostic uncertainty.	I-B
Additional ECG leads (V3R, V4R, V7–V9) when routine leads are inconclusive.	I-C
Cardiac troponins with sensitive or high-sensitivity assays and obtain the results within 60 min	I-A
A rapid rule-out protocol (0 and 3 h), if highly sensitive troponin tests are available.	I-B
A rapid rule-out and rule-in protocol at 0 h and 1 h, if a high-sensitivity cardiac troponin test with a validated 0 h/1 h algorithm is available. Additional testing after 3–6 h if the first two troponin measurements are not conclusive and the clinical condition is still suggestive of ACS.	I-B
Use established risk scores for prognosis estimation	I-B
Use of the CRUSADE score in patients undergoing coronary angiography to quantify bleeding risk	IIb-B
Imaging	
In patients with no recurrence of chest pain, normal ECG findings and normal levels of cardiac troponin (preferably high-sensitivity), but suspected ACS, a non-invasive stress test (preferably with imaging) for inducible ischaemia, before deciding on an invasive strategy.	I-A
Echocardiography to evaluate regional and global LV function and to rule in or rule out differential diagnoses.[a]	I-C
Multidetector computed coronary angiography as an alternative to invasive angiography to exclude ACS when there is a low to intermediate likelihood of CAD and when cardiac troponin and/or ECG are inconclusive.	IIa-A
Monitoring	
Continuous rhythm monitoring until the diagnosis of NSTEMI is established or ruled out.	I-C
Admit NSTEMI patients to a monitored unit.	I-C
Rhythm monitoring up to 24 h or PCI (whichever comes first) in NSTEMI patients at low risk for cardiac arrhythmias.[b]	IIb-C
Rhythm monitoring for >24 h in NSTEMI patients at intermediate to high-risk for cardiac arrhythmias.[c]	IIa-C
In the absence of signs or symptoms of ongoing ischaemia, rhythm monitoring in selected patients (e.g. suspicion of coronary spasm or associated symptoms suggestive of arrhythmic events	IIb-C
AHA/ACC 2014 GL on NSTE-ACS. Early Risk Stratification and Cardiac Biomarkers	
Rapid determination of likelihood of ACS, including a 12-lead ECG within 10 min of arrival at an emergency facility	I-C
Serial ECGs at 15- to 30-min intervals during the first hour in symptomatic patients with initial non-diagnostic ECG	I-C
Cardiac troponin (cTnI or cTnT) in all patients with symptoms consistent with ACS	I-A
Serial cardiac troponin I or T at presentation and 3–6 h after symptom onset in all patients with symptoms	I-A
Additional troponin levels beyond 6 h in patients with initial normal serial troponins with electrocardiographic changes and/or intermediate-/high-risk clinical features	I-A
Consider time of presentation, the time of onset with ambiguous symptom onset for assessing troponin values	I-A
With contemporary troponin assays, CK-MB and myoglobin are not useful for diagnosis of ACS	III-A (no benefit)
Troponin elevations for short- and long-term prognosis	I-B
Remeasurement of troponin value once on day 3 or 4 in patients with MI as an index of infarct size and dynamics of necrosis	IIb-B
Use risk scores to assess prognosis in patients with NSTE-ACS	I-A
Risk-stratification models can be useful in management	IIa-B

(*Continued*)

Table 28.3 Continued

Supplemental electrocardiographic leads V7 to V9 in patients with initial nondiagnostic ECG at intermediate/high risk for ACS	IIa-B
Continuous monitoring with 12-lead ECG with initial non-diagnostic ECG and intermediate/high risk for ACS	IIb-B
BNP or NT-pro-BNP to assess risk and prognosis	IIb-B

a: Does not apply to patients discharged the same day in whom NSTEMI has been ruled out.
b: If none of the following criteria: haemodynamically unstable, major arrhythmias, left ventricular ejection fraction, 40%, failed reperfusion, additional critical coronary stenoses of major vessels or complications related to percutaneous revascularization.
c: If one or more of the above criteria are present.
ESC 2015 Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2016;**37**:267–315 with permission from Oxford University Press.
AHA/ACC 2014 Guideline for the management of patients with non-ST-elevation acute coronary syndromes. *J Am Coll Cardiol*. 2014;**64**:e139–228, with permission from Elsevier.

Table 28.4 AHA/ACC 2014 GL on NSTE-ACS. Discharge from the emergency department or chest pain unit

Observe patients with symptoms consistent with ACS without objective evidence of myocardial ischaemia (non-ischaemic initial ECG and normal cardiac troponin) in a chest pain unit or telemetry unit with serial ECGs and cardiac troponin at 3- to 6-hour intervals	IIa-B
For patients with possible ACS who have normal serial ECGs and cardiac troponins before discharge or within 72 h after discharge:	
Treadmill ECG	IIa-A
Stress myocardial perfusion imaging	IIa-B
Stress echocardiography	IIa-B
In possible ACS and a normal ECG, normal cardiac troponins, and no history of CAD:	
Coronary CT angiography (without serial ECGs and troponins)	IIa-A
Rest myocardial perfusion imaging with a technetium-99m radiopharmaceutical	IIa-B
Give low-risk patients who are referred for outpatient testing daily aspirin, short-acting nitroglycerin, and other medication if appropriate (e.g. beta blockers), with instructions about activity level and clinician follow-up	IIa-C

AHA/ACC 2014 Guideline for the management of patients with non-ST-elevation acute coronary syndromes. *J Am Coll Cardiol*. 2014;**64**:e139–228, with permission from Elsevier.

Therapy

Oxygen Should be administered when the arterial saturation is <90%. Routine use in normoxic patients might be harmful.[1]

Nitroglycerin Sublingually or as a buccal spray (0.4 mg), can be given for pain relief every 5 min for a total of three doses (Table 28.5). If the pain persists or hypertension or heart failure is present, IV nitroglycerin (initial dose 5–10 micrograms/min, with 10 micrograms/min increases until the systolic BP falls below 100 mmHg) can be given. Contraindicated if sildenafil has been taken within the previous 24 h (or tadalafil in the previous 48 h).

Morphine Is used for pain relief, although there are observational indications that it may increase mortality in ACS.[21] Concomitant administration with P2Y12 receptor blockers delays their activity, probably due to delayed absorption.[22]

Table 28.5 Medical therapy

ESC 2015 GL on NSTE-ACS	
Anti-ischemic drugs	
Early initiation of beta-blocker in patients with ongoing ischaemic symptoms and without contraindications.	I-B
Continue chronic beta-blocker therapy, unless the patient is in Killip class III or higher.	I-B
Sublingual or i.v. nitrates to relieve angina;[a] i.v. treatment in patients with recurrent angina, uncontrolled hypertension or signs of heart failure.	I-C
In suspected/confirmed vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided.	IIa-B

(*Continued*)

Table 28.5 Continued

AHA/ACC 2014 GL on NSTE-ACS. Standard medical therapy	
Oxygen	
Supplemental oxygen only with oxygen saturation <90%, respiratory distress, or other high-risk features for hypoxaemia	I-C
Nitrates	
Sublingual NTG every 5 min × 3 for continuing ischaemic pain and then assess need for IV NTG	I-C
IV NTG for persistent ischaemia, HF, or hypertension	I-B
Nitrates are contraindicated with recent use of a phosphodiesterase inhibitor	III-B(Harm)
Analgesic therapy	
IV morphine sulfate for continued ischaemic chest pain despite maximally tolerated anti-ischaemic medications	IIb-B
NSAIDs (except aspirin) should be discontinued during hospitalization for NSTE-ACS	III-B(Harm)
Beta-adrenergic blockers	
Initiate oral beta blockers within the first 24 h in the absence of HF, low-output state, risk for cardiogenic shock, or other contraindications	I-A
Sustained-release metoprolol succinate, carvedilol, or bisoprolol for beta-blocker therapy with concomitant NSTE-ACS, stabilized HF, and reduced systolic function	I-C
Re-evaluate to determine subsequent eligibility in patients with initial (24 h) contraindications to beta blockers	I-C
Continue beta-blocker therapy in patients with normal LV function with NSTE-ACS	IIa-C
IV beta blockers are potentially harmful when risk factors for shock are present	III-B(Harm)
CCBs	
Non-dihydropyridine CCBs with recurrent ischaemia and contraindications to beta blockers in the absence of LV dysfunction, increased risk for cardiogenic shock, PR interval >0.24 s, or second- or third-degree atrioventricular block without a cardiac pacemaker	I-B
Oral non-dihydropyridine calcium antagonists with recurrent ischaemia after use of beta blocker and nitrates in the absence of contraindications	I-C
CCBs for ischaemic symptoms when beta blockers are not successful, are contraindicated, or cause unacceptable side effects Short-acting dihydropyridine calcium channel antagonists should be avoided.	I-C
Long-acting CCBs and nitrates for patients with coronary artery spasm	I-C
Immediate-release nifedipine is contraindicated in the absence of a beta blocker	III-B(Harm)
Cholesterol management	
Initiate or continue high-intensity statin therapy in patients with no contraindications	I-A
Fasting lipid profile, preferably within 24 h	IIa-C
ACE inhibitors	
Should be started and continued indefinitely in LVEF <0.40 and in hypertension, diabetes mellitus, or stable chronic kidney disease unless contraindicated	I-A
ARBs in patients with HF or MI with LVEF < 0.40 who are ACE inhibitor intolerant	I-A
Aldosterone blockade in patients post-MI without significant renal dysfunction (creatinine >2.5 mg/dL in men or >2.0 mg/dL in women) or hyperkalaemia (K >5.0 mEq/L) who are receiving therapeutic doses of ACE inhibitor and beta blocker and have a LVEF ≤0.40, diabetes mellitus, or HF	I-A
ARBs in other patients with cardiac or other vascular disease who are ACE inhibitor intolerant	IIa-B
ACE inhibitors in all other patients with cardiac or other vascular disease	IIb-B

a: Should not be administered in patients with recent intake of sildenafil or vardenafil (<24 h) or tadalafil (<48 h).
ESC 2015 Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2016;**37**:267–315 with permission from Oxford University Press.
AHA/ACC 2014 Guideline for the management of patients with non-ST-elevation acute coronary syndromes. *J Am Coll Cardiol*. 2014;**64**:e139–228, with permission from Elsevier.

Antiplatelets

Aspirin

It should be administered as soon as possible and then indefinitely, unless if there is a history of documented allergy or active bleeding. A loading dose of 162–325 mg po (ACC/AHA) or 150–300 mg po (ESC) or 150–300 mg IV, followed by 81–162 mg/day po (ACC/AHA), or 75–100 mg/day po (ESC) should be given indefinitely. Aspirin mainly acts by irreversibly inhibiting platelet cyclooxygenase 1 (COX–1) and decreasing the synthesis of thromboxane A_2, which aids in platelet aggregation. In cells with a nucleus, COX can be regenerated. Because platelets have no nucleus, COX-1 cannot be reproduced and is permanently inhibited. This leads to a prolonged antithrombotic effect, lasting several days after a single dose, until enough new platelets have been produced to restore normal function of the thrombotic system. The effects of aspirin are only reversed when new unaffected platelets enter the circulation, which occurs every 7–14 days. Aspirin also inhibits prostacyclin production in gastric endothelial cells and, therefore, carries a slightly greater risk for gastric ulcer formation than the $P2Y_{12}$ inhibitors. A **proton pump inhibitor (PPI)**, preferably not omeprazole, should be added to patients with a history of duodenal ulcer or GI bleeding, age >65 years, or concurrent use of anticoagulants or steroids. In patients at high risk for gastrointestinal ulceration, the use of prophylactic proton pump inhibition (PPI) with aspirin is safer than clopidogrel alone without a proton pump inhibitor. Patients on prolonged PPI therapy, e.g. more than 2 years and with more than one pill a day, should be monitored for B12 deficiency.[23] Aspirin resistance is extremely rare; pseudoresistance, reflecting delayed and reduced drug absorption, may complicate enteric coated but not immediate release aspirin.[24] The administration of NSAIDs (selective COX-2 or not), with or without aspirin, is contraindicated due to increased risk of infarction and myocardial rupture. Aspirin should not be withheld before elective or non-elective CABG.

$P2Y_{12}$ receptor blockers

Added to aspirin or used instead of it in cases of aspirin allergy.

Thienopyridines (ticlopidine, clopidogrel, and prasugrel) are irreversible $P2Y_{12}$ receptor blockers. **Ticagrelor** is a non-thienopyridine reversible $P2Y_{12}$ receptor blocker. **Cangrelor** is an IV, fast-acting, $P2Y_{12}$ inhibitor. Clopidogrel and prasugrel are 'pro-drugs' that require activation in the liver via the cytochrome P450 system. Ticagrelor is not a pro–drug but requires twice daily dosing owing to its short half-life. Ticagrelor is now the preferred $P2Y_{12}$ receptor blocker for patients treated invasively (Tables 28.6 and 28.7, and Figure 28.2). There is no antidote for P2Y12 inhibitors.

Ticlopidine, the first of the ADP receptor blockers, is rarely used in practice because of uncommon, but serious, side effects (e.g. thrombocytopenia purpura and neutropenia due to bone marrow suppression).

Clopidogrel (loading dose 300–600 mg po followed by 75 mg/day, starting on presentation) is recommended for up to one year (CURE trial).[25] A higher dose 150 mg/daily may be used for the first 7 days in patients who had a loading dose of 600 mg for PCI, provided that the risk of bleeding is low.

There is a high degree of clopidogrel response variability related to genetic and non-genetic factors. Binding of metabolized clopidogrel to platelet adenosine diphosphate (ADP) receptors on the platelet surface is catalysed mainly by the cytochrome enzyme CYP2C19. Loss-of-function polymorphisms in the gene encoding for CYP2C19 are associated with a reduced response to clopidogrel (2–14% of patients) and a potentially increased risk of adverse cardiovascular events.[26,27] However, among patients with acute coronary syndromes or atrial fibrillation, the effect of clopidogrel as compared with placebo has been found consistent, irrespective of CYP2C19 loss-of-function carrier status.[28,29] Other genetic variations such as the ABCB1 3435 TT genotype may also affect the pharmacokinetics, and clinical efficacy of clopidogrel.[30] Platelet function assays employ several methods for monitoring platelet reactivity. ADP-stimulated assays that measure the effect of ADP on platelet aggregation, such as VerifyNow P2Y12 (Accumetrics, San Diego, CA) and Multiplate (Roche Diagnostics; Rotkreuz, Switzerland), are perhaps the more standardized and user-friendly.[30] CYP2C19 genotyping is possible only in specialty laboratories and requires several days to deliver results. There is insufficient evidence to recommend either routine genetic or platelet function testing at the present time. In the ARCTIC trial, bedside platelet reactivity testing with treatment adjustment (additional IV aspirin or adding a IIb/IIIa antagonist) did not improve outcomes compared to standard antiplatelet therapy.[31] Higher clopidogrel maintenance (150 mg) doses has not improved outcome in patients with higher residual platelet reactivity that defined poor response.[32,33] Ticagrelor is probably the alternative in high-risk patients with poor response (i.e. patients with stent thrombosis while taking clopidogrel), since insufficient platelet inhibition may also occur with prasugrel.[34]

Omeprazole and esomeprazole are proton-pump inhibitors that also inhibit the cytochrome enzyme CYP (high affinity for CYP2C19 and moderate affinity for CYP3A4), and the FDA has required label cautions in 2009 and 2011, respectively. Pantoprazole inhibits the enzyme less than

omeprazole and should lessen the risk when taken 4 h after clopidogrel.[35] However, randomized clinical trials have produced inconsistent results. A recent meta-analysis of the studies assessing PPIs as a class consistently reported higher 1-year event rates in patients receiving the drugs, while data from RCTs evaluating omeprazole vs placebo showed no difference in ischaemic outcomes.[36] Thus the combination of clopidogrel with a proton-pump inhibitor is now considered safe and should not be avoided in patients who are at increased risk of gastrointestinal bleeding.[37] PPIs may potentiate VKA-induced anticoagulation, resulting in increased INR values and bleeding risk, most likely due to facilitated gastric absorption of warfarin, thus careful monitoring is required.[37] PPIs may be associated with increased risk for adverse cardiovascular outcomes following myocardial infarction, regardless of clopidogrel use,[38] and interference with the clearance of asymmetrical dimethylarginine (ADMA), the endogenous antagonist of nitric oxide synthase, has been reported.[39] However, in a PLATO substudy, a similar association was observed between cardiovascular events and PPI use during ticagrelor treatment as with clopidogrel treatment. This suggests that PPI use may be a marker for, rather than a cause of, higher rates of cardiovascular events in sicker patients who need a PPI.[40]

A diminished pharmacodynamics response to clopidogrel has also been observed when coadministered with lipophilic statins and calcium channel blockers, but in clinical practice no increased cardiovascular risk has been demonstrated with these combinations.[41–43] Clopidogrel metabolites can inhibit the enzymatic activity of cytochrome P4502C9 and lead to increased plasma levels of NSAIDs.

Clopidogrel hypersensitivity is manifested as generalized exanthema and is caused by a lymphocyte-mediated delayed hypersensitivity in most patients. This can be managed with oral steroids (prednisone 30 mg bd for 5 days with gradual tapering over the next 15 days and diphenhydramine 25 mg every 8 h for pruritus) without clopidogrel discontinuation.[44] Allergenic cross-reactivity with ticlopidine, prasugrel, or both is present in a significant number of patients with clopidogrel hypersensitivity.

Although clopidogrel should be ideally stopped 5 days before CABG. However, if needed, CABG can be performed in patients on clopidogrel.[45]

Ticagrelor (loading dose 180 mg po, 90 mg twice daily) is a cyclopentyltriazolopyrimidine and a reversibly binding P2Y12 inhibitor, with a plasma half-life of <12 h. It is an active drug (clopidogrel and prasugrel are pro-active drugs) and has been shown to reduce mortality in ACS compared to clopidogrel without increased bleeding regardless of revascularization (PLATO trial).[46,47] In a substudy of the PLATO trial, elevated hs-TnT predicted substantial benefit of ticagrelor over clopidogrel both in invasively and non-invasively managed patients, but no apparent benefit was seen at normal hs-TnT.[11] A slightly greater increase in serum creatinine was seen in the PLATO trial with ticagrelor, compared with clopidogrel, but the difference was no longer apparent 1 month after cessation of treatment. Rates of gastrointestinal disturbance and rash are similar with ticagrelor, compared with clopidogrel. Ticagrelor, compared with clopidogrel, was associated with similar total major bleeding, but increased non-procedure-related major bleeding.[48] In addition, compared with clopidogrel, ticagrelor reduces the incidence of stent thrombosis in patients with acute coronary syndromes.[49] Patients with acute coronary syndrome, with a prior history of ischaemic stroke or TIA, have higher rates of adverse cardiac events, and stroke and ticagrelor may be preferable to clopidogrel.[50] Ticagrelor increases levels of drugs metabolized through CYP3A, such as simvastatin, whilst moderate CYP3A inhibitors, such as diltiazem, increase the levels and reduce the speed of offset of the effect of ticagrelor. Ventricular pauses, mostly in the acute phase of ACS due to sinus node suppression, and mild dyspnoea without any adverse effect on cardiac or pulmonary function may be seen and are believed to be adenosine-mediated.[51] They are of no clinical significance,[52] and higher adenosine levels induced by inhibiting adenosine uptake by red blood cells probably contribute to its efficacy.[53] A lack of efficacy among American patients and a probable reduced effect in co-administration with high-dose aspirin (325 mg as opposed to 75 mg, attributed to increased vascular resistance through inhibition of cyclooxygenase within blood vessels) are probably not matters of concern.[54,55]

Prasugrel (60 mg loading dose, then 10 mg od) is more consistent than clopidogrel, with faster onset of action and fewer potential drug interactions. It has been shown to be better than clopidogrel in patients with NSTEACS, particularly in those with diabetes, for reducing adverse cardiac events and late stent thrombosis, but at an increased risk of major bleeding (TRITON-TIMI 38 trial).[56] The rate of other adverse effects in the TRITON study was similar with prasugrel and clopidogrel. Thrombocytopenia occurred at the same frequency in each group (0.3%) while neutropenia was less common with prasugrel (<0.1% vs 0.2%; $p = 0.02$). In patients who do not undergo revascularization, prasugrel does not significantly reduce mortality and myocardial infarction, as compared with clopidogrel (TRILOGY ACS).[57] In the ACCOAST trial on patients with NSTE myocardial infarction who were scheduled to undergo catheterization within 48 h after admission, pretreatment with prasugrel at the time of diagnosis did not reduce the rate of major ischaemic events up to day 30 but increased the rate of major bleeding complications.[58] Concerns have been raised regarding

a possible increased risk of cancer with prasugrel. Platelets inhibit angiogenesis through the activity of platelet factor 4 and facilitate tumour cell adhesion and trapping in capillaries through the expression of P-selectin. Disruption of tumour platelet aggregates by chronic profound oral platelet inhibition may cause extensive dissemination of initially silent tumours. A 2010 FDA report had concluded that cancer risks after prasugrel are higher in women and after 4 months of therapy, at least, for solid, highly metastatic cancers. However, the frequency of neoplasm detection was similar with prasugrel and clopidogrel in the TRILOGY ACS trial.[59] Further data are needed for certain conclusions. It can be used instead of clopidogrel in patients undergoing PCI in a 60 mg loading dose followed by 10 mg daily or 5 mg if patient has a weight <60 kg. Not recommended in patients >75 years or if the risk of CABG is high. Contraindicated in patients with a history of TIA/stroke. Prasugrel should not be administered routinely to patients with UA/NSTEMI before angiography, such as in an emergency department, or used in patients with UA/NSTEMI who have not undergone PCI.[60]

Cangrelor, is an IV, fast-acting $P2Y_{12}$ inhibitor (30 μg/kg bolus followed by an infusion of 4 μg/kg for at least 2h) that in ACS has reduced PCI periprocedural thrombotic complications at the expense of increased bleeding.[61] Its fast action makes it attractive in the absence of pretreatment, but its comparative efficacy to drugs such as prasugrel or ticagrelor is not known. FDA approved its use for PCI in June 2015.

Cilostazol

Cilostazol is a selective inhibitor of 3-type phosphodiesterase, is commonly used in East Asia as an antiplatelet agent but, outside of peripheral arterial disease, has not found wider acceptance in western populations due to side effects, cost considerations, and lack of definitive evidence of its efficacy. It is recommended (100 mg po bd) for the pharmacological treatment of intermittent claudication in patients with peripheral artery disease (Class I-A, ACCF/AHA 2011 GL on peripheral disease[62]).

Glycoprotein IIb/IIIa antagonists

Glycoprotein IIb/IIIa receptor inhibitors block the final common pathway of platelet activation. **Abciximab** is a Fab fragment that targets the glycoprotein IIb/IIIa receptor and may be specifically used in percutaneous coronary intervention. The small molecule inhibitors **eptifibatide** and **tirofiban** are short-acting and require dose adjustment in patients with poor renal function. They are now the recommended agents in UA/NSTEMI when a IIb/IIIa is indicated; abciximab may be used only in high-risk patients undergoing PCI. In elderly patients, lower efficacy and higher rates of bleeding are seen. IIb/IIIa antagonists initiated early after admission reduce death and myocardial infarction but increase the risk of bleeding.[63] Most studies, however, have been conducted without the use of clopidogrel or new $P2Y_{12}$ receptor blockers.

The benefits of GP IIb/IIIa inhibition are probably greater for high-risk patients with elevated troponin, diabetes, and recurrent angina. Patients treated medically and who develop recurrent ischaemia, heart failure, or serious arrhythmias should be referred for urgent coronary angiography. In these patients, IIb/IIIa antagonists may be added to dual antiplatelet therapy and heparin. The main risk is bleeding, usually at the site of the arterial puncture. They should be given with caution if urgent CABG is anticipated. Reversibility of action is slow with abciximab (48 h to 1 week) and faster with tirofiban (4–8 h) and eptifibatide (2–4 h).

They may also be used, instead of clopidogrel loading, on presentation or in addition to dual antiplatelet therapy and heparin in:

- High-risk patients with recurrent symptoms despite dual antiplatelet therapy and heparin or elevated troponin or visible thrombus.
- High-risk patients proceeding to angiography.

Recommendations for acute medical therapy and doses are provided in Tables 28.6 and 28.7. Abciximab is cleared via the reticuloendothelial system, and no current recommendations exist for dose adjustment for patients with chronic kidney disease.

Anticoagulants

A low molecular weight heparin (such as enoxaparin) or **unfractionated heparin** is given as soon as possible (Tables 28.6 and 28.7).

Heparins

Unfractionated heparin (UFH) is a heterogeneous group of negatively charged, sulfated glycosaminoglycans (molecular weight 3000 to 30 000 Da) from animal sources. Low molecular weight heparins (LMWHs; molecular weight 2000 to 10 000 Da) are produced from unfractionated heparin by chemical or enzymatic processes. UFH activates antithrombin through the formation of a heparin-antithrombin complex that inhibits other coagulation factors.[64] The protein-binding properties of heparin are mainly responsible for the lack of linear relationship between dose, activated partial thromboplastin time (aPTT), and clinical outcomes. There is a variable therapeutic response, depending on age, weight, and renal function, and also a requirement for aPTT monitoring. Elimination of the drug is mainly by the reticuloendothelial system and secondary by the kidneys,[65] and the half-life is approximately 6 hours.

Protamine sulfate is an effective antidote (1 mg/100 U heparin IV). Very rarely, allergic shock may occur with its use.

Low molecular weight heparins (LMWH) (enoxaparin, dalteparin, nadroparin) are specific inhibitors of thrombin and factor Xa with high bioavailability. Low-molecular-weight heparins (LMWHs; molecular weight, 2000 to 10000 Da) are produced from unfractionated heparin by chemical or enzymatic processes. When given subcutaneously, they provide more consistent anticoagulation, avoiding the need for monitoring, and are associated with a lower risk for heparin-induced thrombocytopenia than unfractionated heparin. Disadvantages are the only partial reversibility by protamine, renal excretion, and reduced efficacy against the contact activation pathway (factors XIa and XIIa) that contributes to thrombosis on catheter tips, stents, and filters (Figures 28.2 and 28.3).[64] Enoxaparin is preferred over UFH by the ESC. Not much data exist about other LMWH, but they might be used if enoxaparin is not available (ESC 2011). **Enoxaparin** reduces death and myocardial infarction compared to unfractionated heparin in NSTE-ACS.[66] If PCI is indicated, no additional dose is needed if the last SC dose was given <8 h. If CABG is planned LMWH should be discontinued 12-24 h before and replaced with UFH. LMWH are not recommended in haemodialysis patients.

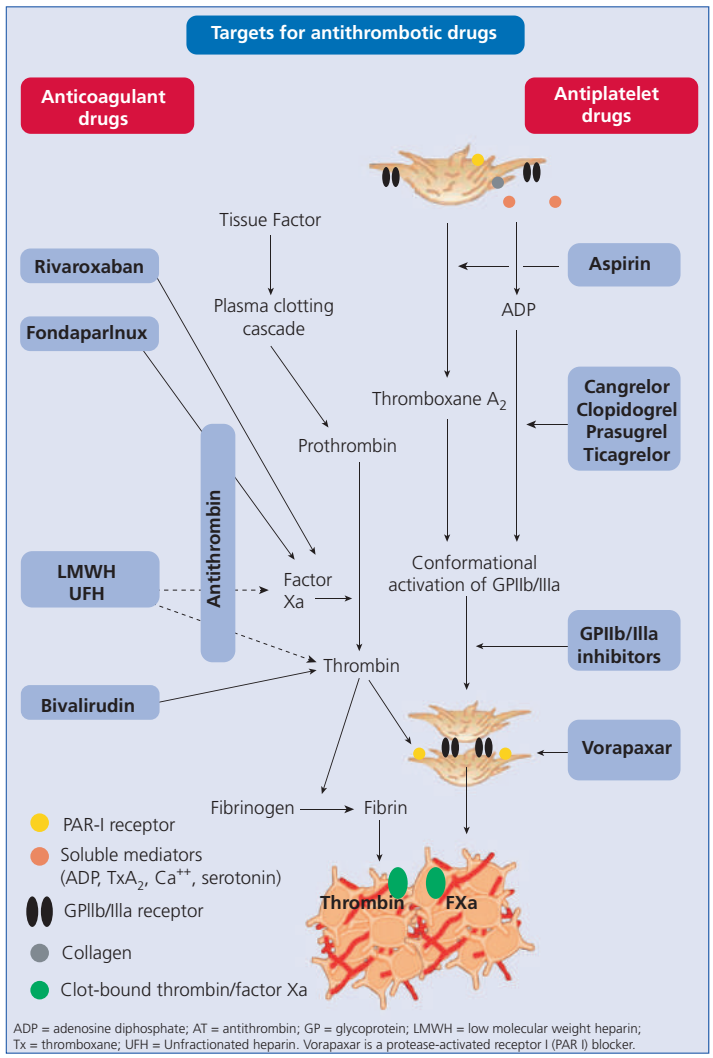


Figure 28.2 ESC 2015 GL on NSTE-ACS. Antithrombotic drugs for non-ST-elevation acute coronary syndromes. The figure depicts the targets of available antithrombotic drugs that can be used to inhibit blood coagulation and platelet aggregation during and after thrombus formation.

ESC 2015 Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2016;**37**:267–315 with permission from Oxford University Press.

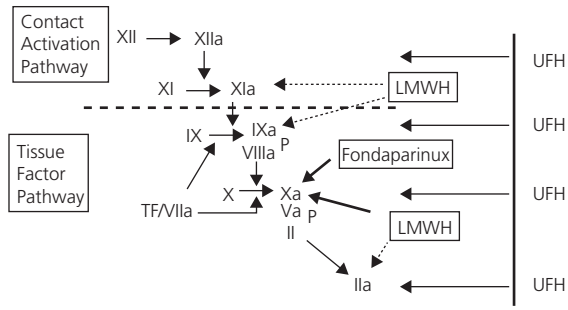


Figure 28.3 Tissue factor pathway: initiation of coagulation is triggered by the tissue factor/factor VIIa complex (TF/VIIa), which activates factor IX (IX) and factor X (X). **Contact activation pathway**: initiation of coagulation is triggered by activation of factor XII (XIIa), which activates factor XI (XIa). Factor XIa activates factor IX, and activated factor IX (IXa) propagates coagulation by activating factor X in a reaction that utilizes activated factor VIII (VIIIa) as a cofactor. Activated factor X (Xa), with activated factor V (Va) as a cofactor, converts prothrombin (II) to thrombin (IIa). Thrombin then converts fibrinogen to fibrin. **UFH** targets steps in both the contact activation pathway (inactivates XIa and XIIa) and tissue factor pathway (inactivates IXa, Xa, and IIa). **Bivalirudin** is cleaved by thrombin, thereby reducing its antithrombotic activity. **Fondaparinux** modulates the tissue factor pathway by inactivating factor Xa. **LMWH** also modulates the tissue factor pathway by inactivating factor Xa and, to a lesser degree, factor IIa. LMWH exerts weak activity against the contact activation pathway. P indicates phospholipid surface; TF, tissue factor.

Hirsh J, *et al*. Beyond unfractionated heparin and warfarin: current and future advances. *Circulation*. 2007;**116**:552–60 with permission from Wolters Kluwer.

Thrombin inhibitors

Bivalirudin is a reversible direct thrombin inhibitor with additional mild antiplatelet activity. It has a very short half-life and is less likely to accumulate in patients with renal insufficiency. It can be used as an alternative to heparin if an invasive strategy is planned instead of heparin, and plus provisional IIb/IIIa instead of UFH plus IIb/IIIa, especially in patients at high risk of bleeding (Tables 28.6 and 28.7). In moderate and high-risk patients, bivalirudin alone has similar ischaemic benefit as either unfractionated heparin or enoxaparin with a IIb/IIIa antagonist but with a reduction in major bleeding (ACUITY, ISAR-REACT 4, and EVENT Registry).[67–69] However, the MATRIX trial,[70] as well as recent meta-analyses, has shown that bivalirudin increases the risk of myocardial infarction and stent thrombosis compared to heparin, while the reduction of bleeding may depend on concomitant use of GP IIb/IIIa inhibitors.[71,72] Bivalirudin should be stopped 3 h before CABG and replaced by UFH.

Dabigatran (an oral direct thrombin inhibitor) has not been successful due to increased bleeding risk without reducing ischaemic events (RE-DEEM trial).[73]

Vorapaxar, an inhibitor of the protease-activated receptor PAR-1 through which thrombin activates platelets, when added to standard therapy in UA/NSTEMI patients, did not significantly reduce the primary composite end point, but significantly increased the risk of major bleeding, including intracranial haemorrhage,[74] although in patients undergoing CABG, it was associated with a significant reduction in ischaemic events and no significant increase in major CABG-related bleeding.[75]

Direct factor Xa inhibitors

Fondaparinux reduces major bleeding and improves clinical outcomes compared to enoxaparin with or without a IIb/IIIa (OASIS-5).[76] In patients managed conservatively, it is preferred over LMWH, especially when there is high risk of bleeding.[77] If these patients proceed to coronary intervention, a single bolus of UFH (85 IU/kg adapted to ACT, or 60 IU in the case of concomitant use of GP IIb/IIIa receptor inhibitors) should be given. Fondaparinux is the longest acting of the anticoagulants, with a half-life approaching 24 hours through renal clearance. It is contraindicated in patients with creatinine clearance <30 mL/min, but a much lower risk of bleeding complications was observed in OASIS-5 with fondaparinux when compared with enoxaparin, even in patients with severe renal failure. It is not recommended when an invasive approach is planned. Fondaparinux should be stopped 24 h before CABG and replaced by UFH.

Rivaroxaban (an oral Xa inhibitor) has been used post-discharge. It was shown to reduce the risk of the composite endpoint of death from cardiovascular causes, myocardial infarction, or stroke in patients with a recent acute coronary syndrome, when added to standard antiplatelet therapy (2.5–5 mg bd), but at an increased risk of major bleeding and intracranial haemorrhage (ATLAS 2 trial).[78] The 2.5 mg bd dose also reduced cardiovascular

Table 28.6 Antiplatelet and anticoagulant therapy

ESC 2015 GL on NSTE -ACS	
Platelet Inhibition in NSTE-ACS	
Oral antiplatelet therapy	
Aspirin for all patients without contraindications at an initial oral loading dose[a] of 150–300 mg (in aspirin-naive patients) and a maintenance dose of 75–100 mg/ day long-term regardless of treatment strategy.	I-A
A P2Y12 inhibitor, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds.	I-A
Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications,[b] for all patients at moderate-to-high risk of ischaemic events (e.g. elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel	I-B
Prasugrel (60 mg loading dose, 10 mg daily dose) in patients who are proceeding to PCI if no contraindication.[b]	I-B
Clopidogrel (300–600 mg loading dose, 75 mg daily dose) is for patients who cannot receive ticagrelor or prasugrel or who need oral anticoagulation.	I-B
P2Y12 inhibitor administration for a shorter duration of 3–6 months after DES implantation in patients deemed at high bleeding risk.	IIb-A
Do not administer prasugrel in patients in whom coronary anatomy is not known.	III-B
Intravenous antiplatelet therapy	
GPIIb/IIIa inhibitors during PCI for bailout situations or thrombotic complications.	IIa-C
Cangrelor in P2Y12 inhibitor–naive patients undergoing PCI.	IIb-A
Do not administer GPIIb/IIIa inhibitors in patients in whom coronary anatomy is not known.	III-A
Long-term P2Y12 inhibition	
P2Y12 inhibitor in addition to aspirin beyond 1 year may be considered after careful assessment of the ischaemic and bleeding risks of the patient.	IIb-A
General recommendations	
A proton pump inhibitor in combination with DAPT in patients at higher than average risk of gastrointestinal bleeds (i.e. history of gastrointestinal ulcer/haemorrhage, anticoagulant therapy, chronic NSAID/corticosteroid use or two or more of the following: age ≥65 years, dyspepsia, gastro-oesophageal reflux disease, Helicobacter pylori infection, chronic alcohol use).	I-B
In patients on P2Y12 inhibitors who need to undergo non-emergency major non-cardiac surgery, postponing surgery for at least 5 days after cessation of ticagrelor or clopidogrel, and for 7 days for prasugrel, if clinically feasible and unless the patient is at high risk of ischaemic events.	IIa-C
In case of a non-cardiac surgical procedure that cannot be postponed or of a bleeding complication, discontinuation of the P2Y12 inhibitor after a minimum of 1 and 3 months from PCI with BMS and new-generation DES, respectively.	IIb-C
Anticoagulation in NSTE-ACS	
Parenteral anticoagulation at the time of diagnosis according to both ischaemic and bleeding risks.	I-B
Fondaparinux (2.5 mg s.c. daily), favourable efficacy–safety profile regardless of the management strategy.	I-B
Bivalirudin (0.75 mg/kg i.v. bolus, followed by 1.75 mg/kg/h for up to 4 h after the procedure) as an alternative to UFH plus GPIIb/IIIa inhibitors during PCI.	I-A
UFH 70–100 IU/kg i.v. (50–70 IU/kg if concomitant with GPIIb/IIIa inhibitors) in patients undergoing PCI who did not receive any anticoagulant.	I-B
In patients on fondaparinux (2.5 mg s.c. daily) undergoing PCI, a single i.v. bolus of UFH (70–85 IU/kg, or 50– 60 IU/kg in the case of concomitant use of GPIIb/IIIa inhibitors) during the procedure.	I-B
Enoxaparin (1 mg/kg s.c. twice daily) or UFH when fondaparinux is not available.	I-B
Enoxaparin for PCI in patients pretreated with s.c. enoxaparin.	IIa-B
Additional ACT-guided i.v. boluses of UFH during PCI following initial UFH treatment.	IIb-B
Discontinuation of anticoagulation after PCI, unless otherwise indicated.	IIa-C
Crossover between UFH and LMWH is not recommended.	III-B
In NSTEMI patients with no prior stroke/TIA and at high ischaemic risk as well as low bleeding risk receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily for approximately 1 year) after discontinuation of parenteral anticoagulation.	IIb-B

(*Continued*)

Table 28.6 Continued

AHA/ACC 2014 GL on NSTE-ACS and 2016 update on duration of DAPT. Initial antiplatelet/anticoagulant therapy in patients with definite or likely NSTE-ACS treated with an initial invasive or ischaemia-guided strategy	
Aspirin	
Non-enteric-coated aspirin (162–325 mg) to all patients promptly after presentation and maintenance dose (81–162 mg) continued indefinitely	I-A
In patients treated with DAPT, aspirin 81 mg od (range 75–100 mg)	I-B-NR
P2Y12 inhibitors	
Clopidogrel (loading and maintenance) in aspirin hypersensitivity or intolerance	I-B
P2Y12 inhibitor, in addition to aspirin, for up to 12 months:	I-B
Clopidogrel 300-mg or 600-mg loading dose, then 75 mg/day, or	
Ticagrelor 180-mg loading dose, then 90 mg bd	
Ticagrelor in preference to clopidogrel for patients treated with PCI	IIa-B
In patients treated medically who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT (clopidogrel, prasugrel, or ticagrelor) for longer than 12 months	IIb-A-SR
GP IIb/IIIa inhibitors	
Eptifibatide or tirofiban in early invasive strategy and dual antiplatelet therapy with intermediate-/high-risk features (e.g. positive troponin)	IIb-B
Initial parenteral anticoagulant therapy in patients with definite NSTE-ACS	
Subcutaneous enoxaparin for duration of hospitalization or until PCI is performed 1 mg/kg SC every 12 h (reduce dose to 1 mg/kg/d SC in patients with CrCl <30 mL/min). Initial IV loading dose 30 mg	I-A
Bivalirudin until diagnostic angiography or PCI is performed in patients with early invasive strategy only. Loading dose 0.10 mg/kg loading dose followed by 0.25 mg/kg/h Only provisional use of GP IIb/IIIa inhibitor in patients also treated with DAPT	I-B
Subcutaneous fondaparinux 2.5 mg SC daily for the duration of hospitalization or until PCI is performed	I-B
Administer additional anticoagulant with anti-IIa activity (UFH or bivalirudin) if PCI is performed while patient is on fondaparinux	I-B
IV UFH for 48 h or until PCI is performed Initial loading dose 60 IU/kg (max 4,000 IU) with initial infusion 12 IU/kg/h (max 1,000 IU/ h). Adjusted to therapeutic aPTT range	I-B
IV fibrinolytic treatment not recommended in patients with NSTE-ACS	III-A (Harm)

DAPT: dual oral antiplatelet therapy
BMS. bare-metal stent; CABG. coronary artery bypass graft; DAPT. dual (oral) antiplatelet therapy; DES. drug-eluting stent; GPIIb/IIIa. glycoprotein IIb/IIIa; NSAID. non-steroidal anti-inflammatory drug; NSTE-ACS. non-ST elevation acute coronary syndromes; PCI. percutaneous coronary intervention.
a: Non-enteric coated formulation; 75–150 mg intravenously if oral ingestion is not possible.
b: Contraindications for ticagrelor: previous intracranial haemorrhage or ongoing bleeds. Contraindications for prasugrel: previous intracranial haemorrhage, previous ischaemic stroke or transient ischaemic attack or ongoing bleeds; prasugrel is generally not recommended for patients ≥75 years of age or with a bodyweight <60 kg.
ESC 2015 Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2016;**37**:267–315 with permission from Oxford University Press.
AHA/ACC 2014 Guideline for the management of patients with non-ST-elevation acute coronary syndromes. *J Am Coll Cardiol*. 2014;**64**:e139–228 with permission from Elsevier.
2016 ACC/AHA Guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. *Circulation*. 2016 Mar 29. [Epub ahead of print].

mortality but at the expense of increased intracranial haemorrhage.

Apixaban (oral Xa inhibitor) has been tried in doses similar to those used in AF (5 mg bd) in addition to standard antiplatelet therapy, but did not reduce ischaemic events (APPRAISE 2 trial).[79] Apixaban was also associated with increased major bleeding, including intracranial haemorrhage.

In a recent meta-analysis, addition of a novel anticoagulant to dual antiplatelet therapy reduced cardiovascular events by 13%, but more than doubled the bleeding.[80]

Synopsis of the antiplatelet/anticoagulant therapeutic scheme

All patients should receive:

- **Aspirin**, and
- **P2Y$_{12}$ receptor blocker** (preferably ticagrelor or clopidogrel), and
- **Heparin** (**LMWH** or **UFH**) or **bivalirudin** (invasive therapy) or **fondaparinux** (conservative therapy).

In stable patients selected for medical therapy, aspirin, ticagrelor or clopidogrel, and enoxaparin or preferably

Table 28.7 ESC 2015 GL on NSTE-ACS.

P2Y12 inhibitors

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Chemical Class	Thienopyridine	Thienopyridine	Cydopentyl-triazolpyrimidine	Stabilized ATP analogue
Administration	Oral	Oral	Oral	Intravenous
Dose	300–600 mg orally then 75 mg a day	60 mg orally then 10 mg a day	180 mg orally then 90 mg twice a day	30 μg/kg bolus and 4 μg/kg/min infusion
Dosing in CKD				
• Stage 3 (eGFR 30–59 mL/min/1.73m^2)	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
• Stage 4 (eGFR 15–29 mL/min/1.73m^2)	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
• Stage 5 (eGFR <15 mL/min/1.73m^2)	Use only for selected indications (e.g. stent thrombosis prevention)	No dose adjustment	No dose adjustment	No dose adjustment
Binding reversibility	Irreversible	Irreversible	Reversible	Reversible
Activation	Prodrug, with variable liver metabolism	Prodrug, with variable liver metabolism	Active drug, with additional active metabolite	Active drug
Onset of loading close effect[a]	2–6 hours[b]	30 min[b]	30 min[b]	2 min
Duration of effect	3–10 days	7–10 days	3–5 days	1–2 hours
Withdrawal before surgery	5 days[c]	7 days[c]	5 days[c]	1 hour
Plasma half-life of active $P2Y_{12}$ inhibitor[d]	30–60 min	30–60 min[e]	6–12 hours	5–10 min
Inhibition of adenosine reuptake	No	No	Yes	Yes ('inactive' metabolite only)

ADP = adenosine diphosphate; ATP = adenosine triphosphate; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.
[a]50% inhibition of ADP-induced platelet aggregation.
[b]Onset of effect may be delayed if intestinal absorption is delayed (e.g. by opiate).
[c]Shortening may be considered if indicated by platelet function tests and low bleeding risk.
[d]Affecting the response to platelet transfusion.
[e]The distribution phase half-life is reported since it most likely reflects duration of clinically-relevant plasma level, while the corresponding elimination phase half-life is approximately 7 hours.

Dosing of glycoprotein IIb/IIIa inhibitors in patients with normal and impaired renal function

Drug	Recommendations			
	Normal renal function or stage 1–2 CKD (eGFR≥60 mL/min/1.73m^2)	Stage 3 CKD (eGFR 30–59 mL/min/1.73m^2)	Stage 4 CKD (eGFR 15–29 mL/min/1.73m^2)	Stage 5 CKD (eGFR <15mL/min/1.73m^2)
Eptifibatide	Bolus 180μg/kg IV infusion 2 μg/kg/min	No adjustment of bolus, reduce infusion rate to 1μg/kg/min if eGFR <50 mL/min/1.73m^2	Not recommended	Not recommended
Tirofiban	Bolus 25 μg/kg or 10 μg/kg IV infusion 0.15 μg/kg/min	No dose adjustment	No adjustment of bolus, reduce infusion to 0.05 μg/kg/min	Not recommended
Abciximab	Bolus 0.25 mg/kg I.v. infusion 0.125 μg/kg/min (max. 10 μg/min)	No specific recommendations for the use of abciximab, or for dose adjustment in the case of renal failure. Careful evaluation of haemorrhagic risk is needed		

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate
Recommendations for the use of drugs listed in this table may vary depending on the exact labeling of each drug in the country where it is used.

(*Continued*)

Table 28.7 Continued

Dosing of anticoagulants in patients with normal and impaired renal function

Drug	Recommendations		
	Normal renal function or stage 1–3 CKD (eGFR≥30 mL/min/1.73m^2)	Stage 4 CKD (eGFR 15–29 mL/min/1.73m^2)	Stage 5 CKD (eGFR <15mL/min/1.73m^2)
Unfractionated heparin	◆ Prior to coronary angiography. 60–70 IU/kg I.v. (max 5000 IU) and infusion (12–15 IU/kg/h) (max 1000 IU/kg/h), target aPTT 1.5–2.5x control ◆ During PCI: 70–100 IU/kg I.v. (50–70 IU/kg if concomitatant with GPIIb/IIIa inhibitors)	No dose adjustment	No dose adjustment
Enoxaparin	I mg/kg s.c. twice a day	I mg/kg s.c. once a day	Not recommended
Fondaparinux	2.5 mg s.c once a day	Not recommended if eGFR <20 mL/min/1.73m^2	Not recommended
Bivalirudin	Bolus 0.75 mg/kg I.v. infusion 1.75 mg/kg/h	No adjustment of bolus, reduce infusion rate to I mg/kg/h	On dialysis, no adjustment of bolus, reduce infusion rate to 0.25 mg/kg/h

aPTT, activation partial thromboplastin time; CKD, chronic kidney disease; eGFR. estimated glomerular filtration rate; IU, international units;
Recommendations for the use of drugs listed in this table may vary depending on the exact labeling of each drug in the country where it is used.
ESC 2015 Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2016;**37**:267–315 with permission from Oxford University Press.

fondaparinux are given. A IIb/IIIa may be given only in patients with recurrent ischaemia or high troponin. If the patient is stable, a stress test should be performed. If, after the test, the patient is classified as low-risk, enoxaparin or fondaparinux are continued for the duration of hospitalization (up to 8 days), and IIb/IIIa, if given, is discontinued. Aspirin is given indefinitely and the $P2Y_{12}$ receptor blocker for at least 1 month and ideally 1 year. In patients in whom angiography is possible, pretreatment with a high-dose $P2Y_{12}$ has been questioned before demonstration of significant coronary disease needing intervention,[81,82] but this notion is controversial.[83]

In patients selected for PCI, aspirin, a $P2Y_{12}$ receptor blocker (preferably ticagrelor) and enoxaparin should be given or continued if already started. Pretreatment with prasugrel before angiography in patients scheduled for PCI within the next 48 h is avoided; the drug may be given only immediately before indicated intervention.[58] A IIb/IIIa antagonist might be initiated only in high-risk patients. Bivalirudin (with or preferably without IIb/IIIa) may be given instead of the combination of enoxaparin and a IIb/IIIA. Enoxaparin or bivalirudin may be discontinued after PCI in stable, uncomplicated cases.

In patients in whom CABG is indicated after angiography, aspirin and UFH are continued. Ticagrelor and clopidogrel should be ideally stopped 5 days and prasugrel 7 days before CABG, if this is possible, although CABG, if needed, can also be performed, especially in patients on clopidogrel. Recent data suggest that CABG within 24 hours of non–ST-segment–elevation MI is associated with in-hospital mortality and long-term outcomes similar to those of CABG performed after 3 days, despite dual antiplatelet therapy.[84] Recommendations have been provided by the ESC (Table 30.31 of Chapter 30). A position statement has also given similar recommendations.[85] If the patient has already received a stent, cangrelor (a selective P2Y12 inhibitor) may be more effective as bridging therapy than heparin.[86] Enoxaparin should be stopped 12–24 h, fondaparinux 24 h, and bivalirudin 3 h before the procedure, respectively, and replaced by UFH. IIb/IIIa (eptifibatide or tirofiban) are discontinued 4 h before surgery (abciximab requires much longer time, at least 48 h).

Other medications

Beta blockers

They should be initiated within the first 24 h for patients who do not have signs of acute heart failure or a low-output state, increased risk for cardiogenic shock, or other relative contraindications to beta blockade such as PR interval >0.24 s, second or third degree heart block, active asthma, or reactive airway disease (but COPD is not a contraindication) (Table 28.5). In patients with mild to moderate asthma (not in the acute phase) cardioselective beta blockers may also be used in minimum doses.[87] Beta blockers reduce the incidence of recurrent ischaemia and subsequent MI. IV beta blockade may also be considered in the absence of contraindications (mainly patients with Killip class ≥III). Oral therapy should be started and continued indefinitely in patients with reduced LV function. Patients on chronic β-blocker therapy admitted with ACS should continue β-blocker therapy if not in Killip class ≥III.

Calcium channel blockers

In the presence of recurrent symptoms or Prinzmetal variant angina or in patients in whom beta blockers are contraindicated, a non-dihydropyridine calcium channel blocker (e.g. **verapamil** or **diltiazem**) should be given as initial therapy

in the absence of clinically significant left ventricular dysfunction or other contraindications. Dihydropyridines are contraindicated in the absence of a beta blocker.

ACE inhibitors (or angiotensin receptor blockers)

Should be administered orally within the first 24 h to patients with pulmonary congestion or LVEF ≤0.40, in the absence of hypotension (systolic blood pressure <100 mmHg or <30 mmHg below baseline) or other contraindications. They may also be used in all patients, provided the systolic blood pressure is >100 mmHg.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Because of the increased risks of mortality, reinfarction, hypertension, HF, and myocardial rupture associated with their use, NSAIDs, except for ASA, whether non-selective or COX-2 selective agents, should be discontinued at the time a patient presents with UA/NSTEMI.

Invasive vs conservative management

Criteria for an invasive strategy are presented in Table 28.8 and Figure 28.4. Thus, current evidence suggests that in **high-risk, unstable patients, intervention within 12–72 hours is preferred** while either an early or a delayed approach may be adopted in other patients. Several (FRISC II, TACTICS-TIMI 18, RITA 3, ISAR-COOL, TIMACS, RIDDLE-NSTEMI, After Eighty),[88–92] although not all (ICTUS, ELISA, OPTIMA, ABOARD, LIPSIA-NSTEMI),[93–97] randomized trials have provided evidence in favour of an invasive strategy compared to conservative medical therapy in NSTEACS. Overall, the invasive strategy provides better long-term outcomes,[98,99] although this may not be translated into a longer benefit, i.e. up to 10 years.[100] Elevated hs-TnT, NT-proBNP, and growth differentiation factor-15 (GDF-15) are predictors of cardiovascular death, myocardial infarction, and stroke in patients managed noninvasively.[11] In addition, 5-year follow–up of patients with non-ST elevation acute coronary syndrome from FRISC II, ICTUS, and RITA-3 trials showed no association between a procedure-related MI and long-term cardiovascular mortality, although there was a substantial increase in long-term mortality after a spontaneous MI.[101] This is particularly true in high-risk patients whereas in low-risk patients, and especially women,[102] a conservative management with a view to intervention, if indicated, can be adopted. An invasive approach is also beneficial in diabetic patients.[103] The optimal timing of coronary angiography and subsequent intervention, if indicated, i.e. immediately after admission or after pre-treatment with optimal medical therapy, including potent antiplatelet agents, is also debated.[104,105] Delayed catheterization has been thought to allow plaque passivation by pre-treatment with optimal antithrombotic medication and avoidance of adverse outcomes, perhaps due to embolic phenomena, by early intervention. However, very early angiography (<14 h) with a view to PCI, if indicated, may be superior to a strategy of preceding anticoagulation and subsequent intervention in patients with NSTE-ACS, by reducing residual ischaemia and the duration of hospital stay and may also reduce complications, such as bleeding, and major events (death, MI, or stroke).[105]

If an invasive strategy is indicated and semi-urgent surgery is anticipated, the use of new-generation DES, BMS, or even balloon angioplasty is recommended (ESC on 2014 GL on non-cardiac surgery, I-B).[106] Drug-eluting stents

Table 28.8 Conservative vs Invasive Strategies

ACCF/AHA 2014 GL on NSTE-ACS

Factors associated with appropriate selection of early invasive strategy or ischaemia-guided strategy in patients with NSTE-ACS

Generally preferred strategy	Patient characteristics
Immediate invasive (within 2 h)	Refractory angina
	Signs or symptoms of HF or new or worsening mitral regurgitation
	Haemodynamic instability
	Recurrent angina or ischaemia at rest or with low-level activities despite intensive medical therapy
	Sustained VT or VF
Ischaemia-guided strategy	Low-risk score (e.g. TIMI [0 or 1], GRACE [<109])
	Low-risk Tn-negative female patients
	Patient or clinician preference in the absence of high-risk features
Early invasive (within 24 h)	None of the above, but GRACE risk score >140
	Temporal change in Tn
	New or presumably new ST depression

(*Continued*)

Table 28.8 Continued

Delayed invasive (within 25–72 h)	None of the above but diabetes mellitus	
	Renal insuffucinency (GFR<60mL/min/1.73 m^2)	
	Reduced LV systolic function (EF <0.40)	
	Early post-infarction angina	
	PCI within 6 mo	
	Prior CABG	
	GRACE risk score 109–140; TIMI score ≥2	
Early invasive and ischaemia-guided strategies		
Urgent/immediate invasive strategy (diagnostic angiography with intent to perform revascularization) is indicated in patients, men and women with refractory angina or haemodynamic or electrical instability (without serious co-morbidities or contraindications to such procedures)		I-A
Early invasive strategy in initially stabilized patients with an elevated risk for clinical events (see above)		I-B
Early invasive strategy (within 24 hours of admission) over a delayed invasive strategy (within 25–72 hours) for initially stabilized high-risk patients, delayed invasive approach for those not at high/intermediate risk		IIa-B
Ischaemia-guided strategy for initially stabilized patients, and elevated risk for clinical events		IIb-B
Decision to implement an ischaemia-guided strategy in initially stabilized patients after considering clinician and patient preference.		IIb-C
1. An early invasive strategy not recommended in:		
a. Extensive comorbidities (e.g. hepatic, renal, pulmonary failure, cancer), in whom the risks of revascularization and comorbid conditions are likely to outweigh the benefits of revascularization.		III-C (no benefit)
b. Acute chest pain and a low likelihood of ACS who are troponin negative, especially women.		III-C/B(no benefit)
ESC 2015 GL on NSTE-ACS		
Risk criteria mandating invasive strategy in NSTE-ACS		
Very-high-risk criteria		
Haemodynamic instability or cardiogenic shock		
Recurrent or ongoing chest pain refractory to medical treatment		
Life-threatening arrhythmias or cardiac arrest		
Mechanical complications of MI		
Acute heart failure		
Recurrent dynamic ST-T wave changes, particularly with intermittent ST-elevation		
High-risk criteria		
Rise or fall in cardiac troponin compatible with MI		
Dynamic ST- or T-wave changes (symptomatic or silent)		
GRACE score >140		
Intermediate-risk criteria		
Diabetes mellitus		
Renal insufficiency (eGFR <60mL/min/1.73 m^2)		
LVEF <40% or congestive heart failure		
Early post-infarction angina		
Prior PCI		
Prior CABG		
GRACE risk score >109 and <140		

(*Continued*)

Table 28.8 Continued

Low-risk criteria	
Any characteristics not mentioned above	
Invasive coronary angiography and revascularization in NSTE-ACS	
An immediate invasive strategy (<2 h) in patients with at least one of the following very-high-risk criteria:	I-C
haemodynamic instability or cardiogenic shock	
recurrent or ongoing chest pain refractory to medical treatment	
life-threatening arrhythmias or cardiac arrest	
mechanical complications of MI	
acute heart failure with refractory angina or ST deviation	
recurrent dynamic ST- or T-wave changes, particularly with intermittent ST-elevation.	
An early invasive strategy (<24 h) in patients with at least one of the following high-risk criteria:	I-A
rise or fall in cardiac troponin compatible with MI	
dynamic ST- or T-wave changes (symptomatic or silent)	
GRACE score >140.	
An invasive strategy (<72 h) in patients with at least one of the following intermediate-risk criteria:	I-A
diabetes mellitus	
renal insufficiency (eGFR <60 mL/min/1.73 m^2)	
LVEF <40% or congestive heart failure	
early post-infarction angina	
recent PCI	
prior CABG	
GRACE risk score >109 and <140 or recurrent symptoms or ischaemia on non-invasive testing	
In patients with none of the above risk criteria and no recurrent symptoms, non-invasive testing for ischaemia (preferably with imaging) before deciding on an invasive evaluation.	I-A
In experienced centres, a radial approach for coronary angiography and PCI.	I-A
New-generation DES in patients undergoing PCI	I-A
In patients with multivessel CAD, base the revascularization strategy (e.g. ad hoc culprit-lesion PCI, multivessel PCI, CABG) on the clinical status and comorbidities as well as the disease severity (including distribution, angiographic lesion characteristics, SYNTAX score), according to the local Heart Team protocol.	I-C
In patients in whom a short DAPT duration (30 days) is planned because of an increased bleeding risk, a newgeneration DES may be considered over a BMS.	IIb-B

* Immediate catheterization/angiography is recommended for unstable patients.
BMS, bare-metal stent; CAD, coronary artery disease; DAPT, dual (oral) antiplatelet therapy; DES, drug-eluting stent; eGFR, estimated glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; SYNTAX, SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery.
Timing to coronary angiography is calculated from hospital admission
AHA/ACC 2014 Guideline for the management of patients with non-ST-elevation acute coronary syndromes. *J Am Coll Cardiol*. 2014;**64**:e139–228, with permission from Elsevier.
ESC 2015 Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2016;**37**:267–315 with permission from Oxford University Press.

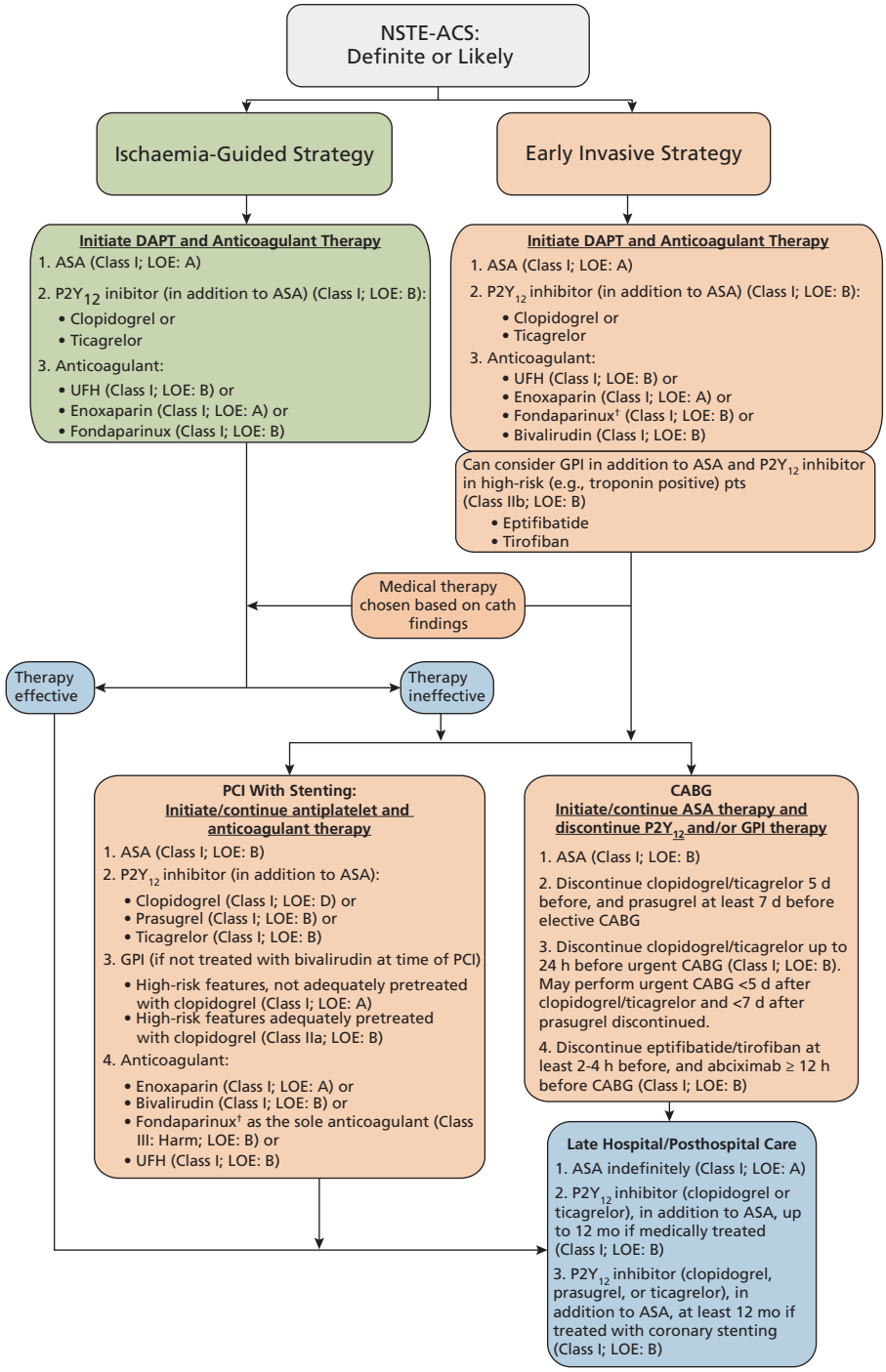


Figure 28.4 AHA/ACC 2014 GL on NSTE-ACS. Algorithm for management of patients with definite or likely NSTE-ACS.

†In patients who have been treated with fondaparinux (as upfront therapy) who are undergoing PCI, an additional anticoagulant with anti-IIa activity should be administered at the time of PCI because of the risk of catheter thrombosis.

AT: antithrombin; GP: glycoprotein; LMWH: low molecular weight heparin.

AHA/ACC 2014 Guideline for the management of patients with non-ST-elevation acute coronary syndromes. *J Am Coll Cardiol*. 2014;**64**:e139–228, with permission from Elsevier.

Table 28.9 AHA/ACC 2014 GL on NSTE-ACS and 2016 update on duration of DAPT. Percutaneous coronary intervention

General considerations	
A strategy of multivessel PCI, in contrast to culprit lesion-only PCI during coronary revascularization as part of treatment for NSTE-ACS	IIb-B
Oral and IV antiplatelets	
Patients already taking daily aspirin should take 81–325 mg non-enteric-coated aspirin before PCI	I-B
Patients not on aspirin therapy should be given non-enteric-coated aspirin 325 mg as soon as possible before PCI	I-B
In patients treated with DAPT, aspirin 81 mg od (range 75–100 mg)	I-B-NR
A loading dose of a P2Y12 receptor inhibitor should be given before PCI with stenting:	I-A
a. Clopidogrel: 600 mg or	I-B
b. Prasugrel: 60 mg (provided that they were not pretreated with another P2Y12) or	I-B
c. Ticagrelor: 180 mg	I-B
In patients with NSTE-ACS and high-risk features (e.g. elevated troponin) not adequately pretreated with clopidogrel or ticagrelor, administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI	I-A
In patients receiving a stent (bare-metal stent or drug-eluting stent), P2Y12 inhibitor therapy should be given for at least 12 months:	I-B-R
a. Clopidogrel: 75 mg od or	
b. Prasugrel: 10 mg od or	
c. Ticagrelor: 90 mg bd	
In patients treated medically or with stenting, ticagrelor instead of clopidogrel	IIa-B-R
In patients not at high risk of bleeding, and without a history of stroke or TIA, and treated with stenting, prasugrel instead of clopidogrel	IIa-B-R
In patients with NSTE-ACS and high-risk features (e.g. elevated troponin) treated with UFH and adequately pretreated with clopidogrel, administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban) at the time of PCI	IIa-B
In patients with DES who develop a high risk of bleeding (e.g. treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g. major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y12 inhibitor therapy after 6 months	IIb-C-LD
In patients with stenting who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g. prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT (clopidogrel, prasugrel, or ticagrelor) for longer than 12 months	IIb-A-SR
Prasugrel should not be administered to patients with a prior history of stroke or transient ischaemic attack	III-B-R (Harm)
GP IIb/IIIa inhibitors	
GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI in patients with high-risk features (e.g. elevated troponin) and not adequately pretreated with clopidogrel or ticagrelor	I-A
GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI in patients with NSTE-ACS and high-risk features (e.g. elevated troponin) treated with UFH and adequately pretreated with clopidogrel or ticagrelor	IIa-B
Anticoagulant therapy in patients undergoing PCI	
An anticoagulant should be administered to patients with NSTE-ACS to reduce the risk of intracoronary and catheter thrombus formation	I-C
Intravenous UFH in patients with NSTE-ACS undergoing PCI	I-C
Bivalirudin as an anticoagulant with or without prior treatment with UFH in patients undergoing PCI	I-B
An additional dose of 0.3 mg/kg IV enoxaparin should be administered at the time of PCI to patients with NSTE-ACS who have received < 2 therapeutic SC doses or received the last subcutaneous enoxaparin dose 8–12 hours before PCI	I-B
If the patient is on fondaparinux, an additional 85 IU/kg of UFH should be given IV immediately before PCI because of the risk of catheter thrombosis (60 IU/kg IV if a GP IIb/IIIa inhibitor used with UFH dosing based on the ACT)	I-B
Anticoagulant therapy should be discontinued after PCI unless there is a compelling reason to continue such therapy	I-C

(*Continued*)

Table 28.9 Continued

In patients who are at high risk of bleeding, use bivalirudin monotherapy in preference to the combination of UFH and a GP IIb/IIIa	IIa-B
PCI with enoxaparin in patients treated with upstream subcutaneous enoxaparin	IIb-B
Fondaparinux should not be used as the sole anticoagulant to support PCI due to an increased risk of catheter thrombosis	III-B (Harm)

Dosing of Parenteral Anticoagulants During PCI

Drug	In patients who have received prior anticoagulant therapy	In patients who have not received prior anticoagulant therapy
Enoxaparin	• For prior treatment with enoxaparin, if last SC dose was administered 8–12 h earlier or if <2 therapeutic SC doses of enoxaparin have been administered, an IV doses of enoxaparin 0.3 mg/kg should be given • If the last SC dose was administered within prior 8h, no additional enoxaparin should be given	• 0.5 mg/kg-0.75 mg/kg IV loading dose
Bivalirudin	• For patients who have received UFH, wait 30 min, then give 0.75 mg/kg IV loading dose, then 1.75 mg/kg/h IV infusion • For patients already receiving bivalirudin infusion, give additional loading dose 0.5 mg/kg and increase infusion to 1.75 mg/kg/h during PCI	• 0.75 mg/kg loading dose, 1.75 mg/kg/h IV infusion
Fondaparinux	• For prior treatment with fondaparinux, administer additional IV treatment wit anticoagulant possessing anti-lla activity, considering whether GPI receptor antagonists have been administered	N/A
UFH	• IV GPI planned: additional UFH as needed (eg, 2000–5000) U to achieve ACT of 200–250 s • No IV GPI planned: additional UFH as needed (eg, 2000–5000 U) to achieve ACT of 250–300 s for HemoTec, 300–500 s for Hemochron	• IV GPI planned: 50–70 U/kg loading dose to achieve ACT of 200–250 s • No IV GPI planned: 70–100 U/kg loading dose to achieve target ACT of 250–300 s for HemoTec, 300–350 s for Hemochron

ACT indicates activated clotting time; GPI, glycoprotein IIb/IIIa inhibitor; IV, intravenous; N/A not applicable PCI, Percutaneous coronary intervention; SC, subcutaneous; and UFH, unfractionated heparin.
AHA/ACC 2014 Guideline for the management of patients with non-ST-elevation acute coronary syndromes. *J Am Coll Cardiol*. 2014;**64**:e139–228, with permission from Elsevier.
2016 ACC/AHA Guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. *Circulation*. 2016; Mar 29. [Epub ahead of print].

(DES) reduce target lesion revascularization (TLR), but not mortality or the risk of MI, compared to BMS.[107] In patients with spontaneous dissection (up to 40% of them present with a NSTEMI), medical therapy is appropriate in dissection of small and medium-sized vessels with TIMI grade 2 or 3 flow whereas revascularization is indicated in patients with large occluded vessels.[108]

In patients undergoing PCI, the SYNTAX score is an independent predictor of the 1-year rates of death, cardiac death, MI, and target vessel revascularization.[109] Incomplete revascularization after PCI in ACS, defined as additional stenoses with a diameter per cent stenosis 30–70%,[110] or a residual SYNTAX Score >8.0,[111] is associated with a poor prognosis. A radial approach may reduce bleeding complications and all-cause mortality in high radial volume centres (MATRIX trial).[112]

Management of patients in need of PCI and CABG is presented in Tables 28.9 and 28.10.

Table 28.10 CABG in ACS

AHA/ACC 2014 GL on NSTE-ACS and 2016 Update on duration of DAPT. Timing of urgent CABG in patients with NSTE-ACS in relation to use of antiplatelet agents	
Non-enteric-coated aspirin (81–325 mg daily) should be administered preoperatively to patients undergoing CABG	I-B
Clopidogrel and ticagrelor should be discontinued for at least 5 days before surgery	I-B
Prasugrel should be discontinued for at least 7 days before surgery	I-C
In urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding	I-B
Short-acting IV GP IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2–4 hours before surgery and abciximab for at least 12 hours before to limit blood loss and transfusion	I-B
In urgent CABG, perform surgery ≥5 days after clopidogrel or ticagrelor has been discontinued and ≥7 days after prasugrel	IIb-C
P2Y12 should be resumed after CABG to complete 12 months of therapy	I-C-LD
ESC 2015 GL on NSTE-ACS. Perioperative management of antiplatelet therapy in NSTE-ACS patients requiring coronary artery bypass surgery	
Irrespective of the revascularization strategy, a P2Y12 inhibitor in addition to aspirin and maintained over 12 months unless there are contraindications such as excessive risk of bleeding.	I-A
The Heart Team estimates the individual bleeding and ischaemic risks and guide the timing of CABG as well as management of DAPT.	I-C
Perform CABG without delay in haemodynamic instability, ongoing myocardial ischaemia or very-high-risk coronary anatomy, regardless of antiplatelet treatment.	I-C
Aspirin, 6–24 h post-CABG in the absence of ongoing bleeding events.	I-A
Continue low-dose aspirin until CABG.	I-B
In stabilised patients requiring CABG who are on DAPT, discontinuation of ticagrelor and clopidogrel 5 days before and prasugrel 7 days prior to surgery.	IIa-B
After CABG, resuming P2Y12 inhibitor therapy as soon as deemed safe.	IIa-C
Platelet function testing in shortening the time window to CABG following P2Y12 inhibitor discontinuation.	IIb-B

DAPT, dual (oral) antiplatelet therapy.
AHA/ACC 2014 Guideline for the management of patients with non-ST-elevation acute coronary syndromes. *J Am Coll Cardiol*. 2014;**64**:e139–228, with permission from Elsevier.
ESC 2015 Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2015; 2016;**37**:267–315 with permission from Oxford University Press.

Specific clinical settings

Patients on warfarin and non-vitamin K oral anticoagulants (NOACs)

Coronary angiography or PCI can be performed in patients on oral anticoagulation (warfarin or NOAC) and with additional anticoagulation (UFH, LMWH, or bivalirudin), preferably through a radial access.[113–115] IIb/IIIa may also be given in bailout situations, if possible, with an INR <2). In patients at high risk of bleeding, oral anticoagulation may have to be temporarily stopped.[114] In patients on dabigatran, bivalirudin is probably preferable, while, in patients on an Xa inhibitor, enoxaparin is preferred. If possible, DES should be avoided in patients on chronic anticoagulation and with a high HAS-BLED score, and triple therapy (INR 2–2.5) should be given for 4 weeks, followed by warfarin with either clopidogrel or aspirin for 12 months.[114–116] In patients with HAS-BLED 0–2, DES may be used, and triple therapy is recommended for 3–6 months, followed by warfarin and clopidogrel or aspirin for 12 months. However, the optimum duration of triple therapy with 2 antiplatelet drugs plus an anticoagulant has not been established and may differ on the basis of individual patient, stent, and drug characteristics. A 6-week course of triple therapy has not been found superior to a 6-month therapy when both major bleeding and ischaemic events were considered (almost 70% of patients in this study had stable CAD).[117] In a recent trial on patients

from Medicare and a US national registry, patients ≥65 years receiving triple therapy versus DAPT had higher rates of major bleeding without a measurable difference in composite MI, death, or stroke.[118] Preferred INR with triple therapy is 2–3 and 2–2.5 in the elderly and those at increased risk of bleeding.[119] There has been evidence that use of warfarin and clopidogrel without aspirin might be safer in this setting.[120,121] Thus, a 6 weeks triple therapy seems a reasonable starting point in high-risk patients, with subsequent duration depending on the patient's characteristics.

In patients on oral anticoagulation (warfarin or new oral anticoagulants), a certain period of triple therapy with the addition of aspirin and clopidogrel, but avoiding ticagrelor or prasugrel, is usually necessary, but at an increased risk of bleeding. Warfarin use alone increases the risk of bleeding to 13% per year, and the combination with an antiplatelet agent may triple this risk.[122] The incidence of fatal or non-fatal bleeding per 100 person-years of therapy has been found to be 14.2 for triple therapy, 7–10.6 for dual therapy, and 6.6–7 for monotherapy.[119] The risk of gastrointestinal bleeding with triple therapy is higher in elderly (>60 years) patients.[123] PPIs may potentiate VKA-induced anticoagulation, resulting in increased INR values and bleeding risk, most likely due to facilitated gastric absorption of warfarin; thus, careful monitoring is required. Addition of antiplatelet therapy to NOACs is also associated with a substantially increased risk of bleeding.[124] In the RELY trial, the addition of antiplatelet agents, such as aspirin or clopidogrel or both, was associated with higher risks of bleeding that was not different between dabigatran and warfarin. The relative increase in the risk of a major bleed was 1.6-fold on a single antiplatelet and 2.3-fold on double antiplatelets. However, the absolute risk of bleeding was lowest on dabigatran 110 mg bd.[125] In a subanalysis of the ARISTOTLE trial, apixaban had similar beneficial effects on stroke or systemic embolism and major bleeding, compared with warfarin, irrespective of concomitant aspirin use.[126] In the ROCKET AF trial, the treatment effect of rivaroxaban, compared with warfarin, did not differ, depending on whether aspirin was used. However, patients with a prior MI had more bleeding complications with rivaroxaban, compared with warfarin, that were likely associated with a higher use of aspirin in this group.[127]

Thus, with clopidogrel and/or low-dose aspirin, a target INR range of 2.0–2.5 is recommended. When a NOAC is used, the lowest dose should be administered (dabigatran 110 mg bd, rivaroxaban 15 mg od, or apixaban 2.5 mg bd). Recommendations are provided in Tables 28.11 and 28.12 and Figure 28.5.

Table 28.11 ESC 2015 GL on NSTE-ACS. Strategies to reduce bleeding risk related to PCI

Anticoagulant doses adjusted to bodyweight and renal function, especially in women and elderly patients.
Radial approach preferred.
Proton pump inhibitors in patients on DAPT at higher than average risk of gastrointestinal bleeds (i.e. history of gastrointestinal ulcer/haemorrhage, anticoagulant therapy, chronic NSAIDs/corticosteroid use, or two or more among age ≥65 years, dyspepsia, gastroesophageal reflux disease, *Helicobacter pylori* infection, and chronic alcohol use).
In patients on OAC
– PCI performed without interruption of VKAs or NOACs.
– In patients on VKAs, do not administer UFH if INR value >2.5.
– In patients on NOACs, regardless of the timing of the last administration of NOACs, add additional low-dose parenteral anticoagulation (e.g. enoxaparin 0.5 mg/kg i.v. or UFH 60 IU/kg).
– Aspirin indicated but avoid pretreatment with P2Y12 inhibitors.
– GPIIb/IIIa inhibitors only for bailout of periprocedural complications

DAPT, dual (oral) antiplatelet therapy; NOACs, non-vitamin K antagonist oral anticoagulants; NSAIDs, non-steroidal anti-inflammatory drugs; UFH, unfractionated heparin; VKAs, vitamin K antagonists

ESC 2015 Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2015; 2016;**37**:267–315 with permission from Oxford University Press.

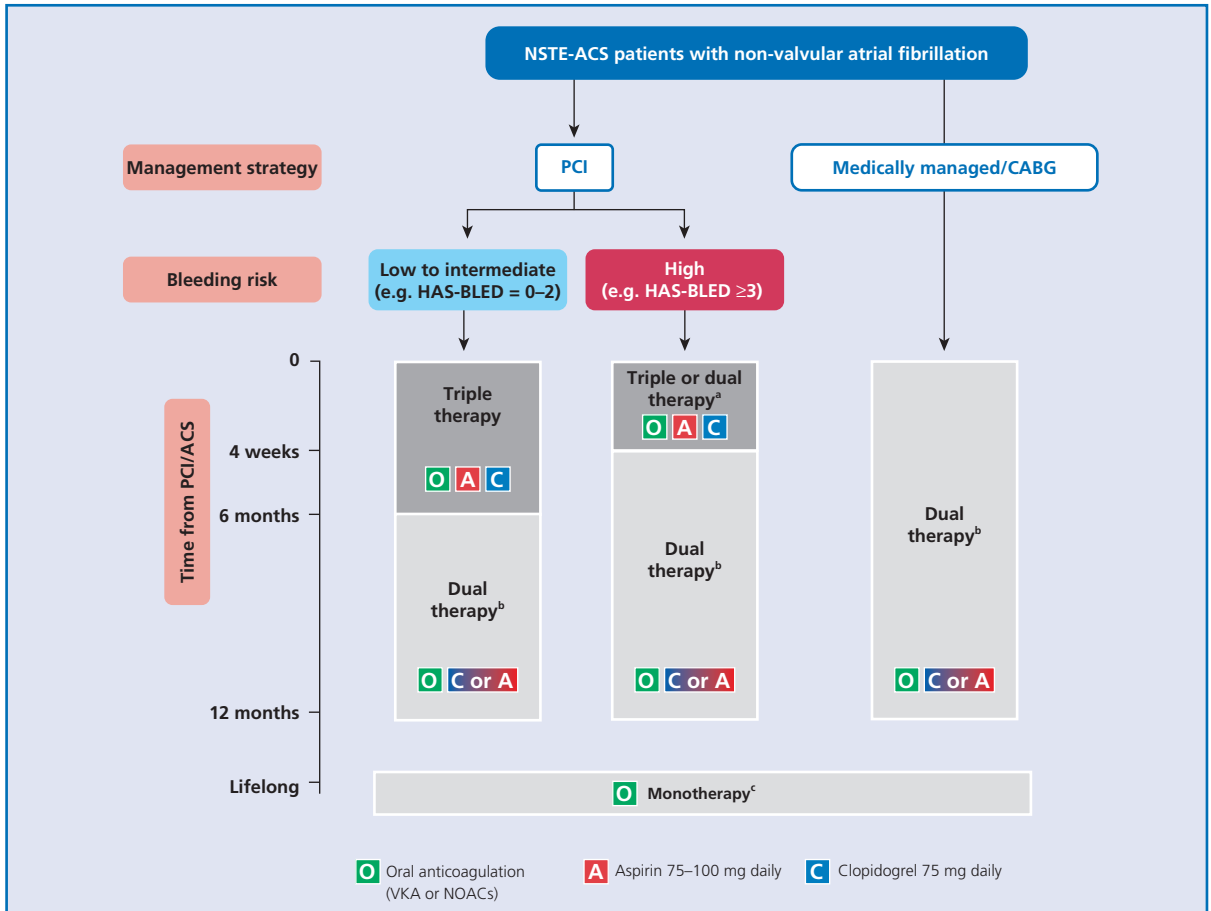
Table 28.12 Management of patients on oral anticoagulants

ESC 2015 GL on NSTE-ACS. Combining antiplatelet agents and anticoagulants in non-ST-elevation acute coronary syndrome patients requiring chronic oral anticoagulation	
In firm indication for OAC (e.g. AF with a CHA2DS2-VASc score ≥2, recent venous thromboembolism, LV thrombus or mechanical valve prosthesis), OAC in addition to antiplatelet therapy.	I-C
Early invasive coronary angiography (within 24 h) in moderate- to high-risk patients, irrespective of OAC exposure, to expedite treatment allocation (medical vs. PCI vs. CABG) and to determine the optimal antithrombotic regimen.	IIa-C
Initial dual antiplatelet therapy with aspirin plus a P2Y12 inhibitor in addition to OAC before coronary angiography is not recommended.	III-C
Patients undergoing coronary stenting	
Anticoagulation	
During PCI, additional parenteral anticoagulation irrespective of the timing of the last dose of all NOACs and if INR is <2.5 in VKA-treated patients.	I-C
Uninterrupted therapeutic anticoagulation with VKA or NOACs during the periprocedural phase.	IIa-C
Antiplatelet treatment	
Following coronary stenting, DAPT including new P2Y12 inhibitors as an alternative to triple therapy for patients with NSTEACS and AF with a CHA2DS2-VASc score of 1 (in males) or 2 (in females).	IIa-C
If at low bleeding risk (HAS-BLED ≤2), triple therapy with OAC, aspirin (75–100 mg/day) and clopidogrel 75 mg/day for 6 months, followed by OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/ day) continued up to 12 months.	IIa-C
If at high bleeding risk (HAS-BLED ≥3), triple therapy with OAC, aspirin (75–100 mg/day) and clopidogrel 75 mg/day for a duration of 1 month, followed by OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months irrespective of the stent type (BMS or new-generation DES).	IIa-C
Dual therapy with OAC and clopidogrel 75 mg/day as an alternative to triple antithrombotic therapy in selected patients (HAS-BLED ≥3 and low risk of stent thrombosis).	IIb-B
The use of ticagrelor or prasugrel as part of triple therapy is not recommended.	III-C
Vascular access and stent type	
Radial over femoral access for coronary angiography and PCI.	I-A
The use of new-generation DES over BMS among patients requiring OAC.	IIa-B
Medically managed patients	
One antiplatelet agent in addition to OAC for up to 1 year.	IIa-C

CHA2DS2-VASc: Cardiac failure, Hypertension, Age ≥75 (2 points), Diabetes, Stroke (2 points)–Vascular disease, Age 65–74, Sex category
DAPT: dual (oral) antiplatelet therapy; NOAC: non-vitamin K antagonist oral anticoagulant; OAC: oral anticoagulant/anticoagulation (it refers to both vitamin K and non-vitamin K antagonist oral anticoagulants); PCI. percutaneous coronary intervention; VKA: vitamin K antagonist.
Triple therapy refers to aspirin, clopidogrel and OAC.
HAS-BLED: bleeding score includes hypertension, abnormal renal and liver function, stroke, bleeding history or predisposition, labile INR (international normalized ratio), elderly (>65 years) and drugs increasing bleeding risk or alcohol abuse.
When NOACs are combined with antiplatelet drugs, they should be used at the lowest dose approved (i.e. dabigatran 2 × 110 mg, rivaroxaban 1 × 15 mg and apixaban 2 × 2.5 mg).
When VKAs are combined with antiplatelet drugs, INR should not exceed 2.5.

AHA/ACC 2014 on NSTE-ACS. Combined oral anticoagulant therapy and antiplatelet therapy	
Minimize the duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a P2Y12 receptor inhibitor in patients with NSTE-ACS	I-C
Proton pump inhibitors in patients with a history of gastrointestinal bleeding who require triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a P2Y12 receptor inhibitor	I-C
Proton pump inhibitor use is reasonable in patients with NSTE-ACS without a known history of gastrointestinal bleeding who require triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a P2Y12 receptor inhibitor	IIa-C
Target oral anticoagulant therapy to an INR of 2–2.5	IIb-C

Triple therapy: warfarin or NOAC and aspirin (75–100 mg/day) and clopidogrel 75 mg/day
Dual therapy: warfarin or NOAC and aspirin (75–100 mg/day) or clopidogrel 75 mg/day
DAPT: dual antiplatelet therapy (aspirin and a P2Y12)
ESC 2015 Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2015; 2016;**37**:267–315 with permission from Oxford University Press.
AHA/ACC 2014 Guideline for the management of patients with non-ST-elevation acute coronary syndromes. *J Am Coll Cardiol*. 2014;**64**:e139–228, with permission from Elsevier.



ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CHA_2DS_2-VASc = Cardiac failure, Hypertension, Age ≥75 [2 points], Diabetes, Stroke [2 points] – Vascular disease, Age 65–74, Sex category; DAPT = dual antiplatelet therapy; NOACs = non-vitamin K antagonist oral anticoagulants; NSTE-ACS = non-ST-elevation acute coronary syndrome; PCI = percutaneous coronary intervention; VKAs = vitamin K antagonists. Adapted from Lip et al.[234]

[a]Dual therapy with oral anticoagulation and clopidogrel may be considered in selected patients (low ischaemic risk).

[b]Aspirin as an alternative to clopidogrel may be considered in patients on dual therapy (i.e., oral anticoagulation plus single antiplatelet); triple therapy may be considered up to 12 months in patients at very high risk for ischaemic events.

[c]Dual therapy with oral anticoagulation and an antiplatelet agent (aspirin or clopidogrel) beyond one year may be considered in patients at very high risk of coronary events. In patients undergoing coronary stenting, dual antiplatelet therapy may be an alternative to triple or a combination of anticoagulants and single antiplatelet therapy if the CHA_2DS_2-VASc score is 1 (males) or 2 (females).

Figure 28.5 ESC 2015 GL on NSTE-ACS. Antithrombotic strategies in patients with non-ST-elevation acute coronary syndromes (NSTE-ACS) and non-valvular atrial fibrillation.

ESC 2015 Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2015; 2016;**37**:267–315 with permission from Oxford University Press.

Diabetics

All patients with ACS should be screened for diabetes (Table 28.13). Tight glycaemic control to achieve normoglycaemia is no more recommended. Instead, insulin infusion to maintain glucose levels <180 mg/dL, while avoiding hypoglycaemia (>90 mg/dL), is recommended by ACCF/AHA. However, intensive glucose regulation aiming at a plasma glucose level of 85 to 110 mg/dL by using intravenous insulin, did not reduce infarct size in non-insulin-dependent hyperglycaemic (up to 288 mg/dL) patients with ACS treated with PCI as compared to conventional expectative glucose management, and was associated with harm.[128] An early invasive strategy is recommended for diabetic patients with NSTE-ACS, and DES are preferred to BMS. CABG is preferable to PCI in multivessel disease. Diabetic patients with NSTE-ACS may receive intravenous GP IIb/IIIa inhibitors as part of the initial medical management which should be continued through the completion of PCI. No more recommended as a routine medication.

Chronic kidney disease

Renal function should be assessed with creatinine clearance (CrCl) estimation in all patients with ACS (Table 28.14). Chronic kidney disease (defined as estimated creatinine clearance [CrCl] <60 mL·min^{-1}·1.73 m^{-2}) has a prevalence of 42.9% among patients presenting with non–ST-segment–elevation myocardial infarction.[65] An invasive strategy, with preparatory hydration and low doses of contrast media, is reasonable in patients with mild (stage II) and moderate (stage III) chronic kidney disease, but no data exist for patients with advanced disease (stages IV and V). Drug dosage adjustments have been recently reviewed by AHA.[65]

Elderly

Patients older than 75 years of age should be investigated at low level of suspicion due to often atypical presentation of ACS. In the After Eighty study, an invasive strategy was also beneficial in patients aged more than 80 years, although this was not clear for patients more than 90 years of age.[129] Despite an increased risk for major bleeding, a routine early invasive strategy can significantly improve ischaemic outcomes in elderly patients with unstable angina and non-ST-segment elevation MI (Tables 28.15 and 28.16). Care is needed due to increased risk of bleeding and possibly concurrent renal dysfunction in this group and drug dosages should be modified accordingly.

Table 28.13 Diabetes mellitus

ESC 2015 GL on NSTE-ACS.	
Blood glucose control	
Screen all patients with NSTE-ACS for diabetes and monitor blood glucose levels frequently in patients with known diabetes or admission hyperglycaemia.	I-C
Glucose-lowering therapy in ACS patients with blood glucose >10 mmol/L (>180 mg/dL), with the target adapted to comorbidities, while episodes of hypoglycaemia should be avoided.	IIa-C
Less stringent glucose control both in the acute phase and at follow-up in patients with more advanced cardiovascular disease, older age, longer diabetes duration and more comorbidities.	IIa-C
Antithrombotic treatment and invasive strategy	
Administer the same antithrombotic treatment in diabetic and non-diabetic patients.	I-C
An invasive strategy over non-invasive management.	I-A
Monitor renal function for 2–3 days after coronary angiography or PCI in patients with baseline renal impairment or on metformin.	I-C
In patients undergoing PCI, new-generation DESs over BMSs.	I-A
In patients with stabilised multivessel CAD and an acceptable surgical risk, CABG over PCI.	I-A
In patients with stabilised multivessel CAD and a SYNTAX score ≤22, PCI as an alternative to CABG.	IIa-B
AHA/ACC 2014 GL on NSTE-ACS	
Recommend medical treatment and decisions for testing and revascularization similar to those for patients without DM	I-A

ESC 2015 Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2015; 2016;**37**:267–315 with permission from Oxford University Press.
AHA/ACC 2014 Guideline for the management of patients with non-ST-elevation acute coronary syndromes. *J Am Coll Cardiol*. 2014;**64**:e139–228, with permission from Elsevier.

Table 28.14 Chronic kidney disease

ESC 2015 GL on NSTE-ACS

Assess kidney function by eGFR in all patients.	I-C
Administer the same first-line antithrombotic treatment as in patients with normal kidney function, with appropriate dose adjustment if indicated.	I-B
Depending on the degree of renal dysfunction, switch parenteral anticoagulation to UFH or adjust the doses of fondaparinux, enoxaparin and bivalirudin, as well as the dose of small molecule GPIIb/IIIa inhibitors.	I-B
Switch s.c. or i.v. anticoagulation to UFH infusion adjusted to the aPTT when eGFR is <30 mL/min/1.73 m^2 (for fondaparinux, when eGFR is <20 mL/min/1.73 m^2).	I-C
Hydration with isotonic saline and low- or iso-osmolar contrast media (at lowest possible volume), in patients undergoing an invasive strategy	I-A
Coronary angiography and, if needed, revascularization after careful assessment of the risk–benefit ratio, in particular with respect to the severity of renal dysfunction.	I-B
In patients undergoing PCI, new-generation DESs over BMSs.	I-B
CABG over PCI in patients with multivessel CAD whose surgical risk profile is acceptable and life expectancy is >1 year.	IIa-B
PCI over CABG in patients with multivessel CAD whose surgical risk profile is high or life expectancy is <1 year.	IIa-B

AHA/ACC 2014 GL on NSTE-ACS

Estimate CrCl and adjust doses of renally cleared medications according to pharmacokinetic data	I-B
Administer adequate hydration to patients undergoing coronary and LV angiography	I-C
Invasive strategy is reasonable in patients with mild (stage 2) and moderate (stage 3) CKD	IIa-B

AHA 2015 Statement on pharmacotherapy in chronic kidney disease patients presenting with acute coronary syndrome

Doses of parenteral antithrombotic agents

Medication	Renal elimination	Dose in patients without CKD	Dose adjustment in CKD
Abciximab	NS	◆ PCI: 0.25 mg/kg bolus followed by infusion of 0.125 μg/kg/min (maximum 10 μg/min) for 12 h after procedure	No adjustment
Bivalirudin	20%	◆ PCI: 0.75 mg/kg bolus followed by infusion of 1.75 mg/kg/h for duration of the procedure	CrCl <30 mL/min: ◆ PCI: 0.75-mg/kg bolus followed by infusion of 1 mg/kg/h for the duration of the procedure Dialysis: ◆ PCI: 0.75 mg/kg bolus followed by infusion of 0.25 mg/kg/h
Enoxaparin	40%	◆ UA/NSTEMI: 1 mg/kg SC every 12 h ◆ STEMI patients <75 y of age receiving fibrinolytic therapy: 30 mg single IV bolus plus a 1 mg/kg SC dose followed by 1 mg/kg SC every 12 h	CRCI <30 ML/min: ◆ UA/NSTEMI: 30 mg single IV bolus plus a 1 mg/kg SC dose followed by 1 mg/kg administered SC once daily ◆ STEMI patients 75 y of age receiving fibrinolytic therapy: No bolus, 1 mg/kg administered SC once daily. Not recommended in dialysis patients

(*Continued*)

Table 28.14 Continued

Eptifibatide	50%	◆ ACS: 180 μg/kg bolus followed by an infusion of 2 $mg \cdot kg^{-1} \cdot mg^{-1}$ for up to 72h ◆ PCI: 180 μg/kg followed by continuous infusion of 2 $mg \cdot kg^{-1} \cdot mg^{-1}$ for up to 18-24h. A second 180-μg/kg bolus given 10 min after the first bolus	CRCI <50 mL/min: ◆ ACS: 180 μg/kg bolus followed by infusion of 1 $mg \cdot kg^{-1} \cdot mg^{-1}$ for up to 72h ◆ PCI: 180 μg/kg bolus followed by infusion of 1 $mg \cdot kg^{-1} \cdot mg^{-1}$ for up to 18-24h. A second 180-g/kg bolus given 10 min after the first bolus Contraindicated in dialysis patients
Fondaparinux	75%	◆ STEMI patients receiving fibrinolytic therapy: 2.5 mg IV followed by 2.5 mg SC daily starting the following day ◆ UA/NSTEMI: 2.5 mg SC daily	CrCI < 30 mL/min: ◆ Avoid use
Unfractionated heparin	NS	◆ UA/NSTEMI (initial dosing): Bolus of 60 U/kg (maximum 4000 U) followed by an infusion of 12 $U \cdot kg^{-1} \cdot h^{-1}$ (maximum 1000 U/h) to maintain aPTT at 1.5–2.0 times control ◆ STEMI patients receiving fibrinolytic therapy: Bolus of 60 U/kg (maximum 4000 U/kg) followed by an infusion of 12 $U \cdot kg^{-1} \cdot h^{-1}$ (maximum 1000 U) initially, adjusted to maintain aPTT at 1.5–2.0 times control for 48 h or until revascularization.	No adjustment recommended
Tirofiban	65%	◆ PCI: 25 μg/kg IV over 3 min followed by an infusion of 0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for up to 18 h post-PCI	CRCI ≤60 mL/min: ◆ PCI 25 μg/kg IV over 3 min followed by an infusion of 0.075 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for up to 18 h post-PCI

aPTT, activated partial thromboplastin time; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UFH, unfractionated heparin.
ESC 2015 Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2015; 2016;**37**:267–315 with permission from Oxford University Press.
AHA/ACC 2014 Guideline for the management of patients with non-ST-elevation acute coronary syndromes. *J Am Coll Cardiol*. 2014;**64**:e139–228, with permission from Elsevier.
AHA 2015 Statement on pharmacotherapy in chronic kidney disease patient presenting with acute coronary syndrome. *Circulation*. 2015;**131**:1123–49 with permission from Wolters Kluwer.

Table 28.15 ESC 2015 GL on NSTE-ACS. Elderly patients

Tailor antithrombotic treatment according to bodyweight and renal function.	I-C
Invasive strategy and, if appropriate, revascularization after careful evaluation of potential risks and benefits, estimated life expectancy, comorbidities, quality of life, frailty and patient values and preferences.	IIa-A
Adjusted dosing regimens of beta-blockers, ACE inhibitors, ARBs and statins to prevent side effects.	IIa-C

ESC 2015 Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2015; 2016;**37**:267–315 with permission from Oxford University Press.

Pregnancy

Recommendations of the ESC guidelines indicate medical therapy for NSTEMI (IIa-C) without high-risk criteria, and PCI for high risk cases (IIa-C).[130]

Heart failure

Coronary revascularization, if amenable, is recommended in patients with ACS and LV dysfunction (Tables 28.16 and 28.17). Patients should be considered, at least, 1 month after the acute event for device therapy, such as CRT and/or ICD.

Anaemia

Anaemia is a marker of ischaemic and bleeding events, and haemoglobin measurements are mandatory on presentation. Blood transfusion is recommended only with Hct <25% or Hb <7g/dL.[3] The use of erythropoiesis-stimulating agents is not recommended in patients with mild to moderate anaemia and coronary heart disease.[131]

Table 28.16 AHA/ACC 2014 GL on NSTE-ACS. Special patient groups

NSTE-ACS in older patients	
Treat older patients (≥75 y of age) with GDMT, early invasive strategy, and revascularization as appropriate	I-A
Individualize pharmacotherapy in older patients, with dose adjusted by weight and/or CrCl	I-A
Patient-centred management for older patients, considering patient preferences/goals, co-morbidities, functional and cognitive status, and life expectancy	I-B
Bivalirudin rather than GP IIb/IIIa inhibitor plus UFH for older patients (≥75 y of age)	IIa-B
CABG over PCI in older patients, particularly those with DM or multivessel disease	IIa-B
HF	
Treatment according to guidelines for patients without HF	I-B
Select a revascularization strategy based on the extent of CAD, associated cardiac lesions, LV dysfunction, and prior revascularization	I-B
Cardiogenic shock	
Early revascularization for cardiogenic shock due to cardiac pump failure	I-B
Post-CABG	
GDMT antiplatelet and anticoagulant therapy and early invasive strategy because of increased risk with prior CABG	I-B
Perioperative NSTE-ACS	
GDMT to perioperative patients with limitations imposed by non-cardiac surgery	I-C
Direct management of underlying cause of perioperative NSTE-ACS	I-C
Women	
Manage women with the same pharmacological therapy as that for men for acute care and secondary prevention, with attention to weight and/or renally calculated doses of antiplatelet and anticoagulant agents to reduce bleeding risk	I-B
Early invasive strategy in women with NSTE-ACS and high-risk features (troponin positive)	I-A
Myocardial revascularization for pregnant women if ischaemia-guided strategy is ineffective for management of life-threatening complications	IIa-C
Women with low-risk features should not undergo early invasive treatment (no benefit)	III-B
Anaemia, bleeding, and transfusion	
Evaluate all patients for risk of bleeding	I-C
Anticoagulant and antiplatelet therapy should be weight-based, where appropriate, and adjusted for CKD to decrease the risk of bleeding	I-B
No benefit of routine blood transfusion in haemodynamically stable patients with haemoglobin levels >8 g/dL (no benefit)	III-B
Cocaine and methamphetamine users	
Manage patients with recent cocaine or methamphetamine use similarly to those without cocaine- or methamphetamine-related NSTE-ACS. The exception is in patients with signs of acute intoxication (e.g. euphoria, tachycardia, and hypertension) and beta blocker use, unless patients are receiving coronary vasodilator therapy	I-C
Use benzodiazepines alone or in combination with NTG to manage hypertension and tachycardia and signs of acute cocaine or methamphetamine intoxication	IIa-C
Do not administer beta blockers to patients with recent cocaine or methamphetamine use who have signs of acute intoxication due to risk of potentiating coronary spasm (Harm)	III-C
Vasospastic (Prinzmetal) angina	
CCBs alone or in combination with nitrates	I-B
HMG-CoA reductase inhibitor, cessation of tobacco use, and atherosclerosis risk factor modification	I-B
Coronary angiography (invasive or non-invasive) for episodic chest pain with transient ST elevation	I-C
Provocative testing during invasive coronary angiography* for suspected vasospastic angina when clinical criteria and non-invasive assessment fail to determine diagnosis	IIb-B

(*Continued*)

Table 28.16 Continued

ACS with angiographically normal coronary arteries	
Invasive physiological assessment (coronary flow reserve measurement) with normal coronary arteries if endothelial dysfunction is suspected	IIb-B
Stress (Takotsubo) cardiomyopathy	
Consider stress-induced cardiomyopathy in patients with apparent ACS and non-obstructive CAD	I-C
Ventriculography, echocardiography, or MRI to confirm or exclude diagnosis	I-B
Treat with conventional agents (ACE inhibitors, beta blockers, aspirin, and diuretics) if haemodynamically stable	I-C
Anticoagulant therapy for LV thrombi	I-C
Administer catecholamines for symptomatic hypotension in the absence of LV outflow tract obstruction	IIa-C
Use IABP for refractory shock	IIa-C
Use beta blockers and alpha-adrenergic agents for LV outflow tract obstruction	IIa-C
Prophylactic anticoagulation to prevent LV thrombi	IIb-C

*Provocative testing during invasive coronary angiography (e.g. using ergonovine, acetylcholine, methylergonovine) is relatively safe, especially when performed in a controlled manner by experienced operators. However, sustained spasm, serious arrhythmias, and even death can also occur but very infrequently. Therefore, provocative tests should be avoided in patients with significant left main disease, advanced three-vessel disease, presence of high-grade obstructive lesions, significant valvular stenosis, significant LV systolic dysfunction, and advanced HF.
GDMT, guidelines-directed medical therapy

AHA/ACC 2014 Guideline for the management of patients with non-ST-elevation acute coronary syndromes. *J Am Coll Cardiol.* 2014;**64**:e139–228, with permission from Elsevier.

Table 28.17 ESC 2015 GL on NSTE-ACS.

Acute heart failure in the setting of NSTE-ACS	
Emergency echocardiography to assess LV and valvular function and exclude mechanical complications.	I-C
Immediate coronary angiography in acute heart failure with refractory angina, ST deviation or cardiogenic shock.	I-B
Immediate PCI for cardiogenic shock if coronary anatomy is suitable.	I-B
Emergency CABG for cardiogenic shock if the coronary anatomy is not amenable to PCI.	I-B
Patients with mechanical complications of NSTE-ACS are immediately discussed by the Heart Team.	I-C
IABP insertion in haemodynamic instability/cardiogenic shock due to mechanical complications.	IIa-C
Short-term mechanical circulatory support in patients with cardiogenic shock	IIb-C
Routine use of IABP in patients with cardiogenic shock is not recommended.	III-B
Heart failure following NSTE-ACS	
An ACE inhibitor (or ARB, if an ACE inhibitor is not tolerated) is recommended in LVEF ≤40% after stabilization, to reduce the risk of death, recurrent MI and hospitalization for heart failure.	I-A
A beta-blocker in LVEF ≤40% after stabilization, to reduce the risk of death, recurrent MI and hospitalization for heart failure.	I-A
Mineralocorticoid receptor antagonists to reduce the risk of heart failure hospitalization and death in persistent symptoms (NYHA class II–IV) and LVEF ≤35% despite treatment with an ACE inhibitor (or an ARB, if an ACE inhibitor is not tolerated) and a beta-blocker.	I-A
Mineralocorticoid receptor antagonists, preferably eplerenone, to reduce the risk of cardiovascular hospitalization and death in LVEF ≤40%.	I-B
Device therapy (CRT-D or ICD, depending on QRS duration) is in symptomatic, severe LV dysfunction (LVEF ≤35%) despite optimal medical therapy. 40 days after the acute event and without options of revascularization. Patients should be expected to survive >1 year with good functional status.	I-A
In CAD and LVEF ≤35%, testing for residual ischaemia and subsequent revascularization prior to primary prophylactic ICD/CRT-D implantation. After revascularization, assessment of reverse LV remodelling up to 6 months prior to primary prophylactic ICD/CRT-D implantation.	IIa-B

CRT-D, cardiac resynchronization therapy defibrillator; ICD, implantable cardioverter defibrillator.
IABP: intra-aortic balloon pump;
ESC 2015 Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2015; 2016;**37**:267–315 with permission from Oxford University Press.

Familial hypercholesterolaemia

Patients who develop an ACS before the age of 55 years or even earlier and in the absence of other high-risk factors, should be considered for familial hypercholesterolaemia (see Chapter 27).[132,133] Familial hypercholesterolaemia is clinically diagnosed by five major criteria including: family history of premature CAD, presence of early CAD in the index case, elevated LDL-C, tendon xanthomas, and corneal arcus.[133,134] The disease has a high prevalence close to one in 200 individuals but is often underdiagnosed.[132] Patients can be heterozygous with total cholesterol values 350–550 mg/dL (9–14 mmol/L) and LDL-C 200–400 mg/dL (5–10 mmol/L), untreated[135] or homozygous (Table 28.8).[134] Criteria have been proposed for diagnosis (Table 28.18) that is confirmed by genetic testing. Aggressive therapy with high-intensity statins, ezetimibe and bile acid-binding resins or even lipoprotein apheresis may be necessary for the prevention of early coronary artery disease (Figure 28.6).[132,135,136] Patients with homozygous familial hypercholesterolaemia (frequency 1 in 1 million), and

Table 28.18 European Atherosclerotic Society: criteria for the diagnosis of homozygous familial hypercholesterolaemia

Genetic confirmation of two mutant alleles at the *LDLR, APOB, PCSK9*, or *LDLRAP1* gene locus
OR
An untreated LDL-C >13 mmol/L (500 mg/dL) or treated LDL-C ≥8 mmol/L (300 mg/dL)* together with either:
○ Cutaneous or tendon xanthoma before age 10 years Or
○ Untreated elevated LDL-C levels consistent with heterozygous FH in both parents

*These LDL-C levels are only indicative, and lower levels, especially in children or in treated patients, do not exclude HoFH

Cuchel M, *et al.* Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the consensus panel on familial hypercholesterolaemia of the european atherosclerosis society. *Eur Heart J.* 2014;**35**:2146–57, with permission from Oxford University Press.

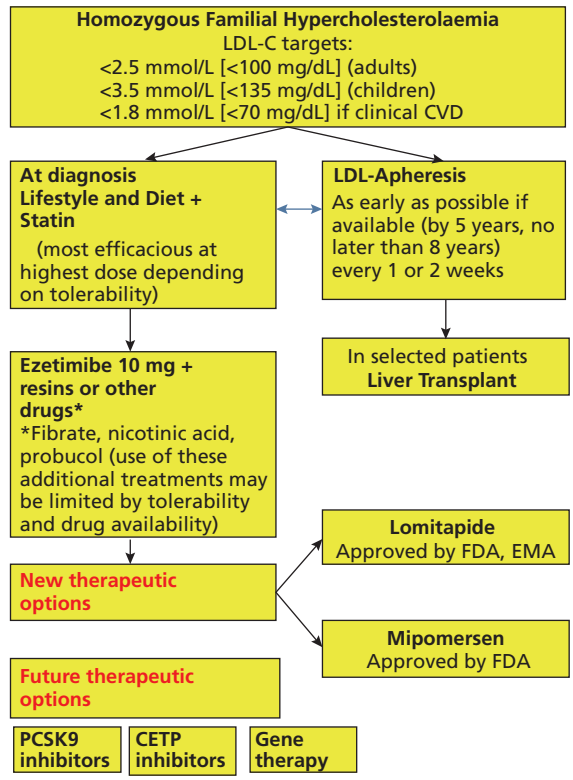


Figure 28.6 European Atherosclerotic Society—criteria for the diagnosis of homozygous familial hypercholesterolaemia.

Suggested algorithm for management of homozygous familial hypercholesterolaemia.

Cuchel M, *et al.* Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the consensus panel on familial hypercholesterolaemia of the european atherosclerosis society. *Eur Heart J.* 2014;**35**:2146–57, with permission from Oxford University Press.

severe forms of heterozygous familial hypercholesterolaemia (frequency 1/500), may not respond to conventional therapy. In these cases, **proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors** may safely reduce LDL and Lp(a) levels alone or combined with statins.[137,138] **Mipomersen**, an antisense oligonucleotide inhibitor of apolipoprotein B, and **lomitapide**, a microsomal triglyceride transfer protein inhibitor, are also effective but at a risk of inducing fatty liver and a rather prohibitive cost.[138–141]

Statins are discussed in detail in Chapter 30.

Complications

Atrioventricular conduction disturbances

In the Global Registry of Acute Coronary Events, the incidence of high-grade AV block in ACS was low (2.9%) and on the decrease, but it carried a high risk of in-hospital death (22.7%), reflecting the severity of ACS.[142]

Tachyarrhythmias

The management of AF is presented in Table 28.19. AF in ACS is also discussed in Chapter 29.

In non-ST elevation acute coronary syndromes, NSVT is detected in 18–25% of patients 2–9 days after admission, and even short episodes of VT lasting 4–7 beats are independently associated with the risk of SCD over the subsequent year (MERLIN-TIMI 36 trial).[143] Earlier episodes within 48 hours after admission do not carry the same risk. The presence of myocardial ischaemia or VT alone, as detected on 7-day continuous electrocardiographic monitoring, and particularly in combination, is independently associated with poor cardiovascular outcomes.[144] Ventricular tachycardia or VF indicate coronary angiography and revascularization within 2 h of hospital admission (ESC 2015 on VA and SCD, I-C). These

Table 28.19 AF in acute coronary syndromes

ESC 2015 GL on NSTE-ACS. Management of AF in NSTE-ACS	
In the absence of contraindications, administer anticoagulant drugs to all patients at presentation.	I-A
Investigations to detect ischaemia in AF and elevated cardiac troponin.	IIa-C
Patients with rapid ventricular rate	
Electrical cardioversion is in haemodynamically unstable patients.	I-C
Electrical or pharmacological cardioversion with amiodarone in patients when a decision is made to restore sinus rhythm non-urgently (rhythm control strategy). Employ this strategy only with the first episode of atrial fibrillation of <48 h duration (or with no evidence of left atrial appendage thrombus on TOE) or if the patient was anticoagulated in the therapeutic range for at least 3 weeks.	I-C
Intravenous beta-blockers to slow the rapid ventricular response to AF in haemodynamically stable patients.	I-C
IV cardiac glycosides for ventricular rate control if the response to beta-blockers is not sufficient.	IIb-C
IV non-dihydropyridine calcium antagonists (verapamil, diltiazem) to slow a rapid ventricular response to atrial fibrillation in patients not on beta-blockers and with no signs of heart failure.	IIb-C
Class I antiarrhythmic agents (e.g. encainide, flecainide) are not recommended.	III-B
Vernakalant is not recommended.	III-C
AHA/ACC/HRS 2014 GL on AF. AF complicating ACS	
Urgent direct current cardioversion of new-onset AF for haemodynamic compromise, ongoing ischaemia, or inadequate rate control.	I-C
IV beta blockers to slow a rapid ventricular response in patients who do not display HF, haemodynamic instability, or bronchospasm.	I-C
For CHA2DS2-VASc score≥2, anticoagulation with warfarin, unless contraindicated.	I-C
Amiodarone or digoxin to slow a rapid ventricular response in severe LV dysfunction and heart failure or haemodynamic instability.	IIb-C
Non-dihydropyridine calcium antagonists to slow a rapid ventricular response only in the absence of significant heart failure or haemodynamic instability.	IIb-C

The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology, Guidelines for the management of atrial fibrillation, *European Heart Journal* (2010) **31**, 2369–2429, by permission of Oxford University Press.
TOE ʘ, transoesophageal echocardiography.
ESC 2015 Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2015; 2016;**37**:267–315 with permission from Oxford University Press.
AHA/ACC/HRS 2014 Guideline for the management of patients with atrial fibrillation. *J Am Coll Cardiol*. 2014;**64**:2246–2280 with permission from Elsevier.

patients may need LV assist device or extracorporeal life support if they are unstable in the context of recurrent VT/VF (ESC 2015 on VA and SCD, IIa-B). Other recommendations are also provided in Chapter 29.

Cardiogenic shock

Patients with ACS and evidence of cardiogenic shock benefit from immediate revascularization versus medical therapy.[145]

Bleeding

Bleeding has an ominous prognosis, with mortality increasing as bleeding severity increases.[146–148] Major bleeding is associated with increase in the risk of death (4-fold), MI (5-fold), and stroke (3-fold). Bleeding risk is increased with higher or excessive doses of antithrombotic agents, length of treatment, combinations of several antithrombotic drugs, switch between different anticoagulant drugs, as well as with older age, reduced renal function, low body weight, female gender, baseline haemoglobin, and invasive procedures. Sex-associated factors, such as lower BMI and lower creatinine clearance, and anatomic differences, such as smaller vessel size, may contribute to the excess risk seen in women.[149] Several definitions and classifications of bleeding have been used in trials,[147,150,151] with the simplest one provided by TIMI (Table 28.20).

Minor bleeding should preferably be managed without interruption of active treatments.

Major bleeding requires interruption and/or neutralization of both anticoagulant and antiplatelet therapy and platelet transfusion, unless bleeding can be adequately controlled by specific haemostatic intervention (Table 28.21). The risk of acute thrombotic events after interruption of antithrombotic/antiplatelet agents is maximum after 4–5 days but persists for up to 30 days.[152]

Blood transfusion has been associated with increased risk of MI and death in ACS patients, probably due to increased platelet aggregation,[153] and should be withheld in haemodynamically stable patients with haematocrit >25% or haemoglobin level >7 g/L.[154]

Aspirin and **clopidogrel** are irreversible platelet inhibitors. Their action is slowly reversed by the continuous generation of new platelets (around 10–20% per day), so antiplatelet effects persist for 5–10 days after cessation of treatment. Platelet transfusion is the only possibility to reverse the effects of clopidogrel/aspirin. The recommended minimum dose in adults is $0.5–0.7 \times 10^2$ platelets/7 kg of body weight.

Unfractionated heparin can be inhibited by an equimolar concentration of protamine sulfate (1–1.5 mg/100 USP units of heparin, not to exceed 50 mg).

Table 28.20 TIMI bleeding definitions

Major
Intracranial haemorrhage or clinically overt bleeding (including imaging), with ≥5 g/dL decrease in the haemoglobin concentration
Minor
Clinically overt bleeding (including imaging), with 3 to <5 g/dL decrease in the haemoglobin concentration
Minimal
Clinically overt bleeding (including imaging), with a <3 g/dL decrease in the haemoglobin concentration

All TIMI definitions take into account blood transfusions, such that haemoglobin values are adjusted by 1 g/dL for each unit of packed red blood transfused.
Rao AK, *et al*. Thrombolysis in Myocardial Infarction (TIMI) Trial–phase I: haemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol*. 2011;**11**:1–11 with permission from Elsevier.

Table 28.21 ESC 2015 GL on NSTE-ACS

Recommendations for bleeding management and blood transfusion in NSTE-ACS.	
In patients with VKA-associated life-threatening bleeding events, rapid reversal of anticoagulation with four-factor prothrombin complex concentrate rather than with fresh frozen plasma or recombinant activated factor VII. In addition, repetitive 10 mg i.v. doses of vitamin K by slow injection.	IIa-C
In patients with NOAC-associated ongoing life-threatening bleeds, administration of prothrombin complex concentrate or activated prothrombin complex concentrates	IIa-C
In patients with anaemia and no evidence of active bleed, blood transfusion may be considered in the case of compromised haemodynamic status or haematocrit <25% or haemoglobin level <7 g/dL.	IIb-C

NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist
ESC 2015 Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2015; 2016;**37**:267–315 with permission from Oxford University Press.

Protamine only partially affects anti-Xa levels, and may be used in reversing bleeding associated with **LMWH** but not with **fondaparinux**. For antidotes to fondaparinux (Xa inhibitor) see Chapter 53.

There is no antidote for **bivalirudin**. Its plasma half-life is 25 min and is partially cleared renally.

Platelet transfusion is needed with **abciximab**. Interruption of **eptifibatide** and **tirofiban** infusion allows platelet function within 4–8 h. In emergencies, fibrinogen supplementation with fresh frozen plasma or cryoprecipitate with or without platelet transfusion are recommended for immediate reversal of the effects of eptifibatide and tirofiban.

Factors that put patients at higher risk of bleeding are older age, female sex, lower body weight, renal insufficiency.[147] In patients undergoing PCI, bleeding is associated with increased in-hospital mortality that is highest with non-access site bleeding.[155]

Additional recommendations to help minimize the risk are:[147]

- Avoid overdosing by adjusting the dose to a patient's weight, age, and renal function.
- Use the shortest possible duration, i.e. 1 month after BMS implantation and 12 months after DES implantation.
- Fondaparinux may be preferred over enoxaparin in NSTE-ACS, and bivalirudin over unfractionated heparin and a glycoprotein IIb/IIIa inhibitor in STEMI.
- Add a proton pump inhibitor in patients at risk for GI bleed.
- Avoid access site bleeding with the use of small sheaths, closure devices, and radial access.
- Prefer BMS over DES in patients on triple therapy for AF.

Heparin–induced thrombocytopenia

Thrombocytopenia is defined as a decrease in platelet count to <100 000/mL or a drop of >50% from baseline platelet count. Thrombocytopenia is considered to be moderate if the platelet count is between 20 000 and 50 000/microlitre and severe if it is < 10 000/microlitre.

Non-immune heparin-associated thrombocytopenia is a mild, transient decline in platelet count that occurs 1–4 days after initiating heparin in 10–20% of patients. It rarely leads to a severe reduction in platelet levels and resolves spontaneously despite continuation of UFH.

Pseudothrombocytopenia is a laboratory artefact due to platelet clumping in EDTA-containing tubes and can be avoided by the use of citrate instead of EDTA for blood sampling.

Immune-mediated heparin-induced thrombocytopenia (HIT) is a serious complication that often leads to severe thromboembolic events.[156] It is not dose-dependent, usually causes a severe drop in platelet levels (<50%), and typically appears 5–10 days after the start of UFH treatment but much earlier in patients with recent (within 3 months) UFH exposure. Delayed-onset HIT, occurring several days or weeks after the cessation of UFH treatment, has also been described. HIT is a hypersensitivity reaction to heparin mediated via an IgG antibody to platelet factor 4. This IgG/heparin/platelet factor 4 complex binds to platelets and cross-links their receptors, which causes platelet activation and thrombosis. Bleeding is rare. HIT occurs in 0.5–5% of patients treated with unfractionated heparin (3000–30 000 daltons) and <1% with LMWH (less antigenic, 2000–9000 daltons).

Thrombocytopenia is very rare with bivalirudin and negligible with fondaparinux,[157] despite weak binding to the platelet factor 4 antigen. All patients diagnosed with thrombocytopenia or a thrombotic complication within 4–14 days after starting heparin therapy should have heparin discontinued immediately and screening tests performed. It has been reported to occur with abciximab (2.5%) and less with tirofiban (0.5%) or eptifibatide (0.2%). Rarely, it may also occur with clopidogrel.[158]

Diagnosis

The diagnosis of HIT is based on its typical clinical picture of '**4 Ts**'.

- Thrombocytopenia: >50% fall or nadir 20–100 × 10^9/L
- Timing of platelet fall: days 5 to 10 or ≤1 day if heparin exposure within past 30 days
- Thrombosis or other sequelae: proven thrombosis, skin necrosis, or, after heparin bolus, acute systemic reaction
- Other cause for thrombocytopenia: none evident.

Thromboembolic complications are predominantly venous and may be devastating; pulmonary embolism, deep-vein thrombosis, myocardial infarction, and stroke may occur. Associated mortality is 5–10%.[157] Diagnosis is confirmed by circulating heparin-PF4 antibodies that remain detectable for 4 months after the diagnosis of HIT in 10–40% of patients, depending on the assay used. These tests have a high negative predictive value but a low positive predictive value.[156] Scoring systems for diagnosis have been developed.[157]

Quinine- or other drug-induced immune thrombocytopenic purpura, as well as glycoprotein IIb/IIIa antagonist-induced thrombocytopenia, typically is associated with more severe thrombocytopenia than that of HIT. Patients with massive, acute venous thromboembolism occasionally develop thrombocytopenia because of platelet consumption on the thrombus surface; their platelet count nadir usually happens within 1 day of heparin initiation. Other causes of repeat thrombotic episodes are the antiphospholipid antibody syndrome, Trousseau's syndrome, cholesterol emboli syndrome, and infective or non-bacterial thrombotic endocarditis. HIT should be also

Table 28.22 ESC 2015 GL on NSTE-ACS. Recommendations for thrombocytopenia

Immediate interruption of GPIIb/IIIa inhibitor and/or heparin (UFH, LMWH, other heparin products) in case of thrombocytopenia <100 000/μL (or >50% relative drop from baseline platelet count) occurring during treatment.	I-C
In patients treated with GP IIb/IIIa inhibitors, platelet transfusion in case of major active bleeding events or in the presence of severe (<10 000/μL) asymptomatic thrombocytopenia.	I-C
Treatment with a non-heparin anticoagulant in case of documented or suspected HIT.	I-C
Use of anticoagulants with low or no risk of HIT or brief administration of UFH or LMWH, when these are chosen, to prevent the occurrence of HIT.	I-C

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considered if a recently hospitalized patient returns with thromboembolism.

Therapy of HIT

Interruption of heparin (UFH or LMWH) is warranted in the case of documented or suspected HIT. Significant thrombocytopenia (<100 000/mL or >50% drop in platelet count) occurring during treatment with GP IIb/IIIa inhibitors and/or heparin (LMWH or UFH) requires the immediate interruption of these drugs (Table 28.22).

Severe thrombocytopenia (<10 000/μL), induced by GP IIb/IIIa inhibitors, requires platelet transfusion, with or without fibrinogen supplementation, with fresh frozen plasma or cryoprecipitate in the case of bleeding.

In the case of **thrombotic complications**, anticoagulation can be achieved with a direct thrombin inhibitor, such as **bivalirudin**. This is also recommended by the ACCP 2012 guideline on antithrombotic therapy (2C) for cardiac surgery or coronary intervention.[159]

The direct thrombin inhibitor **argatroban** (IV infusion of 2.0 mcg/kg/min; 0.5–1.2 mcg/kg/min in liver disease, critical illness or after cardiac surgery to maintain an APTT of 1.5–3.0 times baseline value – max 10 mcg/kg/min) is approved by the FDA for HIT, and is particularly indicated in renal insufficiency (ACCP 2012–2C). Hypercoagulability may occur with discontinuation of the drug, and transition to warfarin may be challenging.

The factor Xa inhibitor **danaparoid** and the direct thrombin inhibitor **lepirudin** are also recommended by the ACCP 2012 guidelines (2C). Danaparoid is recommended in pregnancy (ACCP 2012–2C). **Fondaparinux** may also be used.[156]

Platelet glycoprotein IIb/IIIa inhibitors reduce thrombin generation indirectly and inhibit platelet aggregation. However, they lack direct anticoagulant effects and do not inhibit Fc receptor-mediated activation of platelets by HIT antibody.

Platelet transfusions are recommended by the ACCP for invasive procedures (ACCP 2012–2C). They should not be used routinely for prophylaxis of bleeding in HIT because they may exacerbate the hypercoagulable state, leading to additional thrombosis.

Vitamin K inhibitors such as warfarin are started when platelets are >150000/μL (ACCP 2012–1C). Early introduction should be avoided due to the potential to worsen the prothrombotic state through a rapid reduction of protein C, and an overlap period to allow a therapeutic INR should intervene. Warfarin should be continued for 4–6 weeks, and in patients with thrombosis for 3 months.

Patients with a history of HIT may not invariably have recurrent HIT on heparin re-exposure. In addition, heparin has been tolerated for a brief period, such as during cardiac surgery, in patients in whom heparin-PF4 antibodies have fully waned. Still, it is better to use an alternative anticoagulant.

Risk stratification before discharge

In low- or intermediate-risk patients who have been free of ischaemia at rest or with low-level activity or heart failure for a minimum of 12–24 h, a stress test or an imaging modality are recommended for assessment of ischaemia and risk stratification purposes (Table 28.23). Risk stratification is discussed in detail in Chapter 30 on stable CAD.

Post-hospital discharge care

Aspirin (indefinitely), a P2Y12 inhibitor for one year, and a beta blocker (in the absence of contraindications) are mandatory. In patients receiving a stent, P2Y12 inhibitors should be given for at least 12 months, but the condition of the patient as judged by the DAPT score should be considered.[160] If there is a high risk of bleeding DAPT may be discontinued in 6 months in patients with DAPT score <2. It may also be prolonged beyond 12 months in patients with DAPT score ≥2. Options include clopidogrel 75 mg daily, prasugrel 10 mg daily, and ticagrelor 90 mg twice daily. Rivaroxaban, but not apixaban or dabigatran, has reduced ischaemic events

Table 28.23 ACCF AHA/ACC 2014 GL on NSTE-ACS. Risk stratification before discharge for patients with an ischaemia-guided strategy

Non-invasive stress testing in low- and intermediate-risk patient who have been free of ischaemia at rest or with low-level activity for a minimum of 12–24 h.	I-B
Treadmill exercise is useful in patients able to exercise in whom the ECG is free of resting ST changes that may interfere with interpretation.	I-C
Stress testing with an imaging modality in patients who are able to exercise but have ST changes on resting ECG that may interfere with interpretation. In patients undergoing a low-level exercise test, an imaging modality can add prognostic information.	I-B
Pharmacological stress testing with imaging when physical limitations preclude adequate exercise stress.	I-C
A non-invasive test to evaluate LV function in patients with definite ACS.	I-C

AHA/ACC 2014 Guideline for the management of patients with non-ST-elevation acute coronary syndromes. *J Am Coll Cardiol*. 2014;**64**:e139–228, with permission
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but at an increased risk of bleeding.[73,78,79] Nitrates and calcium channel blockers (other than short-acting dihydropyridines) may also be used for symptomatic relief, especially when beta blockers are contraindicated or ineffective. Patients with LVEF <40%, heart failure, or diabetes should be put on ACE inhibitors or ARBs. In the absence of hyperkalaemia or creatinine clearance <30 mL/min, an aldosterone receptor blocker, such as eplerenone, is also recommended. The addition of ezetimibe to statin therapy may decrease the risk of non-fatal MI and stroke.[160] All patients should be screened for depression, following an ACS (ACC/AHA 2011 GL on secondary prevention I-A).

Other measures for secondary prevention are presented in Table 28.24, and discussed in detail in Chapter 30 on stable CAD.

Table 28.24 AHA/ACC 2014 GL on NSTE-ACS.

Hospital discharge care and risk reduction strategies	
Medical regimen and use of medications at discharge	
Medications required in the hospital to control ischaemia should be continued after hospital discharge in patients who do not undergo coronary revascularization, patients with incomplete or unsuccessful revascularization, and patients with recurrent symptoms after revascularization	I-C
All patients should be given sublingual or spray nitroglycerin with verbal and written instructions for its use	I-C
Patients should be informed about symptoms of worsening myocardial ischaemia and MI and should be given verbal and written instructions about how and when to seek emergency care	I-C
Patients who are designated responsible caregivers should be provided with easily understood and culturally sensitive verbal and written instructions about medication type, purpose, dose, frequency, side effects, and duration of use	I-C
Call 9-1-1 immediately if angina lasts >1 min and does not subside 3 to 5 min after one dose of sublingual or spray GTN	I-C
Contact clinician without delay if the pattern or severity of angina changes	I-C
Patients should be educated about modification of cardiovascular risk factors	I-C
Late hospital and post-hospital oral antiplatelet therapy	
Aspirin should be continued indefinitely. The maintenance dose should be 81 mg daily in patients treated with ticagrelor and 81–325 mg daily in all other patients	I-A
In addition to aspirin, clopidogrel or ticagrelor should be continued for up to 12 months in all patients without contraindications who are treated with an ischaemia-guided strategy	I-B
In patients receiving a stent (bare-metal stent or DES), clopidogrel, prasugrel, or ticagrelor should be given for at least 12 months	I-B
Aspirin maintenance dose of 81 mg per day in preference to higher maintenance doses in patients treated either invasively or with coronary stent implantation	IIa-B
Ticagrelor over clopidogrel for maintenance P2Y12 treatment in patients treated with an early invasive strategy and/or PCI	IIa-B
Prasugrel over clopidogrel for maintenance P2Y12 treatment in patients who undergo PCI who are not at high risk for bleeding complications	IIa-B
If the risk of morbidity from bleeding outweighs the anticipated benefit after stent implantation, earlier discontinuation (e.g. <12 months) of P2Y12 inhibitor therapy	IIa-C
Continuation of DAPT beyond 12 months may be considered in patients undergoing stent implantation	IIb-C

(*Continued*)

Table 28.24 Continued

Cardiac rehabilitation	
All eligible patients should be referred to a comprehensive cardiovascular rehabilitation program	I-B
Patient education	
Patients should be educated about appropriate cholesterol management, BP, smoking cessation, and lifestyle management	I-C
Patients who have undergone PCI or CABG derive benefit from risk factor modification and should receive counselling that revascularization does not obviate the need for lifestyle changes	I-C
Pneumococcal pneumonia	
Pneumococcal vaccine for patients 65 years of age and older and in high-risk patients with cardiovascular disease	I-B
NSAIDs	
Pain treatment before consideration of NSAIDs should begin with acetaminophen, non-acetylated salicylates, tramadol, or small doses of narcotics if these medications are not adequate	I-C
Use non-selective NSAIDs, such as naproxen, if initial therapy with acetaminophen, non-acetylated salicylates, tramadol, or small doses of narcotics is insufficient	IIa-C
NSAIDs with increasing degrees of relative COX-2 selectivity with lowest effective doses and for the shortest possible time only when other therapies fail	IIb-C
NSAIDs with increasing degrees of relative COX-2 selectivity when other therapies provide acceptable pain relief	III-B (Harm)
Hormone therapy	
Hormone therapy with estrogen plus progestin, or estrogen alone, should not be given as new drugs for secondary prevention of coronary events to postmenopausal women after NSTE-ACS and should not be continued in previous users, unless the benefits outweigh the estimated risks	III-A (Harm)
Antioxidant vitamins and folic acid	
Antioxidant vitamin supplements (e.g. vitamins E, C, or beta carotene) or folic acid, with or without vitamins B6 and B12, should not be used for secondary prevention	III-A (No benefit)
Plan of care for patients with NSTE-ACS	
Post-hospital systems of care designed to prevent hospital readmissions should be used to facilitate the transition to effective, coordinated outpatient care	I-B
Appropriate dietary and physical activities, and compliance with interventions for secondary prevention should be provided	I-C
Specific instruction on activities (e.g. lifting, climbing stairs, yard work, and household activities) that are permissible and those to avoid. Specific mention of resumption of driving, return to work, and sexual activity	I-B
An annual influenza vaccination is recommended for patients with cardiovascular disease	I-C
ESC 2015 GL on NSTE-ACS.	
Long-term management after NSTE-ACS	
Advise on lifestyle changes (including smoking cessation, regular physical activity and a healthy diet).	I-A
Start high-intensity statin therapy as early as possible, unless contraindicated, and maintain it long term.	I-A
An ACE inhibitor with LVEF ≤40% or heart failure, hypertension or diabetes, unless contraindicated. An ARB provides an alternative, particularly if ACE inhibitors are not tolerated.	I-A
Beta-blocker therapy in patients with LVEF ≤40%, unless contraindicated.	I-A
Mineralocorticoid receptor antagonists, preferably eplerenone, with LVEF ≤35% and either heart failure or diabetes after NSTE-ACS but no significant renal dysfunction or hyperkalaemia.[a]	I-A
A diastolic blood pressure goal of <90 mmHg (<85 mmHg in diabetic patients).	I-A
Participation in a well-structured cardiac rehabilitation programme to modify lifestyle habits and increase adherence to treatment	IIa-A
In patients with LDL cholesterol ≥70 mg/dL (≥1.8 mmol/L) despite a maximally tolerated statin dose, further reduction in LDL cholesterol with a non-statin agent.[b]	IIa-B
A systolic blood pressure goal of <140 mmHg	IIa-B

a: Serum creatinine <221 mmol/L (2.5 mg/dL) for men and <177 mmol/L (2.0 mg/dL) for women; serum potassium concentration <5.0 mmol/L.
b: At the time of finalizing the guidelines, this recommendation applies only to ezetimibe.
The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily. Patients should receive a loading dose of prasugrel, provided they were not pretreated with another PY12 receptor inhibitor.
AHA/ACC 2014 Guideline for the management of patients with non-ST-elevation acute coronary syndromes. *J Am Coll Cardiol*. 2014;**64**:e139–228, with permission from Elsevier.
ESC 2015 Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2015; 2016;**37**:267–315 with permission from Oxford University Press.

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Chapter 29

Acute myocardial infarction

Definition

According to the third universal definition of myocardial infarction (MI) from the Joint ESC/ACCF/AHA/WHF Task Force, an MI diagnosis requires a **cardiac troponin (I or T)** level above the 99th percentile of a normal reference population **plus one, or more**, of the following:

Symptoms of **ischaemia**
New significant **ST/T wave changes or new LBBB**
Pathologic **Q waves** on ECG
Imaging evidence of new **loss of viable myocardium** or regional wall motion abnormality
Intracoronary thrombus diagnosed by angiography or autopsy.

A classification of MI is provided in Table 29.1.[1]

The pathophysiology and aetiology of MI are described under ACS section in Chapter 27 on the epidemiology and pathophysiology of coronary artery disease. Non-atherosclerotic causes of MI are presented in Table 29.2.

Table 29.1 Joint ESC/ACCF/AHA/WHF 2012. Third universal definition of myocardial infarction

Type 1: spontaneous myocardial infarction
Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection, with resulting intraluminal thrombus in one, or more, of the coronary arteries, leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but, on occasion, non-obstructive, or no, CAD.
Type 2: myocardial infarction secondary to an ischaemic imbalance
In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/bradyarrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without LVH.
Type 3: myocardial infarction resulting in death when biomarker values are unavailable
Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or, in rare cases, when cardiac biomarkers were not collected.
Type 4a: myocardial infarction related to percutaneous coronary intervention (PCI)
Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 × 99th percentile of a normal reference population (URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia, or (ii) new ischaemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

(*Continued*)

Table 29.1 Continued

Type 4b: myocardial infarction related to stent thrombosis
Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.
Type 5: myocardial infarction related to coronary artery bypass grafting (CABG)
Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 × 99th percentile URL in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

ESC/ACCF/AHA/WHF Expert consensus document: Third universal definition of myocardial infarction. *Circulation*, 2012;**126**:2020–35 with permission from Wolters Kluwer.

Table 29.2 Non-atherosclerotic causes of myocardial infarction

Embolic
Infective endocarditis
Neoplasms
Prosthetic valves
Arteritis
Syphilitic aortitis
Takayasu's arteritis
Polyarteritis nodosa
Giant cell arteritis
Systemic lupus erythematosus
Kawasaki disease
Vital infections
Prothrombotic states
Polycythaemia vera
Sickle cell disease
Disseminated intravascular coagulation
Thrombocytosis
Thrombocytopenic purpura
Other
Takotsubo cardiomyopathy, severe AS, prolonged hypotension, thyrotoxicosis, carbon monoxide poisoning, chest trauma, mediastinal radiation, spontaneous coronary dissection, cocaine abuse

Presentation

Prodromal symptoms of chest discomfort may be absent, and retrosternal compressing or heaviness-like pain that lasts more than 30 min is typical. They are described with a clenched fist against the sternum (Levine sign). The pain may radiate to both sites of the chest, with a predilection for the left side, the jaw, or the arms and wrists. It may be epigastric, misdiagnosed as indigestion. Diaphoresis, nausea, and vomiting may appear. In up to 25% of cases, the infarction may be silent. Diabetics, the elderly, and heart transplant recipients may not have symptoms. Silent MIs accounted for 25% of all MIs in the Framingham study, and approximately 17% of diabetics have pathological Q waves.[2] In patients with acute chest pain, the prevalence of acute MI is 80% in the presence of ≥1 mm of new ST segment elevation and 20% with new ST segment depression or T wave inversion. In the absence of electrocardiographic changes consistent with the presence of ischaemia, the risk of acute myocardial infarction is 4% among patients with acute chest pain and a history of coronary artery disease and 2% among patients with no such history.[3]

Physical examination

With uncomplicated MIs, physical examination **may be unremarkable**.
Tachycardia and **elevated respiratory rate** may be present.
Fever may appear between 4 and 48 h and resolves by the fourth day post-MI.
S4 is invariably present.
Pericardial friction rubs are common within the first 2–3 days following a transmural infarct.

Diagnosis

ECG changes

They are essential for diagnosis (Table 29.3) but may not be present, depending on the extent and location of myocardial injury and the presence of pre-existing abnormalities (conduction defects, hypertension and ventricular hypertrophy, electrolyte disturbances, and drugs). The typical ECG patterns of MI seen in leads that face the area of damage are appearance of **Q waves** (>0.03 s, loss of forces directed towards the electrode), **ST segment elevation** (upward convexity), and **T wave inversion** (after 4 hours) (Tables 29.4 and 29.5). ST–T changes are not specific; healthy young men may have concave ST segment elevation of 1 to 3 mm in one, or more, precordial leads.[4] Other conditions associated with ST elevation are shown in Table 29.6 and Figure 29.1. However, ST elevation and symptoms of MI are indications for reperfusion therapy (Class I indication), and the number of leads demonstrating ST elevation has been a useful risk marker in MI. The

Table 29.3 ESC 2012 GL on STEMI

Recommendations for initial diagnosis	
A 12-lead ECG must be obtained as soon as possible at the point of FMC, with a target delay of ≤10 min.	I-B
ECG monitoring must be initiated as soon as possible in all patients with suspected STEMI.	I-B
Blood sampling for serum markers routinely in the acute phase, but one should not wait for the results before initiating reperfusion treatment.	I-C
Additional posterior chest wall leads (V_7–V_9 ≥0.05 mV) in patients with high suspicion of inferobasal myocardial infarction (circumflex occlusion).	IIa-C
Echocardiography may assist in making the diagnosis in uncertain cases but should not delay transfer for angiography.	IIb-C

ECG, electrocardiogram; FMC, first medical contact; STEMI, ST segment elevation myocardial infarction.
ESC 2012 Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012:**33**:2569–619, by permission of Oxford University Press.

Table 29.4 ESC/ACCF/AHA/WHF 2012. Third universal definition of myocardial infarction

ECG manifestations of acute myocardial ischaemia (in absence of LVH and LBBB)
ST elevation
New ST elevation at the J point in two contiguous leads with the cut-points: ≥0.1 mV in all leads other than leads V_2–V_1 where the following cut-points apply: ≥0.2 mV in men ≥40 years; ≥0.25 mV in men <40 years, or ≥0.15 mV in women.
ST depression and T wave changes
New horizontal or downsloping ST depression ≥0.05 mV in two contiguous leads and/or T inversion ≥0.1 mV in two contiguous leads with prominent R wave or R/S ratio >1.

0.1 mV corresponds to 1 mm.
ESC/ACCF/AHA/WHF Expert consensus document: Third universal definition of myocardial infarction. *Circulation*. 2012;**126**:2020–35 with permission from Wolters Kluwer.

Table 29.5 ESC/ACCF/AHA/WHF 2012. Third universal definition of myocardial infarction

ECG changes associated with prior myocardial infarction
Any Q wave in leads V_2–V_3 ≥0.02 s or QS complex in leads V_2 and V_3.
Q wave ≥0.03 s and ≥0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V_4–V_6 in any two leads of a contiguous lead grouping (I, aVL; V_1–V_6; II, III, aVF).[a]
R wave ≥0.04 s in V_1–V_2 and R/S ≥1 with a concordant positive T wave in absence of conduction defect.

0.04 s corresponds to one small square of the ECG trace.
[a] The same criteria are used for supplemental leads V_7–V_9.
ESC/ACCF/AHA/WHF Expert consensus document: Third universal definition of myocardial infarction. *Circulation*. 2012;**126**:2020–35 with permission from Wolters Kluwer.

presence of Q waves does not reliably distinguish between transmural or subendocardial MI. Q-wave regression, however, indicates improved LVEF.[5] The appearance of a tall and broad R wave in lead V1, in the absence of conditions with modified QRS shape, such as right ventricular hypertrophy, complete right bundle-branch block, or WPW syndrome, is more associated with a lateral, than a posterior, MI.[6]

ECG criteria for the identification of the infarct-related artery in anterior and inferior MI are shown in Table 29.7.[4,7]

MI in the presence of LBBB Specific markers of MI are:[8]

- ST segment elevation ≥1 mm that is concordant with the QRS complex (in the same direction as the major QRS vector), or
- ST segment depression ≥1mm in lead V_1, V_2, or V_3.

ST segment elevation ≥5 mm that is discordant with the QRS complex indicates a moderate to high probability of MI.

RV infarction Up to 50% of inferior MIs have involvement of the RV. Suspected when ST elevation in V_1 or V_1 and V_2 but no other precordial leads, and inferior leads, with ST elevation in lead III > ST elevation in lead II. The most sensitive electrocardiographic sign of right ventricular infarction is ST segment elevation of more than 1 mm, with an upright T wave in lead V_4R, but this sign is rarely present more than 12 hours after the infarction.

Atrial infarction PR elevation, the hallmark of diagnosis, is seen in 10% of MI. Although isolated atrial infarction is seen in 3.5% of autopsies of patients with STEMI, it often occurs in conjunction with ventricular infarction and can cause rupture of the atrial wall.[9]

Table 29.6 Causes of ST elevation other than myocardial infarction

ST elevation of normal variant	Seen in V_3 through V_5 with inverted T waves
	Short QT, high QRS voltage
Left ventricular hypertrophy	Concave
	Other features of left ventricular hypertrophy
Left bundle branch block	Concave
	ST segment deviation discordant from the QRS
Acute pericarditis	Diffuse ST segment elevation
	Reciprocal ST segment depression in aVR, not in aVL
	Elevation seldom >5 mm
	PR segment depression
Hyperkalaemia	Widened QRS and tall, peaked, tented T waves
	Low-amplitude or absent P waves
	ST segment usually downsloping
Brugada syndrome (type 1)	rSR′ in V_1 and V_2
	ST segment elevation in V_1 and V_2, typically downsloping
Pulmonary embolism	Changes simulating myocardial infarction seen often in both inferior and anteroseptal leads
Cardioversion	Striking ST segment elevation, often >10 mm, but lasting only 1 or 2 min immediately after direct current shock
Prinzmetal's angina	Same as ST segment elevation in infarction but transient
Hiatus hernia and stomach compression	Concave elevation in anterior chest leads without reciprocal inferior ST depression

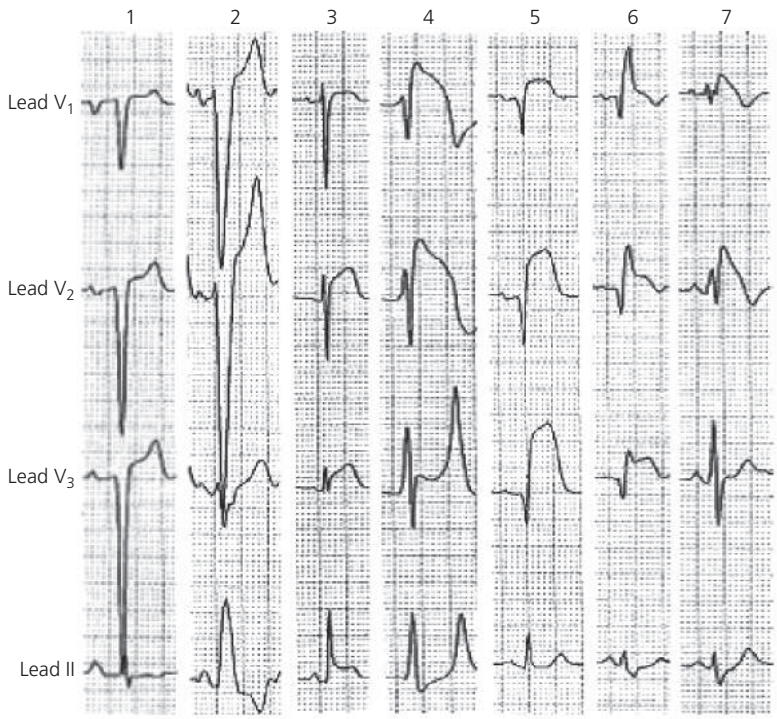


Figure 29.1 ST segment elevation in various conditions. **Tracing 1:** left ventricular hypertrophy. **Tracing 2:** LBBB. **Tracing 3:** acute pericarditis (the only tracing with ST segment elevation in both precordial leads and lead II and PR segment depression). **Tracing 4:** pseudoinfarction pattern in hyperkalaemia. The T wave in V_3 is tall, narrow, pointed, and tented. **Tracing 5**: acute anteroseptal infarction. **Tracing 6**: acute anteroseptal infarction and RBBB (remaining R′ wave and distinct transition between the downstroke of R′ and the beginning of the ST segment). **Tracing 7**: Brugada syndrome type 1 (rSR′ and ST segment elevation limited to V_1 and V_2. The ST segment begins from the top of the R′ and is downsloping).

Wang K, *et al*. ST-segment elevation in conditions other than acute myocardial infarction. *N Engl J Med*. 2003;**349**:2128–35 with permission from Massachusetts Medical Society.

Table 29.7 ECG criteria for identification of the infarct-related artery in anterior and inferior MI

Anterior MI	
Proximal LAD occlusion	ST elevation in V_1 to V_3 (aVL) and ST depression in II, III, aVF
Proximal LAD occlusion	ST elevation >2.5 mm in V_1 or RBBB with initial Q wave (not sensitive but very specific criteria)
LAD occlusion distal to first diagonal	ST elevation in V_1 to V_3 without ST depression in II, III, aVF
Distal LAD occlusion	ST elevation in V_1 to V_3 (aVL) and ST elevation in II, III, aVF (inferoapical LAD extension)
Inferior MI	
RCA occlusion	ST elevation in III > ST elevation in II, and ST depression in I or aVL
Left Cx occlusion	ST elevation in III not greater than ST elevation in II, and ST elevation or isoelectric in I, aVL, V_5, V_6

Enzymatic assays

Creatine kinase (starts rising within 4–8 h and returns to normal within 2–3 days) and **myoglobin** (starts rising 1–4 h, peaks at 6 h, and returns to normal at 24 h) are not specific for myocardial injury. Of the **creatine kinase isoenzymes** (MM in skeletal and heart muscle, BB in brain and kidney), the muscle and brain (CK-MB) isoenzyme is of clinical use by means of immunoassays with anti-MB monoclonal antibodies. It is also present in other tissue (small intestine, tongue, diaphragm, uterus, prostate) and rises after physical exercise. In MI, it usually increases 10–20 times above the upper limit of the reference range. **Troponin** is a regulatory protein complex located on the thin filament of striated muscles. It consists of three subunits encoded by different genes: C binds to Ca, I binds to actin, and T binds to tropomyosin. Cardiac **cTnI** and **cTnT** are of clinical use and quantitative assays use antibodies specific for the cardiac forms. cTnT and cTnI are absent in healthy adult skeletal muscle, but cTnT is present in fetal skeletal muscle and may therefore be involved in muscle regeneration; there has been some preliminary evidence that neuromuscular diseases affect cTnT but not cTnI.[10] In MI, troponins may increase 20–50 times above the upper limit of the reference range. Cut-off values should be set by each laboratory, depending on the assay used. Timing parameters are shown in Table 29.8 and Figure 29.2. False positive results may happen with all assays. Other causes of troponin elevations are presented in Table 29.9.[11]

High-sensitivity troponin assays offer a higher negative predictive value (hsTnT <13 pg/mL) for the exclusion of MI.[12] Both TnT and TnI high sensitivity assays have been developed and appear to offer similar results, although hs-cTnI seems to be superior in early presenters, while hs-cTnT seems to be superior in late presenters (>3 h).[13] However, the increased sensitivity of these new assays makes it possible to detect low levels of Tn even in healthy subjects. In a meta-analysis, cut-off values 3 ng/L or 5 ng/L, measured at varying times and not always after the recommended 3 hours from presentation, detected MI with a sensitivity of 97%, and a specificity of 42%.[14] Thus, troponin assays should always be interpreted within the context of the clinical situation and repeated in 2–3 hours to confirm myonecrosis by consistent elevation.[15] Algorithms that take into account both baseline values and absolute changes within the next 1 or 2 hours have been proposed. MI can be ruled out when baseline hs-TnT is lower than 14 ng/L and the level changes less than 4 ng/L in the following 2 hours. MI can be diagnosed when baseline troponin is either 53 ng/L or higher, or when the 2-hour change is 10 ng/L or more.[16] High sensitivity cTn-assays maintain high diagnostic accuracy also in patients with renal dysfunction, although optimal cut-off levels are slightly higher.[17] High sensitivity assays are approved in Europe but not in the USA. Increases of CK-MB or troponin >20% above the level measured at the time of the recurrent symptoms indicate episodes of reinfarction.[3]

Table 29.8 Markers of cardiac damage

	Initial rise	Peak elevation	Return to normal
CK-MB	3–12 h	24 h	48–72 h
TnT	3–12 h	12–48 h	5–14 d
TnI	3–12 h	24 h	5–10 d

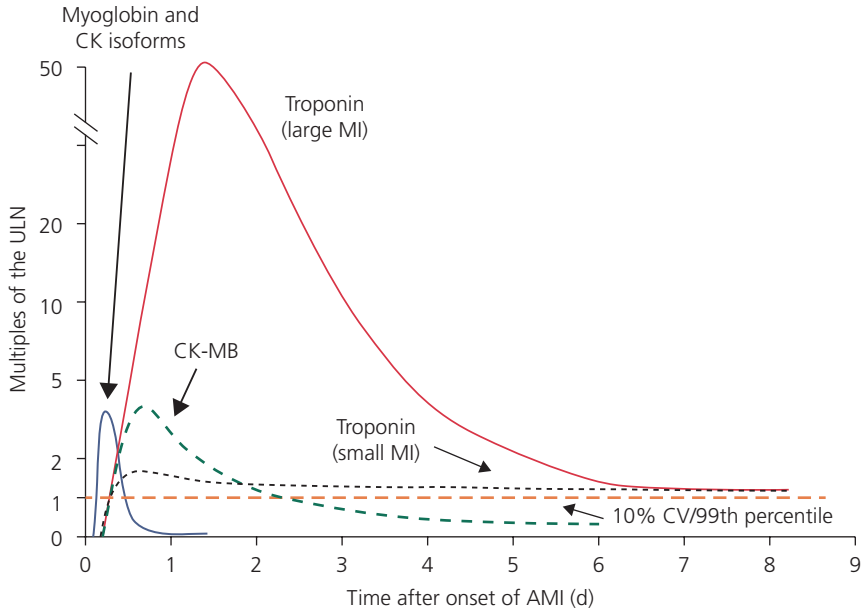


Figure 29.2 Timing of biomarkers after myocardial infarction.

Kumar A, Cannon CP. Acute coronary syndromes: diagnosis and management, part I. *Mayo Clin Proc*. 2009;**84**:917–38 with permission from Elsevier.

Table 29.9 Causes of elevated plasma cardiac troponin other than acute coronary syndromes

Cardiac causes	Non-cardiac causes
Cardiac contusion resulting from trauma	Pulmonary embolism
Cardiac surgery	Severe pulmonary hypertension
Cardioversion	Renal failure
Endomyocardial biopsy	Stroke, subarachnoid haemorrhage
Acute and chronic heart failure	Infiltrative diseases, e.g. amyloidosis
Aortic dissection	Cardiotoxic drugs
Aortic valve disease	Critical illness
Hypertrophic cardiomyopathy	Sepsis
Tachyarrhythmia	Extensive burns
Bradyarrhythmia, heart block	Extreme exertion
Apical ballooning syndrome	
Post-percutaneous coronary intervention	
Rhabdomyolysis with myocyte necrosis	
Myocarditis or endocarditis/pericarditis	

Mahajan VS, Jarolim P. How to interpret elevated cardiac troponin levels. *Circulation*. 2011;**124**:2350–4 with permission from Wolters Kluwer.

Other investigations

Elevation of **WBC** occurs within the first 2 hours, reaches a peak 2 to 4 days after infarction (12–15 × 10^3/mL), and returns to normal in 1 week. **ESR** rises after the second day and remains elevated for several weeks. **Haemoglobin** powerfully predicts cardiovascular events, with mortality increasing progressively as values fall below 14 mg/dL or increase above 17 mg/dL. Iatrogenic bleeding is associated with a 5-fold increase in mortality. There is a fall of **HDL cholesterol** after 48 h; thus, a lipid profile should be obtained before that time or 8 weeks after the MI. The oral glucose tolerance test identifies the largest number of patients with previously undiagnosed diabetes compared to fasting plasma glucose and glycated haemoglobin (HbA1c).[18]

Chest radiography Prominent pulmonary vascular markings reflect raised left ventricular end-diastolic pressure (LVEDP). However, up to 12 h can elapse before pulmonary oedema accumulates after the LVEDP has been raised (pulmonary wedge pressure >18 mmHg), and it takes 48 hours to resorb when LV filling pressures become normal. Signs of cardiomegaly may be seen, with previous infarcts and LV dysfunction.

Echocardiography Areas of abnormal regional wall motion are seen almost universally in patients with large MIs at 2D echocardiography. Apical thrombus and flaps of suspect aortic dissection may be seen, and Doppler imaging may reveal MR, TR, or VSD. Small pericardial effusion may be due to myocardial haemorrhage due to anticoagulants, pericarditis, or heart failure. Moderate effusion early after MI should raise the suspicion of free wall rupture.[19]

Exercise testing In patients of low risk and uncertain diagnosis of MI, tests for ischaemia can be undertaken within 6 to 12 h after admission or even immediately.[1]

Cardiac magnetic resonance (CMR) has high sensitivity for detecting small amounts of myonecrosis, assessing the peri-infarction zone and identifying small scars. First-pass perfusion sequences after IV gadolinium administration can also identify myocardial perfusion abnormalities. CMR may detect MI unrecognized by ECG in older individuals, and this is associated with increased mortality risk.[20]

Computed tomographic (CT) scan and CMR are useful for excluding aortic dissection.

Triple-rule-out CT angiography allows simultaneous CT coronary angiography, pulmonary angiography for the exclusion of pulmonary embolism, and ascending aorta angiogram for the exclusion of dissection.[21]

Initial therapy and medication

Initial therapy

Ambulance teams must be trained and equipped to identify STEMI (with the use of ECG recorders and telemetry, as necessary) and administer initial therapy, including thrombolysis, where applicable. **Pre-hospital thrombolysis** may offer survival rates, even higher than that of primary PCI.[22] All hospitals and emergency medical systems participating in the care of patients with STEMI must record and monitor delay times and work to achieve and maintain quality targets, as presented in Tables 29.10 and 29.11.

In case of resuscitated **cardiac arrest**, therapeutic hypothermia and immediate angiography are indicated (Table 29.12). Early transfer to a specializing centre for angiography and angioplasty results in >60% survival in patients with obvious ST-elevation.[23] Most patients with a cardiac arrest have demonstrable coronary artery disease, but only 38% of cardiac arrest survivors will develop evidence of myocardial infarction, and the use of tenecteplase during advanced life support for out-of-hospital cardiac arrest did not improve outcome.[24] However, approximately 70% of the coronary heart disease deaths annually in the USA occur out of hospital, and, although <30% of them have a shockable initial rhythm (usually VF—see Chapter 68 on SCD), the majority of neurologically intact survivors come from this subgroup.[25] Improved rates of neurologically intact survival can be achieved when comatose patients with out-of-hospital VF or VT cardiac arrest are cooled to 32–36°C for 12 or 24 hours, beginning minutes to hours after the return of spontaneous circulation.[26,27] Cooling should begin before, or at the time of, cardiac catheterization that is indicated in these patients.[26,28]

Table 29.10 ACCF/AHA 2013 on STEMI

Regional systems of STEMI care, reperfusion therapy, and time-to-treatment goals	
All communities should create and maintain a regional system of STEMI care that includes assessment and continuous quality improvement of EMS and hospital-based activities. Performance can be facilitated by participating in programmes, such as Mission: Lifeline and the D2B Alliance.	I-B
Performance of a 12-lead ECG by EMS personnel at the site of first medical contact (FMC) in patients with symptoms consistent with STEMI.	I-B

(*Continued*)

Table 29.10 Continued

Reperfusion therapy should be administered to all eligible patients with symptom onset within the prior 12 hours.	I-A
Primary PCI is the recommended method of reperfusion when it can be performed in a timely fashion by experienced operators	I-A
EMS transport directly to a PCI-capable hospital for primary PCI is the recommended triage strategy, with an ideal FMC-to-device time system goal of 90 minutes or less.*	I-B
Immediate transfer to a PCI-capable hospital for primary PCI is the recommended triage strategy for patients with STEMI who initially arrive at, or are transported to, a non-PCI-capable hospital, with an FMC-to-device time system goal of 120 minutes or less.*	I-B
In the absence of contraindications, fibrinolytic therapy should be administered at non-PCI-capable hospitals when the anticipated FMC-to-device time at a PCI capable hospital exceeds 120 minutes.	I-B
When fibrinolytic therapy is indicated or chosen as the primary reperfusion strategy, it should be administered within 30 minutes of hospital arrival.*	I-B
Reperfusion therapy for patients with STEMI and symptom onset within the prior 12 to 24 hours who have clinical and/or ECG evidence of ongoing ischaemia. Primary PCI is the preferred strategy in this population.	IIa-B

* The proposed time windows are system goals. For any individual patient, every effort should be made to provide reperfusion therapy as rapidly as possible.
EMS, emergency medical system; FMC, first medical contact.
2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2013;**61**:e78–140 with permission from Elsevier.

Table 29.11 ESC 2012 GL on STEMI

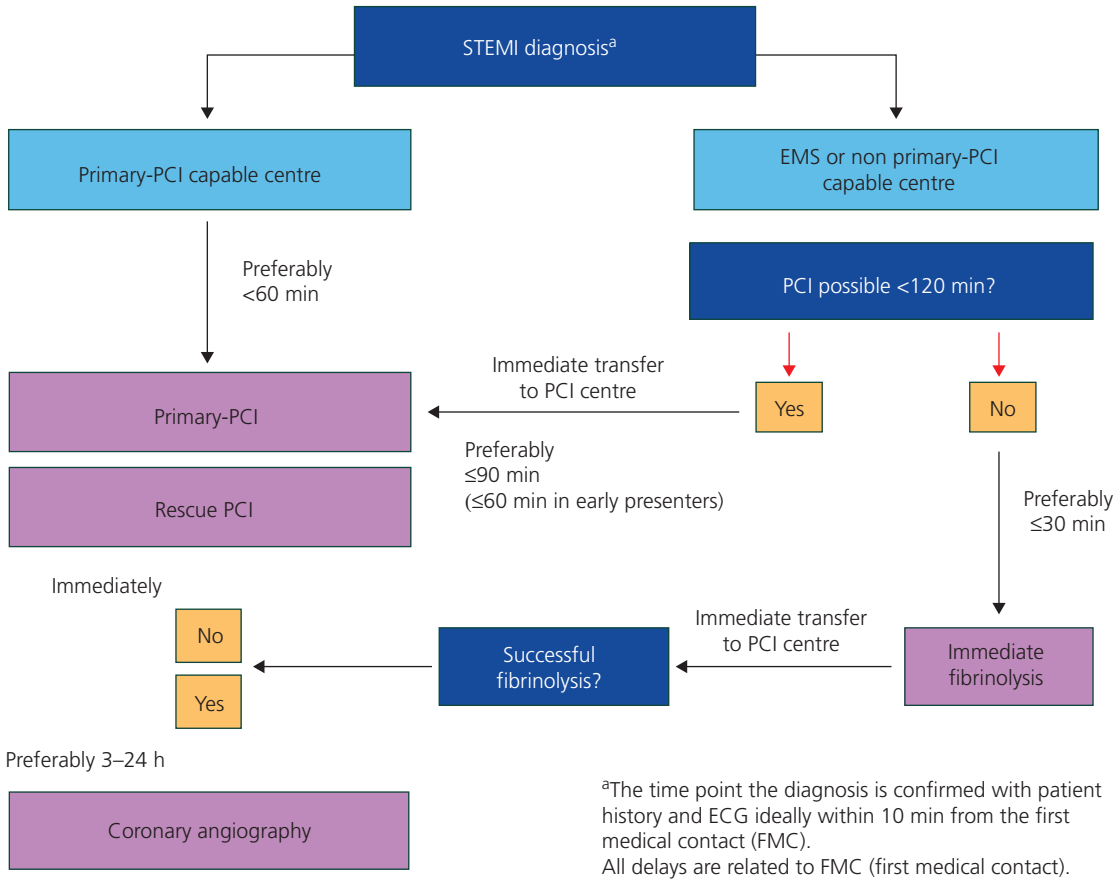
Logistics of pre-hospital care	
Ambulance teams must be trained and equipped to identify STEMI (with use of ECG recorders and telemetry as necessary) and administer initial therapy, including thrombolysis where applicable.	I-B
The pre-hospital management of STEMI patients must be based on regional networks designed to deliver reperfusion therapy expeditiously and effectively, with efforts made to make primary PCI available to as many patients as possible.	I-B
Primary PCI-capable centres must deliver a 24/7 service and be able to start primary PCI as soon as possible but always within 60 min from the initial call.	I-B
All hospitals and EMSs participating in the care of patients with STEMI must record and monitor delay times and work to achieve and maintain the following quality targets:	I-B
◆ First medical contact to first ECG ≤10 min	
◆ First medical contact to reperfusion therapy	
◆ For fibrinolysis ≤30 min	
◆ For primary PCI ≤90 min (≤60 min if the patient presents within 120 min of symptom onset or directly to a PCI-capable hospital).	
All EMSs, emergency departments, and coronary care units must have a written updated STEMI management protocol, preferably shared within geographic networks.	I-C
Patients presenting to a non-PCI-capable hospital and awaiting transportation for primary or rescue PCI must be attended in an appropriately monitored area.	I-C
Patients transferred to a PCI-capable centre for primary PCI should bypass the emergency department and be transferred directly to the catheterization laboratory.	IIa-B

24/7, 24 hours a day, seven days a week.
ESC 2012 Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012:**33**:2569–619, by permission of Oxford University Press.

Table 29.12 Cardiac arrest patients

ESC 2012 GL on STEMI. Cardiac arrest	
All medical and paramedical personnel caring for a patient with suspected MI must have access to defibrillation equipment and be trained in cardiac life support.	I-C
ECG monitoring at the point of FMC in all patients with suspected MI.	I-C
Therapeutic hypothermia early after resuscitation of cardiac arrest patients who are comatose or in deep sedation.	I-B
Immediate angiography with a view to primary PCI in patients with resuscitated cardiac arrest whose ECG shows STEMI.	I-B
Immediate angiography with a view to primary PCI in survivors of cardiac arrest without diagnostic ECG ST segment elevation but with a high suspicion of ongoing infarction.	IIa-B
ACCF/AHA 2013 GL on STEMI. Evaluation and management of patients with STEMI and out-of-hospital cardiac arrest	
Therapeutic hypothermia started as soon as possible in comatose patients with STEMI and out-of-hospital cardiac arrest caused by VF or pulseless VT, including patients who undergo primary PCI.	I-B
Immediate angiography and PCI when indicated in resuscitated out-of-hospital cardiac arrest patients whose initial ECG shows STEMI.	I-B

ESC 2012 Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J.* 2012:**33**:2569–619, by permission of Oxford University Press.
AHA/ACC 2013 Guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol.* 2013;**61**:e78–e140 with permission from Elsevier.



Cath=catheterization laboratory; EMS=emergency medical system; FMC=first medical contact; PCI= percutaneous coronary intervention; STEMI ST-segment elevation myocardial infarction.

Figure 29.3 ESC 2012 GL on STEMI. Pre-hospital and in-hospital management of MI (first 24 hours).

ESC 2012 Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J.* 2012:**33**:2569–619, by permission of Oxford University Press.

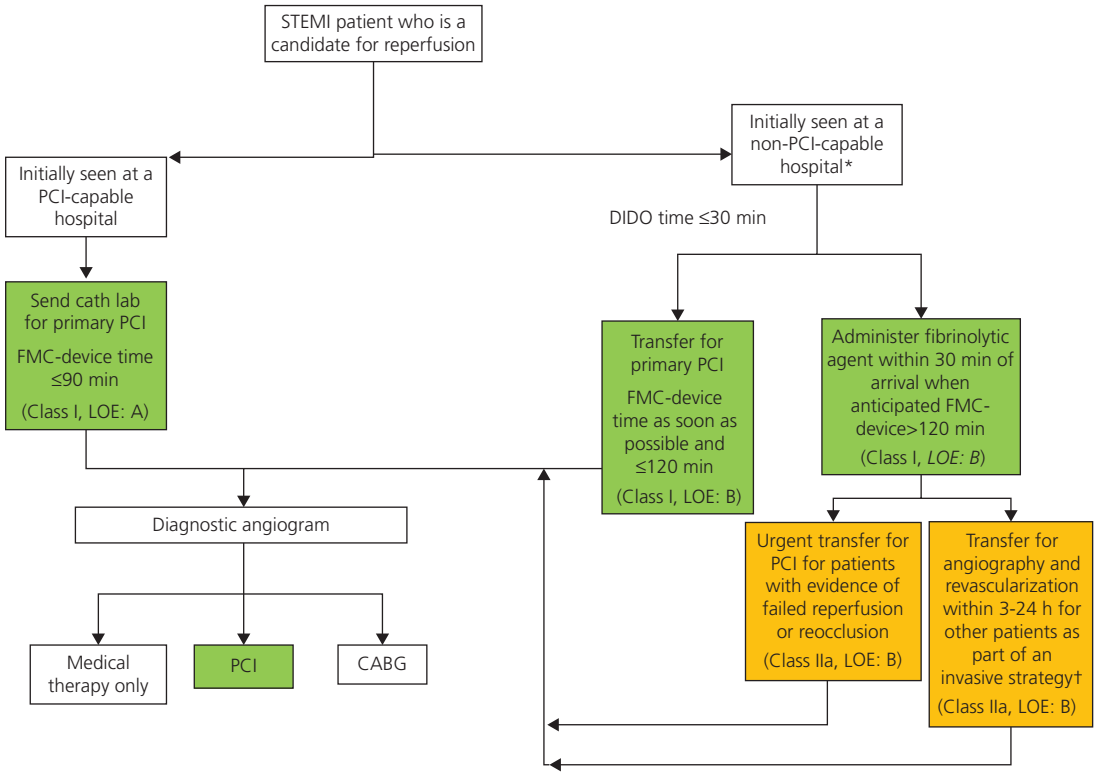


Figure 29.4 ACCF/AHA 2013 GL on STEMI. Reperfusion therapy for patients with STEMI.
The bold arrows and boxes are the preferred strategies. Performance of PCI is dictated by an anatomically appropriate culprit stenosis.

* Patients with cardiogenic shock or severe heart failure, initially seen at a non-PCI-capable hospital, should be transferred for cardiac catheterization and revascularization as soon as possible, irrespective of time delay from MI onset (Class I, LOE: B). † Angiography and revascularization should not be performed within the first 2–3 hours after administration of fibrinolytic therapy. CABG indicates coronary artery bypass graft; DIDO, door-in-door-out; FMC, first medical contact; LOE, level of evidence; MI, myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST elevation myocardial infarction.
2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2013;**61**:e78–140 with permission from Elsevier.

Medication

All patients should receive:[25,29]

- **aspirin** (unless there is true aspirin allergy),
- a **$P2Y_{12}$ inhibitor, such as clopidogrel, ticagrelor (especially for PCI), or prasugrel (especially for PCI)**, and
- an **anticoagulant (enoxaparin or unfractionated heparin or bivalirudin or fondaparinux)**.

Morphine sulfate

Two to 8 mg IV, repeated at 5–15 min intervals, or diamorphine (5 mg IV, causes less nausea) are the analgesics of choice in acute MI (Table 29.13). Administration of morphine appears to delay the antiplatelet effects of newer P2Y12 inhibitors in the hours after primary PCI, perhaps due to delayed absorption.[30] **Oxygen** (4–5 L/min) only when saturation is <90%. Oxygen, and especially at high rates of 8 L/min, should be avoided in normoxic patients due to potential of increased myocardial injury (AVOID trial).[31]

Aspirin

Chewable, not enteric-coated, aspirin is given: ACC/AHA 162–325 mg and maintenance dose of 81–325 mg, indefinitely; ESC 150–300 mg po or 80–150 mg IV. Higher doses of aspirin are no more recommended following stent implantation, and in a post hoc analysis of the TRANSLATE-ACS trial, maintenance dose of 325 mg od aspirin was not associated with lower risk of MACE, but was associated with an increased risk of minor bleeding events.[32] If NSAIDs, non-selective or COX-2 selective, are already given, they are discontinued due to increased risk of re-infarction, heart failure, and myocardial rupture.

Table 29.13 Initial therapy

ESC 2012 GL on STEMI. Recommendations for relief of pain, breathlessness, and anxiety	
Titrated IV opioids are indicated to relieve pain.	I-C
Oxygen in patients with hypoxia (SaO_2 <95%), breathlessness, or acute heart failure.	I-C
Tranquillizer in very anxious patients.	IIa-C

ACCF/AHA 2013 GL on STEMI. Selected routine medical therapies			
Therapy	**Indications**	**Dose/administration**	**Avoid/caution**
Oxygen	Clinically significant hypoxaemia (oxygen saturation <90%)	2 to 4 L/min via nasal cannula	Caution with chronic obstructive pulmonary disease and CO_2 retention
	HF	Increase rate or change to face mask, as needed	
	Dyspnoea		
Morphine	Pain	4 to 8 mg IV initially, with lower doses in elderly	Lethargic or moribund patient
	Anxiety		Hypotension
	Pulmonary oedema	2 to 8 mg IV every 5 to 15 min if needed	Bradycardia
			Known hypersensitivity
Nitroglycerin	Ongoing chest pain	0.4 mg sublingual every 5 min up to three doses as BP allows	Avoid in suspected RV infarction
	Hypertension and HF	IV dosing to begin at 10 microgram/min. Titrate to desired BP effect	Avoid in suspected RV infarction. Avoid with SBP <90 mmHg or if SBP >30 mm Hg below baseline. Avoid if recent (24 to 48 h) use of 5-phosphodiesterase inhibitors

ESC 2012 Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J.* 2012:**33**:2569–619, by permission of Oxford University Press.
2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol.* 2013;**61**:e78–140 with permission from Elsevier.

$P2Y_{12}$ inhibitors

Clopidogrel, ticagrelor or prasugrel may be used (ACCF/AHA 2013 GL on MI). The ESC (2012 on STEMI) gives preference to ticagrelol and prasugrel over clopidogrel. **Clopidogrel** loading is 300 mg po for fibrinolysis or no reperfusion for patients <75 years old.[33] A dose of 600 mg can be used if initiated 24 h after fibrinolysis. For patients >75 years old, the optimum loading dose is not established and much lower doses should be used. Clopidogrel is given for up to 1 year. For ***primary PCI***, the loading dose of clopidogrel is 300–600 mg, or preferably 600 mg. Continuation of clopidogrel beyond 12 months in patients treated with PCI may be beneficial[34] (see also in Chapter 30 on practical aspects of PCI). Clopidogrel has been found less efficacious in post-MI diabetic patients compared to non-diabetic patients.[35] Co-administration of PPIs is discussed in Chapter 28.

Ticagrelor is given in a loading dose 180 mg po, followed by 90 mg twice daily.[36] For primary PCI, **prasugrel** 60 mg po loading dose followed by 10 mg od (5 mg if the patient weighs <60 kg)[37] may also be used in patients less than 75 years old and without a history of previous stroke or TIA or increased bleeding risk. There is an increased bleeding risk with coronary artery bypass grafting within 5 days of taking clopidogrel (7 days with prasugrel), and early initiation needs to be carefully considered in patients where clinical features could suggest the need for early surgical revascularization. Ticagrelor and prasugrel reduce major adverse cardiac effects, cause less stent thrombosis, and decrease mortality without increasing the risk of bleeding following PCI for STEMI patients.[38] For duration of therapy see Chronic therapy below.

Anticoagulants

Unfractionated heparin is given IV for 48 h. Prolonged administration increases the risk of heparin-induced thrombocytopenia, and other anticoagulants are preferred if further anticoagulation is needed. Anticoagulation during hospitalization (up to 8 days) is recommended in non-reperfused patients. **Enoxaparin** has been found superior to UFH after fibrinolysis by reducing the risk of death and MI, although it slightly increases the risk of bleeding.[39] In primary PCI enoxaparin has been found superior to heparin (ATOLL study) by means of reducing ischaemic episodes.[40] Maintenance dosing with enoxaparin should be continued for the duration of the index hospitalization for up to 8 days. In primary PCI, **bivalirudin**, a direct thrombin inhibitor, may be used with or without a IIb/IIIa inhibitor, and can be given if the patient has been treated previously with UFH. The infusion (for dosing see UA/NSTEMI) is terminated at the end of the procedure or up to 4 h later. Bivalirudin reduced mortality as well as major bleeding from 8.3% to 4.9% ($p < 0.001$), compared with unfractionated heparin (60IU/kg with additional doses targeting ACT 200–250) with a IIb/IIIa antagonist in the HORIZONS-AMI trial.[41] Concerns about increased stent thrombosis with bivalirudin have been raised (see also Chapter 28). In the EUROMAX trial (UFH: 100IU/kg or 60IU/kg with concomitant IIb/IIIa, or enoxaparin: 0.5 mg/kg) a reduction of major bleeding was seen but with an increase in acute stent thrombosis, and no difference in death (2.9% vs 3.1% or reinfarction (1.7% vs 0.9%).[42,43] In the HEAT PPCI trial (UFH 70 IU/kg), there was a higher rate of reinfarction and stent thrombosis with bivalirudin without any difference in major bleeding.[44] In the BRAVE 4 trial, there was no difference for ischaemic or bleeding endpoints between a strategy of using prasugrel plus bivalirudin, compared with clopidogrel plus UFH, in patients with STEMI undergoing PPCI.[45] In the BRIGHT trial, bivalirudin reduced bleeding compared to heparin with or without tirofiban without significant differences in major cardiac events.[46] In the MATRIX trial on patients with acute coronary syndromes (including STEMI and NSTEMI) there was also increased stent thrombosis.[47] In a recent meta-analysis on PCI in NSTEMI, STEMI, and stable patients, bivalirudin increased the risk of myocardial infarction and stent thrombosis compared to heparin, while the reduction of bleeding depended on concomitant use of GP IIb/IIIa inhibitors.[48]

Fondaparinux, a synthetic factor Xa inhibitor, has been found to reduce 30-day death or myocardial infarction compared to unfractionated heparin, regardless of administration of fibrinolysis (OASIS-6).[49] In primary PCI, there is no benefit with fondaparinux, with an excess of catheter thrombosis noted. Thus, in the presence of increased bleeding risk, bivalirudin may be preferred when an invasive strategy is planned, and fondaparinux (given until end of hospitalization) when conservative management is anticipated.

Other medications

Glycoprotein IIb/IIIa inhibitors are mainly used for primary PCI, in addition to heparin or bivalirudin, especially in patients without thienopyridine loading or with a large thrombus. In patients undergoing primary PCI, abciximab is associated with a possible reduction of mortality.[50] Small molecule glycoprotein IIb/IIIa inhibitors (tirofiban and eptifibatide) have not been extensively studied, but there is evidence for similar efficacy.[51] They are much cheaper and their shorter duration of action is an advantage. IIb/IIIa inhibitors may be indicated in primary PCI and there has been evidence that intracoronary bolus administration results in improved myocardial

perfusion compared to IV (INFUSE-AMI and CICERO trials),[52,53] although this is not a consistent finding (AIDA-STEMI trial).[54] Routine precatheterization use is not recommended.

The use of early **intravenous beta blockers** in acute MI reduces the risks of re-infarction and ventricular fibrillation but increases the risk of cardiogenic shock, especially during the first day or so after admission.[55] There is increased risk of cardiogenic shock with age >70 years, systolic BP <120 mmHg, sinus tachycardia >110, or bradycardia <60 bpm. IV beta blockers can be used in patients without contraindications, with high blood pressure, tachycardia, and no signs of heart failure. They are also indicated in patients with Killip class ≤2 undergoing primary PCI (up to three boluses of 5 mg metoprolol (METOCARD-CNIC trial).[56] The benefits of early therapy with **aldosterone antagonists** in patients with STEMI but without heart failure are not established, although there is some evidence that they might be beneficial.[57] **Lidocaine** infusion to suppress ventricular ectopy is no more indicated. **Insulin** infusion is used to normalize blood sugar (<180–200 mg/dL, but avoiding hypoglycaemia, i.e. <90 mg/dL). Routine insulin–glucose–potassium infusions are not recommended any more.

No evidence supports the use of **nitrates** or **calcium antagonists** in the acute phase of MI. IV **magnesium** routinely is not indicated, unless a deficit is documented. **NSAIDs** (including selective COX-2 agents) are discontinued due to the increased risk of myocardial rupture and re-infarction. Following MI, NSAIDs (both non-selective and selective COX-2 inhibitors) are associated with a 45% increase of risk of recurrent MI or death, even with only 1 week of treatment. Diclofenac confers the highest risk, whereas naproxen is the safest agent.[58]

Reperfusion therapy

Recommendations for selection of reperfusion method are provided in Figures 29.3 and 29.4 and Table 29.14.

Table 29.14 ESC 2012 on STEMI

Reperfusion therapy	
Reperfusion therapy in all patients with symptoms of <12 h duration and persistent ST segment elevation or (presumed) new LBBB.	I-A
Reperfusion therapy (preferably primary PCI) if there is evidence of ongoing ischaemia, even if symptoms may have started >12 h beforehand or if pain and ECG changes have been stuttering.	I-C
Reperfusion therapy with primary PCI may be in stable patients presenting 12–24 h after symptom onset.	IIb-B
Routine PCI of a totally occluded artery >24 h after symptom onset in stable patients without signs of ischaemia (regardless of whether fibrinolysis was given or not) is not recommended.	III-A

A summary of important delays and treatment goals in the management of acute ST segment elevation myocardial infarction	
Delay	**Target**
Preferred for first medical contact (FMC) to ECG and diagnosis	**≤10 min**
Preferred for FMC to fibrinolysis ('FMC-to-needle')	**≤30 min**
Preferred for FMC to primary PCI ('door-to-balloon') in primary PCI hospitals	**≤60 min**
Preferred for FMC to primary PCI	**≤90 min** (≤60 min if early presenter with large area at risk)
Acceptable for primary PCI rather than fibrinolysis	**≤120 min** (≤90 min if early presenter with large area at risk) if this target cannot be met, consider fibrinolysis.
Preferred for successful fibrinolysis to angiography	**3–24 h**

ESC 2012 Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J.* 2012:**33**:2569–619, by permission of Oxford University Press.

Primary PCI

Primary PCI results in 25–30% lower mortality (7% vs 9%) and less re-infarction (3% vs 7%) and stroke (1% vs 2%) than fibrinolysis.[59] Currently, re-infarction incidence following stent implantation is 1.8% at 30 days and 4% at 1 year, mainly due to stent thrombosis (>75%).[60] Patients who survive the first 30 days after a STEMI treated with primary PCI have an excellent prognosis, with a <1.5% annual risk of successive cardiac death during the next 5 years.[61] The benefit of PCI over fibrinolysis increases with greater delay in presentation, particularly after 120 min of symptom onset and in patients >65 years of age, but is lost with a relative delay (door-to-balloon time vs door-to-needle time) of more than 114 min.[62,63] Each 30-min delay in reperfusion results in a 7.5% increase in 1-year mortality. Delays in door-to-balloon time for PCI greater than 1 h over when thrombolytic reperfusion would have occurred may negate the mortality benefit of PCI (Tables 29.14 to 29.16). The greater the baseline patient risk and the availability of in-hospital PCI facilities, the longer the acceptable primary PCI delays.[64] The largest trial comparing PCI to fibrinolysis (DANAMI) has shown that transfer for PCI is indicated when patients with STEMI present within 12 h from the onset of symptoms and transfer time is <2 h.[65] Both ACCF/AHA and ESC guidelines recommend a <90 min door-to-balloon time for primary PCI. In a report of the CathPCI Registry, as well in other previous studies, reduction to 67 min did not translate into reduced in-hospital mortality,[66] but this has been attributed to the expansion in the use of the procedure during STEMI, as well as changes in patient and procedural factors.[67] LV function at presentation is a strong predictor of short- and long-term mortality following primary PCI.[68]

Primary PCI has been generally recommended for up to 12 h after the onset of symptoms. This time limit may be extended to 24 h in the presence of ongoing ischaemia, or even in stable patients. The ESC 2014 GL on revascularization allow primary PCI up to 48h after symptom onset (IIa-B), but this recommendation is rather controversial. When the patient presents >24 hours after symptoms onset and with an occluded infarct-related artery, the open artery trial (OAT) showed no benefit of PCI in stable patients and is not recommended by current guidelines,[69] although ventricular remodelling is affected by the presence of a patent artery. PCI is also the treatment of choice in cardiogenic shock. The presence of significant stenosis or total occlusions in non-MI related arteries indicates adverse prognosis.[70] It should be also noted that MI with RBBB is frequently caused by the complete occlusion of the infarct-related artery and in-hospital mortality is highest from all ECG presentations of AMI. Thus, RBBB should be considered as a standard indication for reperfusion therapy, in the same way as LBBB.[71]

Thus, PCI is preferred over fibrinolysis if:

- Presentation <12h (and ideally <12h) after onset of symptoms, or even <24h, especially in the presence of ongoing ischaemia
- Can be performed with a delay <120 minutes of first medical contact-to-balloon time
- Cardiogenic shock or severe heart failure
- Contraindications to fibrinolysis or diagnosis of STEMI in doubt.

A reasonable policy in places without PCI facilities is to fibrinolyse all patients who present within 12 hours from onset of symptoms using half-dose for patients ≥75 years of age, and then perform angiography and PCI, if indicated, 3–24 hours later.[72–75]

Thrombus aspiration had been found beneficial,[76,77] and might be considered (Table 29.15), but its value has been questioned in recent trials,[53,78–80] and there has been evidence that manual thrombus aspiration may increase the risk of stroke.[81]

Embolic protection is not beneficial in reducing mortality, compared with PCI alone, whereas mechanical thrombectomy appears to increase mortality.[82] Lesion calcification indicates increased thrombotic complications and mortality.[83]

The use of new-generation **DES**, instead of BMS, is safe and reduces the risk of reintervention.[84,85] Radial access may also reduce bleeding complications with experienced operators.[86,87]

Approximately 50% of patients with spontaneous ***coronary dissection***, present with a STEMI. Revascularization is indicated for large occluded vessels, whereas conservative strategy is appropriate in dissection of small and medium-sized vessels with TIMI grade 2 or 3 flow.[88]

The issue of **non-culprit coronary interventions** at the time of primary PCI is debatable. Observational data indicate that culprit artery-only revascularization is associated with better outcomes.[89,90] (Table 29.15). Recently, however, preventive PCI in non-infarct coronary arteries with >50% diameter stenosis, following primary PCI, significantly reduced a composite end point of cardiac death, MI, or revascularization, compared with angioplasty limited to the infarct artery, in two small randomized trials.[91,92]

Primary PCI can be performed in patients on oral anticoagulation (warfarin or NOAC) and with additional anticoagulation (UFH, LMWH or bivalirudin), preferably through a radial access. Anticoagulation and antiplatelet strategies in this setting are discussed in Chapter 28.

No-reflow phenomenon

Failure to achieve microvascular flow, as assessed by resolution of ST segment elevation or contrast flow by angiography, is seen in up to 25% patients subjected to primary PCI (Table 29.17). Coronary embolization and ischaemia-induced endothelial swelling and neutrophil and platelet activation are thought responsible. Thrombus

aspiration and abciximab 0.25 mg/kg bolus and 0.125 mg/kg/min infusion for 12–24 h may be used for no-reflow. Adenosine, as continuous infusion of 70 microgram/kg/min over 3 hours during and after PCI or intracoronary bolus of 30–60 mg, verapamil, as intracoronary bolus of 0.5–1 mg, and intracoronary nitroprusside may also be used (ACCF/AHA 2011 GL on PCI). A strategy of balloon angioplasty or aspiration with deferred stenting 4–16 h later may also reduce no-reflow, following primary PCI.[93]

Table 29.15 Primary PCI

ESC 2012 GL on STEMI: Primary PCI	
Indications	
Primary PCI is the recommended reperfusion therapy over fibrinolysis if performed by an experienced team within 120 min of first medical contact.	I-A
Primary PCI for patients with severe acute heart failure or cardiogenic shock, unless the expected PCI related delay is excessive and the patient presents early after symptom onset.	I-B
Procedural aspects	
Stenting is recommended (over balloon angioplasty alone) for primary PCI.	I-A
Primary PCI should be limited to the culprit vessel, with the exception of cardiogenic shock and persistent ischaemia after PCI of the supposed culprit lesion.	IIa-B
If performed by an experienced radial operator, radial access should be preferred over femoral access.	IIa-B
If the patient has no contraindications to prolonged DAPT (indication for oral anticoagulation or estimated high long-term bleeding risk) and is likely to be compliant, DES should be preferred over BMS.	IIa-A
Routine thrombus aspiration.	IIa-B
Routine use of distal protection devices is not recommended.	III-C
Routine use of IABP (in patients without shock) is not recommended.	III-A
ESC 2014 GL on revascularization.	
Primary PCI for myocardial reperfusion in STEMI: indications and logistics	
Indication	
Reperfusion with time from symptom onset <12 hours duration and persistent ST segment elevation or (presumed) new LBBB.	I-A
Primary PCI recommended over fibrinolysis if performed by an experienced team in a timely fashion.	I-A
With time from symptom onset >12 hours, primary PCI in the presence of continuing ischaemia, life-threatening arrhythmias or if pain and ECG changes have been stuttering.	I-C
Primary PCI for severe acute heart failure or cardiogenic shock due to STEMI independent from time delay of symptom onset.	I-B
In diabetics, primary PCI is recommended over fibrinolysis if it can be performed within recommended time limits.	I-A
Reperfusion therapy with primary PCI in patients presenting late (12–48 h) after symptom onset.	IIa-B
Logistics	
Prehospital management of STEMI should be based on regional networks designed to deliver reperfusion therapy timely and effectively, to as many patients as possible.	I-B
Emergency departments and catheterization laboratories should have a written updated STEMI management protocol, preferably shared within geographic networks.	I-C
It is recommended that primary PCI-capable centres should deliver a 24-hour/7-day service and ensure for primary PCI to be performed at the latest within 60 minutes of hospital arrival.	I-B
Patients transferred to a PCI-capable centre for primary PCI should bypass the emergency department and be transferred directly to the catheterization laboratory.	IIa-B
Primary PCI for myocardial reperfusion in STEMI: procedural aspects (strategy and technique)	
Strategy	
Primary PCI should be limited to the culprit vessel with the exception of cardiogenic shock and persistent ischaemia after PCI of the supposed culprit lesion.	IIa-B
Staged revascularization of non-culprit lesions in STEMI patients with multivessel disease in case of symptoms or ischaemia within days to weeks after primary PCI.	IIa-B
Immediate revascularization of significant non-culprit lesions during the same procedure as primary PCI of the culprit vessel in selected patients	IIb-B

(*Continued*)

Table 29.15 Continued

CABG in patients with continuing ischaemia and in whom PCI of the infarct-related artery cannot be performed	IIa-C
Technique	
Stenting recommended over balloon angioplasty and new-generation DES over BMS	I-A
Radial access preferred over femoral access if performed by an experienced radial operator	IIa-A
Thrombus aspiration in selected patients	IIb-A
ACCF/AHA 2013 GL on STEMI and 2015 ACC/AHA/SCAI update on Primary PCI	
Primary PCI in STEMI	
Ischaemic symptoms <12 h	I-A
Ischaemic symptoms <12 h and contraindications to fibrinolytic therapy, irrespective of time delay from FMC	I-B
Cardiogenic shock or acute severe HF, irrespective of time delay from MI onset	I-B
Evidence of ongoing ischaemia 12 to 24 h after symptom onset	IIa-B
PCI of a noninfarct artery may be considered in selected patients with STEMI and multivessel disease who are haemodynamically stable, either at the time of primary PCI or as a planned staged procedure	IIb-B-R
Technical aspects for primary PCI in STEMI	
Placement of a stent (bare metal stent [BMS] or drug-eluting stent (DES)).	I-A
BMS† should be used in patients with high bleeding risk, inability to comply with 1 year of dual antiplatelet therapy (DAPT), or anticipated invasive or surgical procedures in the next year.	I-C
Selective and bailout aspiration thrombectomy	IIb-C-LD
Routine aspiration thrombectomy before primary PCI is not useful	III-A
DES should not be used in primary PCI for patients with STEMI who are unable to tolerate or comply with a prolonged course of DAPT because of the increased risk of stent thrombosis with premature discontinuation of one or both agents	III-B

† Balloon angioplasty without stent placement may be used in selected patients.
ESC 2012 guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J.* 2012:**33**:2569–619, by permission of Oxford University Press.
ESC/EACTS 2014 Guidelines on myocardial revascularization. *Eur Heart J.* 2014;**35**:2541–619 with permission from Oxford University Press.
2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol.* 2013;**61**:e78–140 with permission from Elsevier.
2015 ACC/AHA/SCAI focused update on primary PCI for patients with STEMI. *J Am Coll Cardiol.* 2016;**67**:1235–1242.

Table 29.16 Medical therapy with Primary PCI

ESC 2014 GL on revascularization.	
Recommendations for antithrombotic treatment in patients with STEMI undergoing primary PCI*	
Antiplatelet therapy	
ASA for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 80–150 mg IV) and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I-A
A P2Y12 inhibitor in addition to ASA and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.	I-A
Options are:	
◆ Prasugrel (60 mg loading dose, 10 mg daily dose) if no contraindication	I-B
◆ Ticagrelor (180 mg loading dose, 90 mg twice daily) if no contraindication	I-B
◆ Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated.	I-B
Give P2Y12 inhibitors at the time of first medical contact.	I-B
GP IIb/IIIa inhibitors for bail-out or evidence of no-reflow or a thrombotic complication	IIa-C
Upstream use of a GP IIb/IIIa inhibitor (vs in-lab use) in high-risk patients undergoing transfer for primary PCI	IIb-B
Anticoagulants	
Anticoagulation for all patients in addition to antiplatelet therapy during PCI.	I-A
The anticoagulation is selected according to ischaemic and bleeding risks, and efficacy-safety profile of the chosen agent.	I-C
Unfractionated heparin: 70–100 U/kg IV bolus when no GP IIb/IIIa inhibitor is planned 50–70 U/kg IV bolus with GPIIb/IIIa inhibitor.	I-C
Bivalirudin 0.75 mg/kg IV bolus followed by IV infusion of 1.75 mg/kg/h for up to 4 hours after the procedure.	IIa-A*

(*Continued*)

Table 29.16 Continued

Enoxaparin IV 0.5 mg/kg with or without GP IIb/IIIa inhibitor.	IIa-B

* The ESC 2012 GL on STEMI preferred bivalirudin over UFH and a GP IIb/IIIa (I-B). Otherwise recommendations were similar

ESC 2012 GL on STEMI.	
Doses of antiplatelet co-therapies	
With primary PCI	
Aspirin	Loading dose of 150–300 mg orally or of 80–150 mg IV if oral ingestion is not possible, followed by a maintenance dose of 75–100 mg/day.
Clopidogrel	Loading dose of 600 mg orally, followed by a maintenance dose of 75 mg/day.
Prasugrel	Loading dose of 60 mg orally, followed by a maintenance dose of 10 mg/day. In patients with body weight <60 kg, a maintenance dose of 5 mg is recommended. In patients >75 years, prasugrel is generally not recommended, but a dose of 5 mg should be used if treatment is deemed necessary.
Ticagrelor	Loading dose of 180 mg orally, followed by a maintenance dose of 90 mg bd.
Abciximab	Bolus of 0.25 mg/kg IV and 0.125 micrograms/kg/min infusion (maximum 10 micrograms/min) for 12 h.
Eptifibatide	Double bolus of 180 micrograms/kg IV (given at a 10-minute interval) followed by an infusion of 2.0 micrograms/kg/min for 18 h.
Tirofiban	25 micrograms/kg over 3 min IV, followed by a maintenance infusion of 0.15 micrograms/kg/min for 18 h.
With fibrinolytic therapy	
Aspirin	Starting dose 150–500 mg orally or IV dose of 250 mg if oral ingestion is not possible.
Clopidogrel	Loading dose of 300 mg orally if aged ≤75 years, followed by a maintenance dose of 75 mg/day.
Without reperfusion therapy	
Aspirin	Starting dose 150–500 mg orally.
Clopidogrel	75 mg/day orally.
Doses of antithrombin co-therapies	
With primary PCI	
Unfractionated heparin	70–100 U/kg IV bolus when no GP IIb/IIIa inhibitor is planned. 50–60 U/kg IV bolus with GP IIb/IIIa inhibitors.
Enoxaparin	0.5 mg/kg IV bolus.
Bivalirudin	0.75 mg/kg IV bolus, followed by IV infusion of 1.75 mg/kg/h for up to 4 h after the procedure, as clinically warranted. After cessation of the 1.75 mg/kg/h infusion, a reduced infusion dose of 0.25 mg/kg/h may be continued for 4–12 h, as clinically necessary.
With fibrinolytic therapy	
Unfractionated heparin	60 U/kg IV bolus with a maximum of 4000 U, followed by an IV infusion of 12 U/kg with a maximum of 1000 U/h for 24–48 h. Target aPTT: 50–70 s or 1.5 to 2.0 times that of control to be monitored at 3, 6, 12, and 24 h.
Enoxaparin	In patients <75 years of age: 30 mg IV bolus, followed 15 min later by 1 mg/kg SC every 12 h until hospital discharge for a maximum of 8 days. The first two doses should not exceed 100 mg. In patients >75 years of age: no IV bolus; start with first SC dose of 0.75 mg/kg with a maximum of 75 mg for the first two SC doses. In patients with creatinine clearance of <30 mL/min, regardless of age, the SC doses are given once every 24 h.

(*Continued*)

Table 29.16 Continued

Fondaparinux	2.5 mg IV bolus followed by a SC dose of 2.5 mg once daily up to 8 days or hospital discharge.	
Without reperfusion therapy		
Unfractionated heparin	Same dose as with fibrinolytic therapy.	
Enoxaparin	Same dose as with fibrinolytic therapy.	
Fondaparinux	Same dose as with fibrinolytic therapy.	
ACCF/AHA 2013 GL on STEMI and 2016 update on duration of DAPT. Adjunctive antithrombotic therapy to support reperfusion with primary PCI		
Antiplatelet therapy		
Aspirin		
162 to 325 mg load before procedure		I-B
81 to 325 mg daily maintenance dose (indefinite)		I-A
In patients treated with DAPT, aspirin 81 mg od (range 75–100 mg)		I-B-NR
$P2Y_{12}$ inhibitors		
Loading doses		
Clopidogrel: 600 mg as early as possible or at time of PCI		I-B
Prasugrel: 60 mg as early as possible or at time of PCI		I-B
Ticagrelor: 180 mg as early as possible or at time of PCI		I-B
Maintenance doses and duration of therapy		
In patients treated with DAPT after BMS or DES, clopidogrel or prasugrel or ticagrelor for at least 12 months		I-B-R
In patients treated with stenting, ticagrelor instead of clopidogrel		IIa-B-R
In patients not at high risk of bleeding, and without a history of stroke or TIA, and treated with stenting, prasugrel instead of clopidogrel		IIa-B-R
In patients with stenting who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g. prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT (clopidogrel, prasugrel, or ticagrelor) for longer than 12 months		IIb-A-SR
In patients with DES who develop a high risk of bleeding (e.g. treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g. major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y12 inhibitor therapy after 6 months		IIb-C-LD
Prasugrel should not be used in patients with a history of stroke or TIA		III-B-R (Harm)
GP IIb/IIIa receptor antagonists in conjunction with UFH or bivalirudin in selected patients		
Abciximab: 0.25 mg/kg IV bolus, then 0.125 micrograms/kg/min (maximum 10 micrograms/min)		IIa-A
Tirofiban: (high-bolus dose): 25 micrograms/kg IV bolus, then 0.15 micrograms/kg/min In patients with CrCl <30 mL/min, reduce infusion by 50%		IIa-B
Eptifibatide (double bolus): 180 micrograms/kg IV bolus, then 2 micrograms/kg/min; a second 180 micrograms/kg bolus is administered 10 min after the first bolus In patients with CrCl <50 mL/min, reduce infusion by 50% Avoid in patients on haemodialysis		IIa-B
Pre-catheterization laboratory administration of IV GP IIb/IIIa receptor antagonist		IIb-B
Intracoronary abciximab 0.25 mg/kg bolus		IIb-B
Anticoagulant therapy		
UFH with GP IIb/IIIa receptor antagonist planned: 50 to 70 U/kg IV bolus to achieve therapeutic ACT‡		I-C
UFH with no GP IIb/IIIa receptor antagonist planned: 70 to 100 U/kg bolus to achieve therapeutic ACT§		I-C
Bivalirudin: 0.75 mg/kg IV bolus, then 1.75 mg/kg/h infusion with or without prior treatment with UFH. An additional bolus of 0.3 mg/kg may be given if needed. Reduce infusion to 1 mg/kg/h with estimated CrCl <30 mL/min		I-B

(*Continued*)

Table 29.16 Continued

Preferred over UFH with GP IIb/IIIa receptor antagonist in patients at high risk of bleeding	IIa-B
Fondaparinux: not recommended as sole anticoagulant for primary PCI	III-B: harm

† Balloon angioplasty without stent placement may be used in selected patients. It might be reasonable to provide P2Y12 inhibitor therapy to patients with STEMI undergoing balloon angioplasty alone, according to the recommendations listed for BMS (*LOE: C*).
‡ The recommended ACT with planned GP IIb/IIIa receptor antagonist treatment is 200–250 s.
§ The recommended ACT with no planned GP IIb/IIIa receptor antagonist treatment is 250–300 s (HaemoTec device) or 300–350 s (Haemochron device).
ACT indicates activated clotting time; BMS, bare metal stent; CrCl, creatinine clearance; COR, class of recommendation; DES, drug-eluting stent; GP, glycoprotein; IV, intravenous; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; TIA, transient ischaemic attack; and UFH, unfractionated heparin.
ESC/EACTS 2014 Guidelines on myocardial revascularization. *Eur Heart J.* 2014;**35**:2541–619 with permission from Oxford University Press.
ESC 2012 Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012:**33**:2569–619, by permission of Oxford University Press.
2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2013;**61**:e78–140 with permission from Elsevier.
2015 ACC/AHA/SCAI focused update on primary PCI for patients with STEMI. *J Am Coll Cardiol*. 2016;**67**:1235–1242.
2016 ACC/AHA Guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. *Circulation*. 2016; Mar 29. [Epub ahead of print].

Table 29.17 Grading of coronary flow and myocardial blush

TIMI flow
TIMI 0 There is no antegrade flow beyond the point of occlusion.
TIMI 1 The contrast material passes beyond the area of obstruction but 'hangs up' and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cine run.
TIMI 2 The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) are perceptibly slower than its entry into, or clearance from, comparable areas not perfused by the previously occluded vessel, e.g. the opposite coronary artery or the coronary bed proximal to the obstruction.
TIMI 3 Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery.
Myocardial blush grade
MBG 0 No myocardial blush or staining of blush (due to leakage of dye into the extravascular space)
MBG 1 Minimal myocardial blush
MBG 2 Moderate myocardial blush, less than that obtained during angiography of a contralateral or ipsilateral non-infarct-related artery
MBG 3 Normal myocardial blush, comparable with that obtained during angiography of a contralateral or ipsilateral non-infarct-related artery
Myocardial blush grade (MBG) is a densitometric, semi-quantitative parameter which depends on the tissue phase of myocardial perfusion that appears as a 'blush' or a 'ground glass' after a sufficiently long, 25 frames/s, X-ray acquisition. MBG is measured on patients with TIMI 3 flow and is based on the principle that a functionally preserved microvascular bed allows the injected contrast to pass easily from the arterial to the venous side of coronary circulation, showing an appreciable 'blush' at the myocardial level.

van't Hof AW, *et al*. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Zwolle Myocardial Infarction Study Group. *Circulation*. 1998;**97**:2302–6 with permission from Wolters Kluwer.

Pharmaco-invasive therapy

Initial studies on **facilitated PCI**, i.e. full of half-dose thrombolysis with or without IIb/IIIa inhibitors followed by immediate PCI, documented an increased incidence of major adverse cardiac events.[94,95] However, in the FAST-MI trial on patients presenting ≤3 h from symptoms onset, the 5-year survival was similar between primary PCI and fibrinolysis followed by coronary angiography and high rates of subsequent PCI at varying time intervals.[96] Most of the existing evidence indicates that routine PCI within 24 h but later than 3 h after fibrinolysis is the optimal strategy and may offer reduced rates of reinfarction and composite outcomes of myocardial infarction and death compared to ischaemia-guided PCI.[72–75] Thus, in patients presenting early after symptoms or when a timely PCI is not available, fibrinolysis followed by PCI at least 3 (or 6) h and up to 24 h later, may be at least as good as primary PCI. In the CAPTIM trial, patients treated within 2 h of symptom onset, had a lower 5-year mortality with pre-hospital fibrinolysis.[73] In the STREAM trial, prehospital fibrinolysis with tenecteplase in patients who presented within 3 hours after symptom onset and who were unable to undergo

primary PCI within 1 hour (with half the dose in those >75 years) resulted in effective reperfusion compared to late primary PCI (6–24 h from symptom onset), but with a slightly increased risk of intracranial bleeding,[72] although 1-year mortality was similar in the two groups.[97] In the TRANSER-AMI trial on high-risk patients who were treated with fibrinolysis, transfer for PCI within 6 h after fibrinolysis was associated with significantly fewer ischaemic complications than was standard treatment.[74]

Fibrinolysis

Fibrinolysis is given **within the next 12 h after the onset of symptoms or the next 24 h in case of ongoing ischaemia** (Tables 29.18 to 29.20 and Figures 29.3 and 29.4). Patients presenting beyond the 12 h limit should receive heparin or fondaparinux, regardless of whether reperfusion is attempted. Despite previous reservations, fibrinolyis is recommended in the elderly (>75 years) when primary PCI is not available.[98] Urgent pharmacological reperfusion with fibrinolysis, either pre-hospital within 30 minutes or after transfer with a door-to-needle time <30 min, remains the principal treatment for improving survival after STEMI, unless an absolute contraindication exists (Table 29.14). In patients presenting <2 hours after symptom onset, fibrinolysis can achieve mortality rates of <4%, which are similar to those achieved by primary PCI. The earlier the fibrinolysis, the greater the benefit by means of preservation of left ventricular function and reduction in mortality.[99]

Bolus-only fibrin-specific agents **reteplase (rPA) and tenecteplase (TNK-tPA)** are tissue plasminogen activator (tPA) mutants that achieve greater vessel patency than non-fibrin specific agents (streptokinase and urokinase) and similar mortality benefit, but with less systemic bleeding than infusion of tPA.[100,101] In patients receiving fibrin-specific fibrinolytic agents, and perhaps streptokinase, **unfractionated heparin**, or **enoxaparin**, commenced early after fibrinolysis is recommended. UFH should not be given for more than 48 h due to the risk of heparin-induced thrombocytopenia. Maintenance dosing with enoxaparin or fondaparinux should be continued for the duration of the index hospitalization, up to 8 days.

Combination of half-dose fibrinolytics and glycoprotein **IIb/IIIa inhibition** for pharmacological reperfusion achieves more rapid ST segment resolution and less recurrent infarction than with standard fibrinolytic therapy, but no reduction in mortality.[102] It is contraindicated in patients >75 years old.

Intracranial haemorrhage

The occurrence of a change in neurological status during or after reperfusion therapy, particularly within the first 24 h after initiation of treatment, is considered to be due to intracranial haemorrhage until proven otherwise. The incidence of intracranial haemorrhage following thrombolysis has been estimated between 0.2 and 2%.[103] Certain patient groups, such as the elderly, women, hypertensive patients, and diabetics, are at an increased risk of intracranial haemorrhage when subjected to thrombolysis. Fibrinolytic, antiplatelet, and anticoagulant therapies should be discontinued until brain imaging scan shows no evidence of intracranial haemorrhage. Cryoprecipitates, fresh frozen plasma, protamine, and platelets are given, and intracranial pressure is reduced with mannitol, endotracheal intubation, and hyperventilation. Blood pressure and glucose levels are optimized, and neurosurgical consultation is sought.

Failed reperfusion

Criteria of successful thrombolysis are:

- **ST resolution (>70%) within the first 90 min after treatment**
- **T wave inversion <4 h after treatment**
- **Rapid release of biochemical markers**
- **Accelerated idioventricular rhythm 60–120 bpm (benign rhythm)**.

Failed reperfusion is defined as continuing chest pain or failure of ST segment resolution by >50% at 90 min after fibrinolysis and is seen in 40% of cases with fibrinolysis.

Patients with **recurrent ischaemia** should be considered candidates for coronary arteriography and PCI or CABG. Fibrinolytic therapy (other than streptokinase) may be repeated if PCI is not available within the next 60 min.

Rescue PCI

This is better than repeat fibrinolysis after failed reperfusion,[104] and associated with lower rates of heart failure (5% absolute reduction) and re-infarction (4% absolute reduction) by 6 months but a 3% increase in stroke, compared to a conservative strategy with PCI only, for recurrent ischaemia after fibrinolysis.[105] Coronary angiography with intent to perform PCI is also recommended in patients who received thrombolysis and develop cardiogenic shock, pulmonary oedema or heart failure, and haemodynamically compromising ventricular arrhythmias (Table 29.21).

Routine angiography following fibrinolysis

ST recovery is an imperfect discriminator between TIMI grade 2 and TIMI grade 3 flow, with up to 50% of patients with persistent ST elevation having a patent infarct-related artery at the time of angiography (Table 29.17).[106] Thus, routine coronary angiography and, if indicated, PCI may be recommended in all patients after successful thrombolysis. This should be done within the next 24 hours and delayed for at least 3 hours following the fibrinolysis, though the optimal timing remains uncertain.[107–109] In stable patients who did not receive reperfusion, routine angiography before discharge is an option (Table 29.22).

Table 29.18 Contraindications to fibrinolysis

ACC/AHA 2013 on STEMI. Contraindications and cautions for fibrinolytic therapy in STEMI*
Absolute contraindications
Any prior ICH
Known structural cerebral vascular lesion (e.g. arteriovenous malformation)
Known malignant intracranial neoplasm (primary or metastatic)
Ischaemic stroke within 3 mo-EXCEPT acute ischaemic stroke within 4.5 h
Suspected aortic dissection
Active bleeding or bleeding diathesis (excluding menses)
Significant closed-head or facial trauma within 3 mo
Intracranial or intraspinal surgery within 2 mo
Severe uncontrolled hypertension (unresponsive to emergency therapy)
For streptokinase, prior treatment within the previous 6 mo
Relative contraindications
History of chronic, severe, poorly controlled hypertension
Significant hypertension on presentation (SBP >180 mmHg or DBP >110 mmHg)
History of prior ischaemic stroke >3 mo
Dementia
Known intracranial pathology not covered in absolute contraindications
Traumatic or prolonged (>10 min) CPR
Major surgery (<3 wk)
Recent (within 2–4 wk) internal bleeding
Non-compressible vascular punctures
Pregnancy
Active peptic ulcer
Oral anticoagulant therapy
ESC 2012 on STEMI. Condraindications to fibrinolysis
Absolute
Previous intracranial haemorrhage or stroke of unknown origin at any time
Ischaemic stroke in the preceding 6 months
Central nervous system damage or neoplasms or atrioventricular malformation
Recent major trauma/surgery/head injury (within the preceding 3 weeks)
Gastrointestinal bleeding within the past month
Known bleeding disorder (excluding menses)
Aortic dissection
Non-compressible punctures in the past 24 h (e.g. liver biopsy, lumbar puncture)
Relative
Transient ischaemic attack in the preceding 6 months
Oral anticoagulant therapy
Pregnancy or within 1 week post-partum
Refractory hypertension (systolic blood pressure >180 mmHg and/or diastolic blood pressure >110 mmHg)
Advanced liver disease
Infective endocarditis
Active peptic ulcer
Prolonged or traumatic resuscitation

* Viewed as advisory for clinical decision-making and may not be all-inclusive or definitive.
CPR indicates cardiopulmonary resuscitation; DBP; diastolic blood pressure; ICH, intracranial haemorrhage; SBP, systolic blood pressure; and STEMI, ST elevation myocardial infarction.
2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2013;**61**:e78–140 with permission from Elsevier.
ESC 2012 Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012:**33**:2569–619, by permission of Oxford University Press.

Table 29.19 Fibrinolysis

ESC 2012 GL on STEMI.	
Fibrinolytic therapy	
Fibrinolytic therapy is recommended within 12 h of symptom onset in patients without contraindications if primary PCI cannot be performed by an experienced team within 120 min of FMC.	I-A
In patients presenting early (<2 h after symptom onset) with a large infarct and low bleeding risk, fibrinolysis should be considered if time from FMC to balloon inflation is >90 min.	IIa-B
If possible, fibrinolysis should start in the pre-hospital setting.	IIa-A
A fibrin-specific agent (tenecteplase, alteplase, reteplase) is recommended (over non-fibrin specific agents).	I-B
Oral or IV aspirin must be administered.	I-B
Clopidogrel is indicated in addition to aspirin.	I-A
Antithrombin co-therapy with fibrinolysis	
Anticoagulation is recommended in STEMI patients treated with lytics until revascularization (if performed) or for the duration of hospital stay up to 8 days. The anticoagulant can be:	I-A
◆ Enoxaparin IV, followed by SC (using the regimen described below) (preferred over UFH)	I-A
◆ UFH given as a weight-adjusted IV bolus and infusion	I-C
In patients treated with streptokinase, fondaparinux IV bolus, followed by SC dose 24 h later	IIa-B
Transfer to a PCI-capable centre following fibrinolysis	
Is indicated in all patients after fibrinolysis.	I-A
Interventions following fibrinolysis	
Rescue PCI is indicated immediately when fibrinolysis has failed (<50% ST segment resolution at 60 min).	I-A
Emergency PCI is indicated in the case of recurrent ischaemia or evidence of reocclusion after initial successful fibrinolysis.	I-B
Emergency angiography with a view to revascularization is indicated in heart failure/shock patients.	I-A
Angiography with a view to revascularization (of the infarct-related artery) is indicated after successful fibrinolysis.	I-A
Optimal timing of angiography for stable patients after successful lysis: 3–24 h.	IIa-A

Doses of fibrinolytic agents

	Initial treatment	**Specific contraindications**
Streptokinase (SK)	1.5 million units over 30–60 min IV	Prior SK or anistreplase
Alteplase (tPA)	15 mg IV bolus 0.75 mg/kg over 30 min (up to 50 mg), then 0.5 mg/kg over 60 min IV (up to 35 mg)	
Reteplase (r-PA)	10 units + 10 units IV bolus, given 30 min apart	
Tenecteplase (TNK–tPA)	Single IV bolus: 30 mg if <60 kg, 35 mg if 60 to <70 kg, 40 mg if 70 to <80 kg, 45 mg if 80 to <90 kg, 50 mg if ≥90 kg	

ACCF/AHA 2013 GL on STEMI.	
Indications for fibrinolytic therapy when there is a >120-minute delay from FMC to primary PCI	
Ischaemic symptoms <12 h	I-A
Evidence of ongoing ischaemia 12–24 h after symptom onset and a large area of myocardium at risk or haemodynamic instability	IIa-C
ST depression, except if true posterior (inferobasal) MI is suspected or when associated with ST elevation in lead aVR	III-B (harm)

Fibrinolytic agents

Fibrinolytic agent	**Dose**	**Fibrin specificity***	**Antigenic**	**Patency rate (90-minute TIMI 2 or 3 flow)**
Fibrin-specific				
Tenecteplase (TNK-tPA)	Single IV weight-based bolus†	++++	No	85%
Reteplase (rPA)	10 U plus 10 U IV boluses, given 30 min apart	++	No	84%

(*Continued*)

Table 29.19 Continued

Alteplase (tPA)	90-minute weight-based infusion‡	++	No	73–84%
Non-fibrin-specific				
Streptokinase§	1.5 million units IV, given over 30–60 min	No	Yes**	60–68%

FMC, first medical contact; MI, myocardial infarction; and PCI, percutaneous coronary intervention.
* Strength of fibrin specificity; ++++ is more strong; ++ is less strong.
† 30 mg for weight <60 kg; 35 mg for 60–69 kg; 40 mg for 70–79 kg; 45 mg for 80–89 kg; and 50 mg for ≥90 kg.
‡ Bolus 15 mg, infusion 0.75 mg/kg for 30 min (maximum 50 mg), then 0.5 mg/kg (maximum 35 mg) over the next 60 min; total dose not to exceed 100 mg.
§ Streptokinase is no longer marketed in the USA but is available in other countries.
** Streptokinase is highly antigenic and absolutely contraindicated within 6 mo of previous exposure because of the potential for serious allergic reaction.
IV indicates intravenous; rPA, reteplase plasminogen activator; TIMI, Thrombolysis In Myocardial Infarction; TNK-tPA, tenecteplase tissue-type plasminogen activator; and tPA, tissue-type plasminogen activator.
ESC 2012 Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012:**33**:2569–619, by permission of Oxford University Press.
2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2013;**61**:e78–140 with permission from Elsevier.

Table 29.20 ACCF/AHA 2013 GL on STEMI and 2016 update on duration of DAPT

Adjunctive antithrombotic therapy to support reperfusion with fibrinolytic therapy	
Antiplatelet therapy	
Aspirin	
162–325 mg loading dose	I-A
81–325 mg daily maintenance dose (indefinite)	I-A
In patients treated with DAPT, aspirin 81 mg od (range 75–100 mg)	I-B-NR
P2Y12 receptor inhibitors	
Clopidogrel:	I-A
Age ≤75 y: 300 mg loading dose	
Age >75 years: no loading dose, give 75 mg	I-A
In patients with DAPT in conjuction with fibrinolysis:	
clopidogrel 75 mg od for at a minimum of 14 days	I-A
and ideally for 12 months	I-C-EO
In patients who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g. prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT for longer than 12 months	IIb-A-SR
Anticoagulant therapy	
UFH	I-C
Weight-based IV bolus and infusion adjusted to obtain aPTT of 1.5–2.0 times control for 48 h or until revascularization. IV bolus of 60 U/kg (maximum 4000 U), followed by an infusion of 12 U/kg/h (maximum 1000 U) initially, adjusted to maintain aPTT at 1.5–2.0 times control (approximately 50–70 s) for 48 h or until revascularization	
Enoxaparin	I-A
If age <75 years: 30 mg IV bolus, followed in 15 min by 1 mg/kg subcutaneously every 12 h (maximum 100 mg for the first two doses)	
If age ≥75 years: no bolus, 0.75 mg/kg subcutaneously every 12 h (maximum 75 mg for the first two doses)	
Regardless of age, if CrCl <30 mL/min: 1 mg/kg subcutaneously every 24 h	
Duration: for the index hospitalization, up to 8 d or until revascularization	
Fondaparinux	I-B
Initial dose 2.5 mg IV, then 2.5 mg subcutaneously daily starting the following day, for the index hospitalization up to 8 d or until revascularization	
Contraindicated if CrCl <30 mL/min	

aPTT indicates activated partial thromboplastin time; CrCl, creatinine clearance; IV, intravenous; and UFH, unfractionated heparin.
2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2013;**61**:e78–140 with permission from Elsevier.
2016 ACC/AHA Guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. *Circulation*. 2016; Mar 29. [Epub ahead of print].

Table 29.21 ACCF/AHA 2013 GL on STEMI

Indications for PCI of an infarct artery in patients who were managed with fibrinolytic therapy or who did not receive reperfusion therapy	
Cardiogenic shock or acute severe HF	I-B
Intermediate- or high-risk findings on predischarge non-invasive ischaemia testing	I-C
Spontaneous or easily provoked myocardial ischaemia	I-C
Patients with evidence of failed reperfusion or reocclusion after fibrinolytic therapy (as soon as possible)	IIa-B
Stable* patients after successful fibrinolysis, ideally between 3 and 24 h	IIa-B
Stable* patients >24 h after successful fibrinolysis	IIb-B
Delayed PCI of a totally occluded infarct artery >24 h after STEMI in stable patients	III-B (no benefit)
Adjunctive antithrombotic therapy to support PCI after fibrinolytic therapy	
Antiplatelet therapy	
Aspirin	
162–325 mg loading dose given with fibrinolytic agent (before PCI).	I-A
81–325 mg daily maintenance dose after PCI (indefinite)	I-A
In patients treated with DAPT, aspirin 81 mg od (range 75–100 mg)	I-B-NR
P2Y12 receptor inhibitors	
Loading doses	
For patients who received a loading dose of clopidogrel with fibrinolytic therapy:	
Continue clopidogrel 75 mg daily without an additional loading dose	I-C
For patients who have not received a loading dose of clopidogrel:	
If PCI is performed ≤24 h after fibrinolytic therapy: clopidogrel 300 mg loading dose before or at the time of PCI	I-C
If PCI is performed >24 h after fibrinolytic therapy: clopidogrel 600 mg loading dose before or at the time of PCI	I-C
If PCI is performed >24 h after treatment with a fibrin-specific agent or >48 h after a non-fibrin-specific agent: prasugrel 60 mg at the time of PCI	IIa-B
For patients with prior stroke/TIA: prasugrel	III-B (harm)
Maintenance doses and duration of therapy	
In patients treated with DAPT after BMS or DES, clopidogrel or prasugrel or ticagrelor for at least 12 months	I-B-R
In patients treated with stenting, ticagrelor instead of clopidogrel	IIa_B-R
In patients not at high risk of bleeding, and without a history of stroke or TIA, and treated with stenting, prasugrel instead of clopidogrel	IIa-B-R
In patients with stenting who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g. prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT (clopidogrel, prasugrel, or ticagrelor) for longer than 12 months	IIb-A-SR
In patients with DES who develop a high risk of bleeding (e.g. treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g. major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y12 inhibitor therapy after 6 months	IIb-C-LD
Prasugrel should not be used in patients with a history of stroke or TIA	III-B-R (Harm)
Anticoagulant therapy	
Continue UFH through PCI, administering additional IV boluses, as needed, to maintain therapeutic ACT, depending on use of GP IIb/IIIa receptor antagonist†	I-C
Continue enoxaparin through PCI:	I-B
No additional drug if last dose was within previous 8 h	
0.3 mg/kg IV bolus if last dose was 8–12 h earlier	
Fondaparinux:	III-C (harm)
As sole anticoagulant for PCI	

* Although individual circumstances will vary, clinical stability is defined by the absence of low output, hypotension, persistent tachycardia, apparent shock, high-grade ventricular or symptomatic supraventricular tachyarrhythmias, and spontaneous recurrent ischaemia.
* Balloon angioplasty without stent placement may be used in selected patients. It might be reasonable to provide P2Y12 inhibitor therapy to patients with STEMI undergoing balloon angioplasty after fibrinolysis alone, according to the recommendations listed for BMS (level of evidence: C).
† The recommended ACT with no planned GP IIb/IIIa receptor antagonist treatment is 250–300 s (HaemoTec device) or 300–350 s (Haemochron device).
ACT indicates activated clotting time; BMS, bare metal stent; DES, drug-eluting stent; GP, glycoprotein; IV, intravenous; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack; and UFH, unfractionated heparin.
AHA/ACC 2013 Guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2013;**61**:e78–e140 with permission from Elsevier.
2016 ACC/AHA Guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. *Circulation*. 2016; Mar 29. [Epub ahead of print].

Table 29.22 Coronary angiography after fibrinolysis

ACC/AHA 2013 GL on STEMI. Indications for transfer for angiography after fibrinolytic therapy	
Immediate transfer for cardiogenic shock or severe acute HF, irrespective of time delay from MI onset	I-B
Urgent transfer for failed reperfusion or reocclusion	IIa-B
As part of an invasive strategy in stable* patients with PCI between 3 and 24 h after successful fibrinolysis	IIa-B
ACC/AHA 2013 GL on STEMI. Indications for coronary angiography in patients who were managed with fibrinolytic therapy or who did not receive reperfusion therapy	
Cardiogenic shock or acute severe HF that develops after initial presentation	I-B
Intermediate- or high-risk findings on predischarge non-invasive ischaemia testing	I-B
Spontaneous or easily provoked myocardial ischaemia	I-C
Failed reperfusion or reocclusion after fibrinolytic therapy	IIa-B
Stable* patients after successful fibrinolysis before discharge and ideally between 3 and 24 h	IIa-B
ESC 2014 GL on revascularization. Management and revascularization after fibrinolysis	
Transfer to a PCI-capable centre is indicated in all patients within 24 hours.	I-A
Coronary angiography with the intent to revascularize the infarct-related artery after successful fibrinolysis within 24 h.	I-A
Emergency angiography with the intent of revascularization in cardiogenic shock or acute severe heart failure.	I-B
Emergency rescue PCI is when fibrinolysis has failed (<50% ST-segment resolution or persistent pain at 60 min).	I-A
Emergency PCI in recurrent ischaemia, haemodynamic instability, and life-threatening ventricular arrhythmias or evidence of reocclusion	I-A
Optimal timing of angiography for stable patients after successful fibrinolysis: 3–24 h	IIa-A

* Although individual circumstances will vary, clinical stability is defined by the absence of low output, hypotension, persistent tachycardia, apparent shock, high-grade ventricular or symptomatic supraventricular tachyarrhythmias, and spontaneous recurrent ischaemia.
HF, heart failure.
2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2013;**61**:e78–140 with permission from Elsevier.
ESC/EACTS 2014 Guidelines on myocardial revascularization. *Eur Heart J*. 2014;**35**:2541–619 with permission from Oxford University Press.

CABG

CABG mortality is elevated for the first 3–7 days after infarction, and the benefit of revascularization must be balanced against this increased risk. However, emergency surgical revascularization may be necessary and can be undertaken, especially in cases of failed PCI of a large LAD or mechanical complications of the MI (Table 29.23).[110]

Table 29.23 ACCF/AHA 2013 GL on STEMI.

CABG in patients with STEMI	
Urgent CABG in patients with STEMI and coronary anatomy not amenable to PCI who have ongoing or recurrent ischaemia, cardiogenic shock, severe HF, or other high-risk features.	I-B
CABG in patients with STEMI at time of operative repair of mechanical defects.	I-B
Use of mechanical circulatory support in patients with STEMI who are haemodynamically unstable and require urgent CABG.	IIa-C
Emergency CABG within 6 h of symptom onset in patients with STEMI who do not have cardiogenic shock and are not candidates for PCI or fibrinolytic therapy.	IIb-C
Timing of urgent CABG in patients with STEMI in relation to use of antiplatelet agents	
Aspirin should not be withheld before urgent CABG.	I-C
Clopidogrel or ticagrelor should be discontinued at least 24 h before urgent on-pump CABG, if possible.	I-B
Short-acting IV GP IIb/IIIa receptor antagonists (eptifibatide, tirofiban) should be discontinued at least 2–4 h before urgent CABG.	I-B
Abciximab should be discontinued at least 12 h before urgent CABG.	I-B
Urgent off-pump CABG within 24 h of clopidogrel or ticagrelor administration, especially if the benefits of prompt revascularization outweigh the risks of bleeding.	IIIb-B
Urgent CABG within 5 days of clopidogrel or ticagrelor administration or within 7 days of prasugrel administration, especially if the benefits of prompt revascularization outweigh the risks of bleeding.	IIb-C

2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2013;**61**:e78–140 with permission from Elsevier.

Complications of myocardial infarction

Most deaths in hospitalized patients with STEMI are due to heart failure and mechanical complications.

Heart failure (Killip class II and III)

Oxygen by mask (4–5 L/min), loop diuretics (i.e. furosemide 20–40 mg IV, repeated at 1–4 hourly intervals), ACE inhibitors (or ARBs), and nitrates, if the systolic BP >100 mmHg, are mandatory. Dobutamine (can be given through a peripheral line) or dopamine, if there is hypotension (requires central line), can be considered in refractory cases (Table 29.24).

Hypotension

Rapid volume loading and correction of arrhythmias and conduction disturbances are essential in hypotension. If the patient does not respond, consideration of mechanical complications and vasopressor support and/or intra-aortic balloon counterpulsation may be needed.

Cardiogenic shock

Cardiogenic shock is caused by extensive loss of viable myocardial tissue and is characterized by a systolic pressure <90 mmHg and a central filling pressure (wedge pressure) >20 mmHg or a cardiac index <1.8 L/min/m^2. Shock is also considered present if inotropes and/or an intra-aortic balloon pump are needed to maintain a systolic blood pressure >90 mmHg and a cardiac index >1.8 L/min/m^2. Early revascularization by PCI (one or more coronary arteries),[111] or even CABG if necessary, is the only means to possibly reduce mortality that approaches 60% if left untreated (Table 29.24, see also Chapter 32 on CCF). A haemodynamic support device is recommended in patients who do not stabilize with pharmacologic therapy. Although intra-aortic balloon pumping is still recommended, its effectiveness is debated, particularly if revascularization is undertaken (IABP-SHOCK II trial).[112–114]

Table 29.24 Heart failure and cardiogenic shock

ESC 2012 GL on STEMI. Treatment of heart failure and left ventricular dysfunction	
Treatment of mild heart failure (Killip class II)	
Oxygen is indicated to maintain a saturation >95%.	I-C
Loop diuretics, e.g. furosemide 20–40 mg IV, are recommended and should be repeated at 1–4 h intervals, if necessary.	I-C
IV nitrates or sodium nitroprusside should be considered in patients with elevated systolic blood pressure.	IIa-C
An ACE inhibitor is indicated in all patients with signs or symptoms of heart failure and/or evidence of LV dysfunction in the absence of hypotension, hypovolaemia, or renal failure.	I-A
An ARB (valsartan) is an alternative to ACE inhibitors, particularly if ACE inhibitors are not tolerated.	I-B
An aldosterone antagonist (eplerenone) is recommended in all patients with signs or symptoms of heart failure and/or evidence of LV dysfunction, provided no renal failure or hyperkalaemia.	I-B
Hydralazine and isosorbide dinitrate should be considered if the patient is intolerant to both ACE inhibitors and ARBs.	IIa-C
Treatment of moderate heart failure (Killip class III)	
Oxygen is indicated.	I-C
Ventilatory support should be instituted, according to blood gases.	I-C
Loop diuretics, e.g. furosemide 20–40 mg IV, are recommended and should be repeated at 1–4 h intervals, if necessary.	I-C
Morphine is recommended. Respiration should be monitored. Nausea is common, and an antiemetic may be required. Frequent low-dose therapy is advisable.	I-C
Nitrates are recommended if there is no hypotension.	I-C
Inotropic agents:	
Dopamine	IIa-C
Dobutamine (inotropic)	IIa-C
Levosimendan (inotropic/vasodilator).	IIb-C
An aldosterone antagonist, such as spironolactone or eplerenone, must be used if LVEF ≤40%.	I-B
Ultrafiltration should be considered.	IIa-B
Early revascularization must be considered if the patient has not been previously revascularized.	I-C
Treatment of cardiogenic shock (Killip class IV)	
Oxygen/mechanical respiratory support is indicated, according to blood gases.	I-C
Urgent echocardiography/Doppler must be performed to detect mechanical complications, assess systolic function, and loading conditions.	I-C

(*Continued*)

Table 29.24 Continued

High-risk patients must be transferred early to tertiary centres.	I-C
Emergency revascularization, with either PCI or CABG, in suitable patients must be considered.	I-B
Fibrinolysis should be considered if revascularization is unavailable.	IIa-C
Intra-aortic balloon pumping may be considered.	IIb-B
LV assist devices may be considered for circulatory support in patients in refractory shock.	IIb-C
Haemodynamic assessment with balloon floating catheter may be considered.	IIb-B
Inotropic/vasopressor agents should be considered: Dopamine Dobutamine	IIa-C
Norepinephrine (preferred over dopamine when blood pressure is low).	IIb-B
ACC/AHA 2013 on STEMI. Treatment of cardiogenic shock	
Emergency revascularization, with either PCI or CABG, in suitable patients with cardiogenic shock due to pump failure after STEMI, irrespective of the time delay from MI onset.	I-B
In the absence of contraindications, fibrinolytic therapy should be administered to patients with STEMI and cardiogenic shock who are unsuitable candidates for either PCI or CABG.	I-B
Intra-aortic balloon pump (IABP) counterpulsation for patients with cardiogenic shock after STEMI who do not quickly stabilize with pharmacological therapy.	IIa-B
Alternative LV assist devices for circulatory support may be considered in patients with refractory cardiogenic shock	IIb-C

ESC 2012 Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012:**33**:2569–619, by permission of Oxford University Press.
2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2013;**61**:e78–140 with permission from Elsevier.

Right ventricular infarction

Patients with inferior STEMI and haemodynamic compromise should be assessed with a right precordial V_{4R} lead to detect ST segment elevation and an echocardiogram to screen for RV infarction.

The following principles apply to therapy:

- Early reperfusion should be achieved, if possible.
- AV synchrony should be achieved, and bradycardia should be corrected.
- RV preload should be optimized, with initial volume challenge in patients with haemodynamic instability, provided the jugular venous pressure is normal or low.
- RV afterload should be optimized, with therapy for concomitant LV dysfunction.
- Inotropic support should be used for haemodynamic instability not responsive to volume challenge.

Finally, it is reasonable to delay CABG surgery for 4 weeks to allow recovery of contractile performance.

Myocardial free wall rupture

More commonly occurs in the elderly with hypertension, after large anterior MI, and particularly following expansion. Usually, it occurs 1 day after infarction (up to 7 days without reperfusion).[115] Incidence is 1–6%, and PCI, but not fibrinolysis, reduces the risk. Acute free wall rupture is associated with haemopericardium and electromechanical dissociation and is fatal. Subacute rupture (25%), i.e. sealing of the rupture with thrombus or adhesions (**pseudoaneurysm**), may lead to a relatively stable haemopericardium that allows time for surgical intervention. Patients with tamponade, but without electromechanical dissociation, may have a good prognosis with pericardiocentesis and conservative management. When pericardial effusion in a parasternal short-axis view exceeds 10 mm, the risk of free wall rupture is high, and pericardial aspiration for measurement of haematocrit in the effusion is useful.[19] Moderate pericardial effusions without tamponade carry the risk of late rupture. Patients with free wall rupture should be considered for urgent cardiac surgical repair, and CABG should be undertaken at the same time as repair of free wall rupture.

True LV aneurysm may result in intractable VT and/or pump failure, and, in these cases, surgery with concomitant CABG is indicated.

Ventricular septal rupture

Incidence is 0.2–0.31% (1–2% without reperfusion).[115,116] Patients have multivessel disease and anterior MI (apical rupture) or inferior MI (basal rupture with worse prognosis). They develop shortness of breath and hypotension, and a harsh holosystolic murmur with thrill (50%) may be present. Biventricular failure generally ensues within hours or days, and the murmur and thrill are attenuated. It is often

associated with AV block or RBBB. Diagnosis is made by transthoracic or transoesophageal echocardiography that reveals the defect, and probably a dilated RV. Acutely rising mixed venous O_2 saturations in patients with a pulmonary catheter should raise the suspicion of rupture. Early surgery for repair through the atrium and with a CABG, if needed, is indicated. Although difficult because of friable tissue for the first 6 weeks post-MI, it improves survival. Afterload reduction with IV nitroprusside and intra-aortic counterpulsation may be useful, even in patients who remain haemodynamically stable. Percutaneous closure with VSD-specific devices in VSDs <15 mm,[117] or hybrid percutaneous/surgical approaches,[116] are now also available.

Acute mitral regurgitation

This is due to papillary muscle dysfunction or rupture or chordal rupture (see also valve disease). Transverse rupture of a papillary muscle is rare and usually fatal. Most commonly, there is rupture of the tip of the muscle or a chorde and is due to a relatively small inferior (RCA or Cx) infarct. Posteromedial papillary muscle rupture may occur in 1% of MI, usually 1–7 days after inferior infarction. Anterolateral papillary muscle rupture is rare. The murmur is usually soft, but the ensuing pulmonary oedema is gross. Surgery with MV repair or replacement is indicated.

Thromboembolic and bleeding complications

Management of anticoagulation therapy in patients with AF who undergo primary PCI is presented in Table 29.25. Patients, with or without acute ischaemic stroke, who have a cardiac source of embolism (atrial fibrillation, mural thrombus, or akinetic segment) should receive moderate-intensity (INR 2–3) warfarin therapy (in addition to aspirin). Transfusion may be needed for severe bleeding (haematocrit <25% or haemoglobin <7 g/dL). There has been evidence for a 20% relative risk increase with blood transfusion or a liberal blood transfusion strategy compared with a strategy of no transfusion or restricted transfusion in the setting of STEMI,[118] but this may be due to selection bias with transfusions needed in more seriously ill patients.[119]

Table 29.25 ACCF/AHA 2013 on STEMI. Thromboembolic and bleeding complications

Anticoagulation	
Anticoagulant therapy with a vitamin K antagonist to patients with STEMI and AF with CHADS2 score ≥2, mechanical heart valves, venous thromboembolism, or hypercoagulable disorder.	I-C
The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a P2Y12 receptor inhibitor should be minimized to the extent possible to limit the risk of bleeding.*	I-C
Anticoagulant therapy with a vitamin K antagonist for patients with STEMI and asymptomatic LV mural thrombi.	IIa-C
Anticoagulant therapy for patients with STEMI and anterior apical akinesis or dyskinesis.	IIb-C
Targeting vitamin K antagonist therapy to a lower INR (e.g. 2.0–2.5 in patients receiving DAPT).	IIb-C
Selected risk factors for bleeding in patients with ACS	
Advanced age (>75 years)	
Female sex	
HF or shock	
Diabetes mellitus	
Body size	
History of GI bleeding	
Presentation with STEMI or NSTEMI (vs UA)	
Severe renal dysfunction (CrCl <30 mL/min)	
Elevated white blood cell count	
Anaemia	
Use of fibrinolytic therapy	
Invasive strategy	
Inappropriate dosing of antithrombotic medications	
Chronic oral anticoagulant therapy	

ACS indicates acute coronary syndrome; CrCl, creatinine clearance; GI, gastrointestinal; HF, heart failure; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction; and UA, unstable angina.
* Individual circumstances will vary and depend on the indications for triple therapy and the type of stent placed during PCI. After this initial treatment period, consider therapy with a vitamin K antagonist plus a single antiplatelet agent. For patients treated with fibrinolysis, consider triple therapy for 14 days, followed by a vitamin K antagonist plus a single antiplatelet agent.
2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol.* 2013;**61**:e78–140 with permission from Elsevier.

Pericarditis

Pericardial effusions are more common after anterior MI and when congestive failure is present. Usually of no prognostic significance, although it may take months to resorb.

Pericarditis may develop and resolve as late as 6 weeks after MI. The pain typically radiates to either edge of the trapezius ridge and becomes worse with deep inspiration. Anticoagulants are stopped, if not necessary, and aspirin is the treatment of choice (Table 29.26). In non-responders, even to higher doses of aspirin, colchicine 0.6 mg/12 h po, acetaminophen, or narcotic analgesics may be given. NSAIDs and steroids have been associated with increased risk of scar thinning and myocardial rupture. **Dressler syndrome** (fever, leucocytosis, elevated ESR, and pericarditis with effusion due to anti-cardiac antibodies), 1–8 weeks after non-reperfused MIs, is now rarely seen.

Table 29.26 ACCF/AHA 2013 GL on STEMI. Management of pericarditis after STEMI

Aspirin	I-B
Acetaminophen, colchicine, or narcotic analgesics if aspirin, even in higher doses, is not effective.	IIb-C
Glucocorticoids and non-steroidal anti-inflammatory drugs are potentially harmful for treatment of pericarditis after STEMI.	III-B

2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2013;**61**:e78–140 with permission from Elsevier.

Tachyarrhythmias

The development of **atrial fibrillation** carries a worse prognosis and predicts increased mortality, regardless of the type of MI, especially when it develops in patients without a history of AF before MI,[120] or more than 1 month after MI (Table 29.27).[121] In haemodynamic instability, DC cardioversion is indicated. For recurrent episodes or for rate control, IV amiodarone, beta blockade, diltiazem or verapamil, and digoxin (in the presence of LV dysfunction) may be used.

Ventricular arrhythmias—acute phase management

VPBs are of no prognostic significance and should not be treated with antiarrhythmic drugs. **Accelerated idioventricular rhythm** is a slow form of ventricular tachycardia (<100 bpm) which characteristically follows myocardial infarction. It tends to remain stable, usually does not give rise to ventricular fibrillation, and does not require antiarrhythmic treatment. It is the most common arrhythmia during primary PCI (42%).[122] In acute myocardial infarction, NSVT during the first 24 h is frequent (45% in patients without thrombolysis and up to 75% in reperfused patients).[122,123] NSVT during the first 13[124] to 24 hours[123] after acute MI does not carry a prognostic significance. Ventricular fibrillation may be seen during the acute phase (up to 48 hours) due to ischaemia and, although it indicates a higher risk of in-hospital mortality, it does not predict future arrhythmia episodes[125] (Table 29.28 and Figure 29.5). Sustained monomorphic VT indicates pre-existing scar.

VF or unstable, sustained VT requires DC cardioversion. Comatose survivors of out-of-hospital cardiac arrest with electrocardiographic criteria for STEMI on the post-resuscitation ECG should be transfered for immediate coronary angiography and intervention (ESC 2015 GL on VA and SCD, I-B).
Stable VT or unstable VT/VF refractory to cardioversion:

- IV amiodarone (5 mg/kg bolus) and repeat of cardioversion if unstable VT/VF
- Intubation may be necessary in refractory VF/VT
- IV sotalol, procainamide, and overdrive pacing may be also considered.

In haemodynamically unstable patients with recurrent VT or VF despite optimal therapy, an LVAD or extracorporeal life support should be considered (ESC 2015 GL on VA and SCD, IIa-B).

Incessant VT or electrical storm:
Urgent revascularization, IV beta blockade, and IV amiodarone (5 mg/kg over 10 minutes, followed, if necessary, by repeat doses or constant infusion; total dose <2.2 g over 24 h) and electrolyte correction are indicated.[126] IV procainamide may be also considered. In electrical storm, beta blockers are especially indicated.[126,127] The short-acting esmolol is preferred in the presence of reduced LV function, with close monitoring due to the risk of cardiogenic shock.

Normalization of serum K to >4 mEq/L and Mg >2 mEq/L is also recommended.

Ventricular arrhythmias—chronic phase (>48 h) management

Compared with the pre-reperfusion era, late ventricular tachyarrhythmias are now less common, but they are still documented in approximately 20% of patients with recent MI and EF <0.40 within the next 2 years.[128] In the era of reperfusion and use of beta blockers, NSVT after MI may not be an independent predictor of mortality, especially after ejection fraction is taken into account.[128–131]

VF may, or may not, respond to revascularization, and reassessment by electrophysiology study is indicated 3 months after the intervention.[132] Monomorphic VT does not respond to revascularization.[133] Sudden unexpected death is highest in the first month after myocardial infarction, but recurrent

myocardial infarction or myocardial rupture account for a high proportion of sudden unexpected deaths during this period, whereas arrhythmic death may be more likely subsequently.[134] Perhaps, this is why prophylactic ICD in patients with reduced LVEF did not reduce mortality 6–40 days after MI (DINAMIT and IRIS trials)[135,136] Both DINAMIT and IRIS, however, had excluded patients with sustained ventricular arrhythmias during this period, and sudden cardiac death was reduced, despite no effect on overall mortality in the DINAMIT trial. Post-MI patients with LVEF ≤40% may benefit from early ICD implantation, especially if sustained monomorphic VT (CL ≥200 ms, lasting >10 s) is induced at electrophysiology study performed 9 days after the event.[137] Programmed stimulation performed as early as 3 days after MI in patients with LVEF ≤40% induces fast VT (CL >200 ms) in up to 1/3 of patients, and may identify patients at high risk for spontaneous tachyarrhythmia and sudden cardiac death.[138] It is being considered by the ESC 2015 GL on VA and SCD in the early phase of MI in patients with LVEF<40% (IIb-B) or syncope (IIa-C), whereas other non-invasive tests such as T-Wave alternans or signal-averaged ECG are not (III-B). The recent ACC/AHA 2013 GL on STEMI now recommend ICD implantation in patients who spontaneously develop sustained VT/VF >48 h after STEMI, provided the arrhythmia is not due to transient or reversible ischaemia, re-infarction, or metabolic abnormalities (Table 29.28). Patients with an initially reduced LVEF who are possible candidates for ICD therapy should undergo re-evaluation of LVEF ≥40 days after discharge. Amiodarone might be considered for relief of arrhythmia symptoms (ESC 2015 GL on VA and SCD, IIb-B) but its effect on mortality is controversial (see Chapter 56).

Current indications for ICD implantation are also discussed in Chapter 56 on ventricular arrhythmias and Chapter 32 on heart failure.

Table 29.27 ESC 2012 GL on STEMI. Management of AF

Rhythm control should be considered in patients with atrial fibrillation secondary to a trigger or substrate that has been corrected (e.g. ischaemia).	IIa-C
Acute rate control of atrial fibrillation	
Intravenous beta blockers or non-dihydropyridine CCB (e.g. diltiazem, verapamil)[c] are indicated if there are no clinical signs of acute heart failure.	I-A
Amiodarone or IV digoxin is indicated in case of rapid ventricular response in the presence of concomitant acute heart failure or hypotension.	I-B
Cardioversion	
Immediate electrical cardioversion is indicated when adequate rate control cannot be achieved promptly with pharmacological agents in patients with atrial fibrillation and ongoing ischaemia, severe haemodynamic compromise, or heart failure.	I-C
Intravenous amiodarone is indicated for conversion to sinus rhythm in stable patients with recent-onset atrial fibrillation and structural heart disease.	I-A
Digoxin (III-A), verapamil, sotalol, metoprolol (III-B) and other beta-blocking agents (III-C) are ineffective in converting recent-onset atrial fibrillation to sinus rhythm and should not be used for rhythm control (although beta blockers or digoxin may be used for rate control).	III-A/B/C

[c] Calcium antagonists should be used cautiously or avoided in patients with heart failure because of their negative inotropic effects.
ESC 2012 Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012:**33**:2569–619, by permission of Oxford University Press.

Table 29.28 Arrhythmias and conduction disturbances

ACCF/AHA 2013 GL on STEMI. ICD therapy before discharge	
Implantable cardioverter–defibrillator (ICD) therapy is indicated before discharge in patients who develop sustained VT/VF >48 h after STEMI, provided the arrhythmia is not due to transient or reversible ischaemia, reinfarction, or metabolic abnormalities.	I-B
Assessment of risk for SCD	
Patients with an initially reduced LVEF who are possible candidates for ICD therapy should undergo re-evaluation of LVEF ≥40 days after discharge.	I-B
Bradycardia, AV block, and intraventricular conduction defects	
Temporary pacing is indicated for symptomatic bradyarrhythmias unresponsive to medical treatment.	I-C
ACCF/AHA/HRS 2012 GL on device-based therapy. Recommendations for permanent pacing after the acute phase of myocardial infarction	
Persistent second-degree AV block in the His-Purkinje system with alternating bundle branch block or third-degree AV block within or below the His-Purkinje system after ST-segment elevation myocardial infarction.	I-B

(*Continued*)

Table 29.28 Continued

Transient advanced second- or third-degree infranodal AV block and associated bundle branch block. If the site of block is uncertain, an electrophysiological study may be necessary.	I-B
Persistent and symptomatic second- or third-degree AV block.	I-C
Persistent second- or third-degree AV block at the AV node level, even in the absence of symptoms.	IIb-B
Transient AV block in the absence of intraventricular conduction defects.	III-B
Transient AV block in the presence of isolated left anterior fascicular block.	III-B
New bundle branch block or fascicular block in the absence of AV block.	III-B
Persistent asymptomatic first-degree AV block in the presence of bundle branch or fascicular block.	III-B
ESC 2013 on cardiac pacing and CRT. Indications for permanent pacing in acute myocardial infarction	
In the rare cases in which AV block becomes permanent, cardiac pacing is indicated with the same recommendations presented in Chapter 65.	I-C
Cardiac pacing is not indicated after resolution of high-degree or complete AV block complicating the acute phase of myocardial infarction	III-B
ESC 2015 GL on VA and SCD.* Prevention and management of sudden cardiac death associated with acute coronary syndromes: in-hospital phase.	
Beta-blockers for recurrent polymorphic VT.	I-B
IV amiodarone for polymorphic VT.	I-C
Immediate electrical cardioversion or defibrillation in sustained VT or VF.	I-C
Urgent coronary angiography followed, when indicated, by revascularization in recurrent VT or VF when myocardial ischaemia cannot be excluded.	I-C
Correction of electrolyte imbalances in recurrent VT or VF.	I-C
Oral beta-blockers during the hospital stay and continued thereafter in the absence contraindications.	IIa-B
Radiofrequency catheter ablation at a specialized ablation centre followed by the implantation of an ICD should be considered in recurrent VT, VF or electrical storms despite complete revascularization and optimal medical treatment.	IIa-C
Transvenous catheter overdrive pacing if VT is frequently recurrent despite use of anti-arrhythmic drugs and catheter ablation is not possible.	IIa-C
IV lidocaine for recurrent sustained VT or VF not responding to beta-blockers or amiodarone or in the presence of contraindications to amiodarone.	IIb-C
Prophylactic treatment with anti-arrhythmic drugs (other than beta blockers)	III-B
Temporary transvenous pacing in symptomatic for sinus bradycardia despite treatment with positive chronotropic medication.	I-C
Temporary transvenous pacing in symptomatic high-degree AV block without stable escape rhythm.	I-C
Urgent angiography in patients with symptomatic for high-degree AV block who have not received reperfusion.	I-C
Reprogramming a previously implanted ICD for recurrent inappropriate ICD therapies.	I-C
Reprogramming a previously implanted ICD to avoid unnecessary ICD shocks.	IIa-C
ICD implantation or temporary wearable defibrillator <40 days after myocardial infarction in selected patients (incomplete revascularization (inability to treat culprit or non-culprit lesions), pre-existing LVEF dysfunction, occurrence of arrhythmias >48 h after the onset of ACS, polymorphic VT or VF).	IIb-C
ICD implantation for the primary prevention of SCD is generally not indicated <40 days after myocardial infarction.	III-A

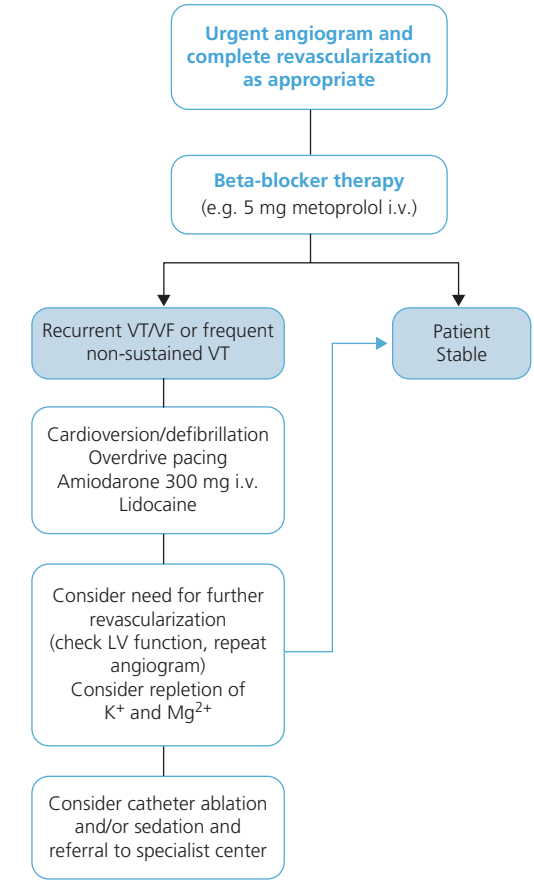
*: similar recommendations were provided by the ESC 2012 GL on STEMI.

AHA/ACC 2013 Guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2013;**61**:e78–e140 with permission from Elsevier.

ACCF/AHA/HRS 2012 focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2013;**61**:e6–75 with permission from Elsevier.

ESC 2013 Guidelines on cardiac pacing and cardiac resynchronization therapy. *Europace*. 2013;**15**:1070–118 with permission from Oxford University Press.

ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015;**36**:2793–867 with permission from Oxford University Press.



ACS = acute coronary syndromes; i.v. = intravenous; K^+ = potassium; LV = left ventricular; Mg^{2+} = magnesium; VF = ventricular fibrillation; VT = ventricular tachycardia.

Figure 29.5 ESC 2015 GL on VA and SCD. Diagnostic work-up in patients with sustained ventricular arrhythmias and ACS.

ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J.* 2015;**36**:2793–867 with permission from Oxford University Press.

Conduction disturbances

The sinus node is supplied by the right coronary (60%) or the left circumflex artery (40%). The atrioventricular node is supplied by the RCA (90%) or the left circumflex artery (10%). The bundle of His is supplied by the atrioventricular nodal branch of the RCA and partially from the septal perforators of the LAD. The right bundle branch receives most of its blood from septal perforators of the left anterior descending artery and may be through collaterals from the RCA and Cx. The left anterior fascicle is supplied by septal perforators from the LAD and is particularly susceptible to ischaemia or infarction. The left posterior fascicle is supplied by the RCA (through the AV nodal artery) and by septals of the LAD.[6]

AV block in the post-MI period is a strong predictor of cardiac death.[128] In the era of primary PCI, high-degree AV block is seen in 3.2% of patients with MI, usually inferior and more often in female patients >65 years of age, and indicates increased mortality.[139] **LBBB** does not suggest isolated LAD occlusion. In patients with LVEF<35%, **RBBB** has been associated with significantly greater scar size than LBBB and occlusion of a proximal LAD septal perforator causes RBBB.[140] In the Global Registry of Acute Coronary Events, the incidence of high-grade AV block in acute coronary syndromes was low (2.9%) and decreasing, but it carried a high risk of in-hospital death (22.7%), reflecting the severity of ACS. High-grade AV block present at the time of presentation to hospital (vs occurring in-hospital) and early (<12 h) percutaneous coronary intervention or fibrinolysis (vs >12 h or no intervention) were associated with improved in-hospital survival, whereas temporary pacemaker insertion was not.[141]

Anterior MI PR prolongation is often associated with a wide QRS complex (>0.12 s) with a right bundle branch block pattern. Second-degree atrioventricular block with anterior myocardial infarction is usually Mobitz

type II, secondary to block in the His–Purkinje system. Complete heart block may occur abruptly during the first 24 h after myocardial infarction and is almost always preceded by the development of right bundle branch block with right or left axis deviation and QR pattern in lead V_1.

Inferior MI Sinus bradycardia and various degrees of AV block (including complete) can occur within the first 2 h, due to increased parasympathetic tone, and resolve within 24 h. Complete AV block complicating inferior MI is usually at the node level, i.e. with a narrow complex escape rhythm. A wide QRS escape rhythm suggests additional LAD disease. Bradycardia during the first 24 h responds to atropine. After the first 24 h, symptomatic conduction disturbances require temporary pacing (Tables 29.28). Prompt opening of the infarcted vessel is indicated in AV block, especially when due to inferior infarction, even in the case of late (>12 h) presentation (ESC 2015 GL on VA and SCD, I-C).

Transcutaneous patches are recommended for all old, or new, conduction disturbances, apart from isolated first-degree or fascicular block.

Permanent pacing is considered for disturbances that persist beyond 2 weeks after the MI (see Chapter 65 on bradyarrhythmias).

Specific patient groups

Recommendations for the management of patients with renal failure are presented in Table 29.29. Chronic kidney disease (defined as estimated creatinine clearance [CrCl] <60 mL/min) has a prevalence of 30.5% among patients presenting with ST-segment–elevation myocardial infarction.[142] Recommendations on diabetes are presented in Table 29.30. See also Chapter 28 for recommendations in ACS in general. The management of patients on warfarin or NOACs who are treated with PCI is presented in Chapter 28.

Table 29.29 ESC 2012 GL on STEMI. Initial dosing of antithrombotic agents in patients with chronic kidney disease (estimated creatinine clearance <60 mL/min)

Aspirin	No dose adjustment.
Clopidogrel	No dose adjustment.
Prasugrel	No dose adjustment. No experience with end-stage renal disease/dialysis.
Ticagrelor	No dose adjustment. No experience with end-stage renal disease/dialysis.
Enoxaparin	No adjustment of bolus dose. Following thrombolysis, in patients with creatinine clearance <30 mL/min, the SC doses are given once every 24 h.
Unfractionated heparin	No adjustment of bolus dose.
Fondaparinux	No dose adjustment. No experience in patients with end-stage renal disease or dialysis patients.
Bivalirudin	◆ In patients with moderate renal insufficiency (GFR 30–59 mL/min), a lower initial infusion rate of 1.4 mg/kg/h should be given. The bolus dose should not be changed. ◆ In patients with severe renal insufficiency (GFR <30 mL/min) and in dialysis-dependent patients, bivalirudin is contraindicated.
Abciximab	No specific recommendation. Careful consideration of bleeding risk.
Eptifibatide	◆ In patients with moderate renal insufficiency (GFR ≥30 to <50 mL/min), an IV bolus of 180 micrograms should be administered, followed by a continuous infusion dose of 1.0 micrograms/kg/min for the duration of therapy. ◆ In patients with severe renal insufficiency (GFR <30 mL/min), eptifibatide is contraindicated.
Tirofiban	In patients with severe renal insufficiency (GFR <30 mL/min), the infusion dose should be reduced to 50%.

ESC 2012 Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J.* 2012:**33**:2569–619, by permission of Oxford University Press.

Table 29.30 ESC 2012 GL on STEMI. Management of hyperglycaemia in ST segment elevation myocardial infarction

Measurement of glycaemia at initial evaluation in all patients and repeated in patients with known diabetes or hyperglycaemia.	I-C
Plans for optimal outpatient glucose control and secondary prevention before discharge.	I-C
In the acute phase, maintain glucose ≤11.0 mmol/L (200 mg/dL) while avoiding <5 mmol/L (<90 mg/dL). This may require a dose-adjusted insulin infusion with monitoring of glucose, as long as hypoglycaemia is avoided.	IIa-B
Fasting glucose and HbA1c and, in some cases, a post-discharge oral glucose tolerance test should be considered in patients with hyperglycaemia but without a history of diabetes.	IIa-B
Routine glucose-insulin potassium infusion is not indicated.	III-A

ESC 2012 Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J.* 2012:**33**:2569–619, by permission of Oxford University Press.

In **pregnant women** with acute MI, there is frequent involvement of LAD and left main system, and LV dysfunction and mortality are high.[143] Acute MI during pregnancy is usually due to coronary dissection (43%), followed by atherosclerotic disease (27%) and thrombosis in the absence of atherosclerosis (17%).[143] Thus, blinded fibrinolysis is not recommended. In high-risk patients, primary PCI is the treatment of choice (ESC GL on pregnancy 2011, I-C).[144] Apart from heparin and aspirin, clopidogrel may also be used, but data on their safety are limited.

Discharge

Stable patients can be transferred from the CCU after 12–24 h, and mobilization is allowed. Uncomplicated MIs may be discharged after 3 days after reperfusion (Table 29.31), and physical activity is gradually resumed.[145] Stable patients following primary PCI can be safely discharged as early as 48 h following reperfusion.[146] Echocardiography for assessment of LVEF is essential. With proper reperfusion, significant LVEF improvement may be seen 1 month after the event.[147] Exercise testing or myocardial perfusion imaging or dobutamine echocardiography with baseline abnormalities that compromise ECG interpretation may be performed as early as 4 days after MI in stable patients (Table 29.32). A positive test as well as diabetes mellitus, LVEF <0.40, CHF, prior revascularization, or life-threatening ventricular arrhythmias are indications for coronary angiography in non-reperfused patients or in patients with fibrinolysis who did not have angiography. Sexual activity is allowed ≥1 week after uncomplicated MI, provided that the patient has no symptoms during mild to moderate physical activity (AHA/ESC 2013 consensus document on sexual counselling, IIa-C).[148] Following a STEMI, the risk of subsequent cardiovascular events is highest in the first year, recurrent

Table 29.31 ESC 2012 GL on STEMI. Logistical issues for hospital stay

All hospitals participating in the care of STEMI patients should have a coronary care unit equipped to provide all aspects of care for STEMI patients, including treatment of ischaemia, severe heart failure, arrhythmias, and common co-morbidities.	I-C
Length of stay in the coronary care unit	
Patients undergoing uncomplicated successful reperfusion therapy should be kept in the coronary care unit for a minimum of 24 h, after which they may be moved to a step-down monitored bed for another 24–48 h.	I-C
Transfer back to a referring non-PCI hospital	
Early transfer (same day) may be considered in selected, low-risk patients after successful primary PCI without observed arrhythmia.	IIb-C
Hospital discharge	
Early discharge (after approximately 72 h) is reasonable in selected low-risk patients if early rehabilitation and adequate follow-up are arranged.	IIb-B

ESC 2012 Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012:**33**:2569–619, by permission of Oxford University Press.

Table 29.32 ACCF/AHA 2013 GL on STEMI. Risk-assessment and post-hospitalization care

Use of non-invasive testing for ischaemia before discharge	
Non-invasive testing for ischaemia before discharge to assess the presence and extent of inducible ischaemia in patients with STEMI who have not had coronary angiography and do not have high-risk clinical features for which coronary angiography would be warranted.	I-B
Non-invasive testing for ischaemia before discharge to evaluate the functional significance of a non-infarct artery stenosis previously identified at angiography.	IIb-C
Non-invasive testing for ischaemia might be considered before discharge to guide the post-discharge exercise prescription.	IIb-C
Post-hospitalization plan of care	
Post-hospital systems of care designed to prevent hospital readmissions should be used to facilitate the transition to effective, coordinated outpatient care for all patients with STEMI.	I-B
Exercise-based cardiac rehabilitation/secondary prevention programmes are recommended for patients with STEMI.	I-B
A clear, detailed, and evidence-based plan of care that promotes medication adherence, timely follow-up with the healthcare team, appropriate dietary and physical activities, and compliance with interventions for secondary prevention should be provided to patients with STEMI.	I-C
Encouragement and advice to stop smoking and to avoid secondhand smoke should be provided to patients with STEMI.	I-A

AHA/ACC 2013 Guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2013;**61**:e78–e140 with permission from Elsevier.

MI in 10% of patients with an approximate cardiovascular mortality of 5%, but remains elevated at least 4 years after MI.[149] A left dominant coronary artery system is associated with a significantly increased risk of 30-day mortality and early reinfarction after STEMI. After surviving the first 30 days post-STEMI, coronary vessel dominance had no influence on long-term outcome.[150]

Chronic therapy

Smoking cessation, loss of excessive weight, regular exercise, and cardiac rehabilitation offer sustained mortality benefits (see Chapter 30 on stable CAD).

Aspirin (75–100 mg) should be continued indefinitely (Table 29.33). A **P2Y12** inhibitor is continued for at least one year (ACCF/AHA 2013 GL on STEMI) after stenting, regardless of whether a DES or a BMS was used (ESC 2014 GL on revascularization and ACC/AHA 2016 update on duration of DAPT). Depending on the condition of the patient DAPT duration may be restricted to 6 months or extended beyond 12 months. Following DES, continuation beyond 12 months may also be considered in certain cases (bifurcation stenting, long stents, etc.). In patients with a myocardial infarction 1–3 years previously, and high risk for ischaemic events, treatment with ticagrelor significantly reduced the risk of cardiovascular death, myocardial infarction, or stroke and increased the risk of major bleeding over a 33-month follow-up. A dose of 60 mg bd had a better benefit-risk profile than 90 mg bd (PEGASUS-TIMI 54).[151] Similar conclusions about the benefit of extended dual antiplatelet therapy without any excess in fatal or intracranial bleeding in patients with a previous MI were reported by other sudies.[152,153] Gastric protection with a proton pump inhibitor is given to patients at high risk of bleeding. In selected patients who receive aspirin and clopidogrel, low-dose ***rivaroxaban*** may be considered if the patient is at low bleeding risk (ESC IIb-B).[154] ***Vorapaxar***, an inhibitor of the protease-activated receptor PAR-1 through which thrombin activates platelets, reduces the risk of major cardiovascular events when added to aspirin and clopidogrel, and particularly in diabetics, but at increased risk of bleeding.[155,156] It is FDA-approved for secondary prevention in patients with a history of MI or peripheral arterial disease, but not a previous stroke or TIA (see Chapter 30). If ***oral anticoagulants*** are indicated they may be combined with aspirin and thienopyridines but at an increased risk of bleeding. In patients with a clear indication for oral anticoagulation (eg atrial fibrillation with CHA2DS2-VASc Score ≥2 or mechanical valve prosthesis), oral anticoagulation must be implemented in addition to antiplatelet therapy (ESC 2012 I-C), but the duration of dual antiplatelet therapy should be minimized to reduce bleeding risk. The lowest efficacious INR (2–2.5) should be targeted. In patients with left ventricular thrombus, anticoagulation should be instituted for a minimum of 3 months (ESC 2012 IIa-B).

Angiotensin-converting enzyme inhibitors are probably indicated in all patients, regardless of the presence of reduced LV function,[157] and especially in reduced LVEF. **Angiotensin II receptor blockers** are used when ACE inhibitors are not tolerated.[158] In the absence of severe renal dysfunction (creatinine >2.5 mg/dL) or hyperkalaemia, post-myocardial infarction patients with an ejection fraction of less than 40% or heart failure should receive an **aldosterone antagonist**,[159] such as eplerenone. Steroids or NSAIDs, given early after MI, can cause tissue thinning and MI expansion. **Statins** provide substantial reductions in mortality as well as in non-fatal ischaemic events (see Chapter 30). Polypill strategies (i.e. combining aspirin, a statin, and an ACE inhibitor) may improve adherence to medication.[160] The relative benefit of **beta blockers** after myocardial infarction, in the context of more aggressive revascularization, is less clear, but these agents are recommended for indefinite oral therapy when the haemodynamic condition after MI has stabilized. Early trials have indicated that metoprolol, propranolol, and timolol unequivocally reduce mortality after MI,[161] and this was reconfirmed by a recent data analysis.[162] They may not confer a survival benefit in patients with a remote MI (> 1 year),[163]

Table 29.33 Long-term therapy

ACCF/AHA 2013 GL on STEMI. Routine medical therapies	
Beta blockers	
Oral beta blockers in the first 24 h in patients without: signs of heart failure, evidence of a low output state, increased risk for cardiogenic shock,* PR interval >0.24 s, second- or third-degree AV block, active asthma, or reactive airway disease.	I-B
During and after hospitalization in the absence of contraindications.	I-B
Patients with early contraindications within the first 24 hours of STEMI should be re-evaluated for subsequent eligibility.	I-C
Beta blockers IV at presentation to patients without contraindications and with hypertension or ongoing ischaemia.	IIa-B
Renin–angiotensin–aldosterone system inhibitors	
ACE inhibitor within the first 24 h to all patients with STEMI with anterior location, HF, or LVEF <0.40, unless contraindicated.	I-A

(*Continued*)

Table 29.33 Continued

ARB to patients who have indications for, but are intolerant of, ACE inhibitors.	I-B
An aldosterone antagonist to patients with no contraindications who are already receiving an ACE inhibitor and beta blocker and who have LVEF ≤0.40 and either symptomatic HF or have diabetes mellitus.	I-B
ACE inhibitors for all patients with STEMI and no contraindications.	IIa-A
Lipid management	
High-intensity statin therapy should be initiated or continued in all patients with STEMI and no contraindications to its use.	I-B
Obtain a fasting lipid profile in patients with STEMI, preferably within 24 h of presentation.	I-C

ACCF/AHA 2013 GL on STEMI. Selected routine medical therapies

Therapy	Indications	Dose/administration	Avoid/caution
Beta receptor antagonists	◆ Oral: all patients without contraindication ◆ IV: patients with refractory hypertension or ongoing ischaemia without contraindication	Individualize: ◆ Metoprolol tartrate 25–50 mg every 6–12 h orally, then transition over next 2–3 d to twice daily dosing of metoprolol tartrate or to daily metoprolol succinate; titrate to daily dose of 200 mg as tolerated ◆ Carvedilol 6.25 mg twice daily, titrate to 25 mg twice daily, as tolerated ◆ Metoprolol tartrate IV 5 mg every 5 min, as tolerated, up to three doses; titrate to heart rate and BP	◆ Signs of HF ◆ Low output state ◆ Increased risk of cardiogenic shock ◆ Prolonged first-degree or high-grade AV block ◆ Reactive airways disease
ACE inhibitors	◆ For patients with anterior infarction, post-MI LV systolic dysfunction (EF ≤0.40) or HF ◆ May be given routinely to all patients without contraindication	Individualize: ◆ Lisinopril 2.5–5 mg/d to start; titrate to 10 mg/d, or higher, as tolerated ◆ Captopril 6.25–12.5 mg three times/d to start; titrate to 25–50 mg three times/d as tolerated ◆ Ramipril 2.5 mg twice daily to start; titrate to 5 mg twice daily as tolerated ◆ Trandolapril test dose 0.5 mg; titrate up to 4 mg daily as tolerated	◆ Hypotension ◆ Renal failure ◆ Hyperkalaemia
ARB	◆ For patients intolerant of ACE inhibitors	◆ Valsartan 20 mg twice daily to start; titrate to 160 mg twice daily, as tolerated	◆ Hypotension ◆ Renal failure ◆ Hyperkalaemia
Statins	◆ All patients without contraindications	◆ High-dose atorvastatin 80 mg daily	◆ Caution with drugs metabolized via *CYP3A4*, fibrates ◆ Monitor for myopathy, hepatic toxicity ◆ Combine with diet and lifestyle therapies ◆ Adjust dose as dictated by targets for LDL cholesterol and non–HDL cholesterol reduction

ESC 2012 GL on STEMI. Routine therapies in the acute, subacute, and long-term phase of ST segment elevation myocardial infarction

Active smokers with STEMI must receive counselling and be referred to a smoking cessation programme.	I-B
Each hospital participating in the care of STEMI patients must have a smoking cessation protocol.	I-C
Exercise-based rehabilitation	I-B
Antiplatelet therapy with low dose aspirin (75–100 mg) indefinitely after STEMI.	I-A
In patients who are intolerant to aspirin, clopidogrel as an alternative to aspirin.	I-B
DAPT with a combination of aspirin and prasugrel or aspirin and ticagrelor is recommended (over aspirin and clopidogrel) in patients treated with PCI.	I-A
DAPT with aspirin and an oral ADP receptor antagonist must be continued for up to 12 months after STEMI, with a strict minimum of:	I-C

(*Continued*)

Table 29.33 Continued

◆ 1 month for patients receiving BMS	I-C
◆ 6 months for patients receiving DES	IIb-B
In patients with left ventricular thrombus, anticoagulation for a minimum of 3 months.	IIa-B
In patients with a clear indication for oral anticoagulation (e.g. atrial fibrillation with CHA_2DS_2-VASc score ≥2 or mechanical valve prosthesis), oral anticoagulation in addition to antiplatelet therapy.	I-C
If patients require triple antithrombotic therapy, combining DAPT and OAC, e.g. because of stent placement and an obligatory indication for OAC, the duration of dual antiplatelet therapy should be minimized to reduce bleeding risk.	I-C
In selected patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) if the patient is at low bleeding risk.	IIb-B
DAPT should be used up to 1 year in patients with STEMI who did not receive a stent.	IIa-C
Gastric protection with a proton pump inhibitor for the duration of DAPT therapy in patients at high risk of bleeding.	IIa-C
Oral treatment with beta blockers during hospital stay and continued thereafter in all STEMI patients without contraindications.	IIa-B
Oral treatment with beta blockers is indicated in patients with heart failure or LV dysfunction.	I-A
Intravenous beta blockers must be avoided in patients with hypotension or heart failure.	III-B
Intravenous beta blockers at the time of presentation in patients without contraindications, with high blood pressure, tachycardia, and no signs of heart failure.	IIa-B
A fasting lipid profile must be obtained in all STEMI patients as soon as possible after presentation.	I-C
Initiate or continue high-dose statins early after admission in all STEMI patients without contraindication or history of intolerance, regardless of initial cholesterol values.	I-A
Reassessment of LDL cholesterol after 4–6 weeks to ensure that a target value of ≤1.8 mmol/L (70 mg/dL) has been reached.	IIa-C
Verapamil for secondary prevention in patients with absolute contraindications to beta blockers and no heart failure.	IIb-B
ACE inhibitors, starting within the first 24 h of STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes, or an anterior infarct.	I-A
An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure or LV systolic dysfunction, particularly those who are intolerant of ACE inhibitors.	I-B
ACE inhibitors in all patients in the absence of contraindications.	IIa-A
Aldosterone antagonists, e.g. eplerenone, in patients with an ejection fraction ≤40% and heart failure or diabetes, provided no renal failure or hyperkalaemia.	I-B

* Risk factors for cardiogenic shock (the greater the number of risk factors present, the higher the risk of developing cardiogenic shock) are age >70 years, systolic BP <120 mmHg, sinus tachycardia >110 bpm or heart rate <60 bpm, and increased time since onset of symptoms of STEMI.
ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AV, atrioventricular; BP, blood pressure; CO_2, carbon dioxide; EF, ejection fraction; HDL, high density lipoprotein; HF, heart failure; IV, intravenous; LDL, low density lipoprotein; LV, left ventricular; MI, myocardial infarction; RV, right ventricular; and SBP, systolic blood pressure.
AHA/ACC 2013 Guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2013;**61**:e78–e140 with permission from Elsevier.
ESC 2012 Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012:**33**:2569–619, by permission of Oxford University Press.

but this observation should be considered in the context of a documented increased risk for up to 4 years after an MI.[149] COPD is not a contraindication for their use.[164]

Non-dihydropyridine calcium antagonists may be used when necessary (contraindications to beta blockers and no heart failure). ***Non-steroidal anti-inflammatory*** drugs (NSAIDs), with as little as 3 days of use, increase the risk of bleeding, especially in patients on 2 or 3 antithrombotic regiments.[165] Influenza vaccination should be provided to all patients with CAD. **Chelation** therapy is not recommended. There has been some recent evidence that it might be beneficial in combination with high-dose vitamins in post-MI patients.[166]

The ACC/AHA and ESC recommendations for risk reduction and secondary prevention are discussed in Chapter 30 on stable CAD.

Stem cell transplantation

Since the discovery that the heart is not a post-mitotic organ and myocardial tissue regeneration is possible, human embryonic stem cells, skeletal myoblasts, and adult

bone marrow stem cells have been used to limit infarct size. Human embryonic stem cells form heart teratomas and have to be differentiated into cardiac progenitor cells prior to transplantation, and immune rejection must be prevented. Transplanted autologous skeletal myoblasts do not form electromechanical connections with host cardiomyocytes, and thus reentrant ventricular arrhythmias can occur. Autologous bone marrow mononuclear cells that mainly contain haematopoietic, mesenchymal, and endothelial stem cells do not have these side effects, and several trials have used them for myocardial regeneration after myocardial infarction. Increases in LVEF and reduction of infarct size have been shown, but mortality benefits are not established.[167,168] Stem cell transplantation is a promising therapeutic modality, but several questions regarding clinical efficacy, mechanism of action, optimal timing of transplantation, and type of cells used remain.

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Chapter 30

Stable coronary artery disease

Definition

Stable coronary artery disease is a non-acute condition due to coronary artery atherosclerosis of epicardial coronary arteries and/or microcirculation, and is diagnosed following a diagnostic ischaemia test or an acute coronary syndrome.

Presentation

Patients with coronary artery disease (CAD) may be asymptomatic or present with angina pectoris or an acute coronary syndrome (unstable angina or MI), congestive heart failure, cardiac arrhythmias, or sudden death. **Angina pectoris** is characterized by substernal discomfort, heaviness, or a pressure-like feeling, which may radiate to the jaw, shoulder, back, or arm. It does not resemble localized, stabbing pain. These symptoms are usually brought on by exertion, emotional stress, cold, or a heavy meal and are relieved by rest or nitrates (Table 30.1). Angina equivalents are shortness of breath on exertion (SOBOE), epigastric discomfort, fatigue, or faintness, particularly in elderly patients. Pain that is stabbing, positional, or reproducible with palpation is usually non-cardiac.

Table 30.1 Grading of angina pectoris by the Canadian Cardiovascular Society classification system

Class I
Ordinary physical activity does not cause angina, such as walking, climbing stairs. Angina (occurs) with strenuous, rapid, or prolonged exertion at work or recreation.
Class II
Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals or in cold, in wind, or under emotional stress, or only during the few hours after awakening. Angina occurs on walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal condition.
Class III
Marked limitations of ordinary physical activity. Angina occurs on walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace.
Class IV
Inability to carry on any physical activity without discomfort—anginal symptoms may be present at rest.

Campeau L. The Canadian Cardiovascular Society grading of angina pectoris revisited 30 years later. *Can J Cardiol*. 2002;**18**:371–9 with permission from Elsevier

Physical examination

May be unremarkable. Hypertension, xanthelasma, decreased peripheral pulses, carotid or renal artery bruits, and abdominal aortic aneurysm may be present. **History** may reveal smoking, diabetes, or family history of MI before age of 60 years.

Cardiac auscultation may reveal S_3 or S_4 or MR, particularly during an episode of chest pain (LV or papillary muscle dysfunction).

Crepitations over the lung bases in ischaemic heart failure.

Investigations

Basic biochemistry are essential **(FBC, lipids, glucose, creatinine, markers of myocardial damage** as well as **thyroid function tests** and **oral glucose tolerance test** if clinically indicated) (Table 30.2 and Figure 30.1).[1,2] In patients with established coronary artery disease, the oral glucose tolerance test identifies the largest number of patients with previously undiagnosed diabetes compared to fasting plasma glucose and glycated haemoglobin (HbA1c).[3] High-sensitivity assayed troponin I, with values above the limit of detection in about 75% of a general, middle-aged population is a cardiac-specific marker of global cardiovascular risk.[4] Young patients with early CAD should be also investigated for the possibility of familial hypercholesterolaemia[5]

Diagnostic tests for the detection of myocardial ischaemia are most useful in patients with an intermediate pretest probability of CAD (Bayes theorem) and are recommended for all patients with an intermediate or high probability of CAD (Table 30.3, Figures 30.1, 30.2, and 30.3, and Figure 27.2.) Sensitivity and specificity data of used tests are presented in Table 30.4. When considering cardiac imaging, the risks and benefits of the test should be taken into account.[6]

12-lead resting ECG is essential. It is normal in approximately half of patients with stable angina, even with severe CAD. ST–T wave changes, Q waves, LV hypertrophy, LBBB, AV block, AF, and ventricular arrhythmias may be present and are associated with worse prognosis. During an episode of angina pectoris, 50% of patients with normal

findings on resting electrocardiography develop ECG abnormalities, usually ST–T depression.

Chest X-ray is indicated in suspected heart failure, valvular heart disease, pericardial disease or aortic dissection/aneurysm, or clinical evidence of pulmonary disease.

Echocardiography LV function is the major predictor of long-term survival in patients with CAD, and LVESD is the best predictor of survival after MI. MR or other concomitant abnormalities may be seen. Correspondence of LV segments with coronary arteries is presented in Figure 30.4.

Exercise treadmill test is indicated in all patients with angina or intermediate pretest probability of CAD (Table 30.5). All stress tests are contraindicated within 2 days after acute MI, in severe AS, and decompensated heart failure. Exercise treadmill test is non-diagnostic in patients with LBBB, WPW syndrome, paced rhythm, intraventricular conduction delay, and digoxin therapy. Due to low sensitivity and specificity, the test is of less prognostic value in low-risk populations such as women. However, exercise testing can be still used as the initial diagnostic strategy in symptomatic women with suspected CAD.[7] The use of myocardial perfusion imaging in this clinical setting should be reserved for those with abnormal, equivocal, or non-diagnostic studies.

The **Duke treadmill score** incorporates exercise capacity, ST segment deviation, and angina as major risk determinants. The score is calculated using the following formula:

> Exercise time in minutes – (5 × the maximum ST segment deviation in millimetres) – (4 × the angina index [0, no pain; 1, angina; and 2, angina that caused discontinuation of the test]).

Low risk (≥5%) indicates a 97% 5-year survival, moderate risk (–10 to 4) 91%, and high risk (≤–11) 72% survival. Other risk factor determinants include extensive and prolonged ST segment depression, transient ST segment elevation, abnormal heart rate recovery, and delayed systolic blood pressure response to exercise. Stress test-induced ST elevation in lead aVR is highly suggestive of left main or ostial LAD disease.[8] The **exercise stress test is terminated** for one of the following reasons:

- Symptom limitation, e.g. pain, fatigue, dyspnoea, and claudication
- Combination of symptoms, such as pain with significant ST changes
- Marked ST depression (>2 mm ST depression can be taken as a relative indication for termination and >4 mm as an absolute indication to stop the test)
- ST elevation ≥1 mm
- Significant arrhythmia
- Sustained fall in systolic blood pressure >10 mmHg
- Marked hypertension (>250 mmHg systolic or >115 mmHg diastolic)
- Achievement of maximum predicted heart rate.

Stress echocardiography The most popular test is dobutamine stress echocardiography (DSE) which is more specific but less sensitive, than perfusion imaging for detection of ischaemia. Both **ischaemia** and myocardial viability can be assessed. Life-threatening events, mainly ventricular arrhythmias, are rare (0.01%)[9] and the prognostic significance of induced VT remains uncertain. The diagnostic accuracy of DSE is reduced in patients with poor acoustic window (obese, COPD), severe LV dysfunction, prior cardiac surgery, and severe hypertension. Detection of ≥3 dobutamine-induced dysfunctional segments indicates high risk.[2]

Myocardial contrast echocardiography is a useful modality for assessment of myocardial perfusion. **Single-photon emission tomography (SPECT)** is used for assessment of exercise myocardial perfusion (Table 30.5). Technetium or thallium (better for detection of myocardial viability) are used, and there is a relatively good correlation of standardized left ventricular segments with each coronary artery.[10] Adenosine or dipyridamole nuclear perfusion imaging is the preferred test for patients with LBBB or ventricular paced rhythm because of increased false positive findings with exercise or dobutamine echocardiography. In asthmatics, adenosine may cause bronchospasm and dipyridamole is preferred, unless the patient has significant hepatic impairment. Nuclear imaging exposes the patient to a moderate amount of ionizing radiation (approximately 15 mSv). Attenuation artefacts (obese patients and women with large breasts) decrease the specificity of nuclear testing. Global ischaemia (left main or severe multivessel disease) may also produce false negative results. Because higher myocyte fraction is needed to maintain contractile reserve than to achieve radiotracer uptake, nuclear imaging has higher sensitivity but lower specificity than dobutamine stress echocardiography in the detection of viability. However, the predictive accuracy of dobutamine stress echocardiography for functional recovery is higher than SPECT.[11]

Magnetic resonance imaging is an imaging technique that may be used for myocardial perfusion, wall motion imaging, and myocardial viability.[12] It has high spatial and temporal resolution and, apart from ischaemia, identifies non-viable scar tissue, myocarditis, and detects subendocardial ischaemia that may be missed by other tests. It can be performed in patients with stents and most orthopaedic implants. Patients with pacemakers and defibrillators may also undergo CMR under specific conditions and protocols. Following the intravenous administration of gadolinium, first-pass perfusion sequences can identify myocardial perfusion abnormalities. Low-dose dobutamine, adenosine, or

dipyridamole are used, and late gadolinium-enhancement protocols are also employed.[13]

Administration of gadolinium is contraindicated in patients with a creatinine clearance >30 mL/min due to the rare, but potentially life-threatening, complication of nephrogenic systemic fibrosis. CMR may show false positive defects related to transient dark rim artefacts in the subendocardium. If not properly recognized, such artefacts may limit the specificity of CMR perfusion imaging for detecting small subendocardial perfusion defects.[14] Recently, the possibility of CMR-induced damage of human lymphocyte DNA integrity was raised.[15] CMR requires some of the strongest and fastest switching electromagnetic gradients available in MR, exposing the patients to the highest administered energy levels. Thus, similar restrictions might apply as for X-ray based and nuclear imaging techniques in order to avoid potential carcinogenic effects.

Ambulatory ECG monitoring may also be useful in suspected arrhythmias or vasospastic angina (Table 30.1).

Coronary artery computed tomography (CCT) with multidetector scanners may visualize the coronary artery lumen and detect calcification (Table 30.5).[16] It is still limited by a high number of false positive results (up to 50% with severe calcification and coronary stents). Furthermore, its prognostic value as a substitute for conventional angiography has not been validated in clinical studies. In patients with acute chest pain, CT angiography in an experienced centre is faster to obtain than a stress test and improves diagnostic ability, albeit at an increased radiation exposure.[17,18] Recently, consideration of high-risk plaque features (positive remodelling, low <30 Hounsfield units plaque, napkin-ring sign, spotty calcium) in patients with acute chest pain but negative initial electrocardiogram and troponin, increased the likelihood of a subsequent acute coronary syndrome independent of significant CAD and clinical risk assessment (age, sex, and number of cardiovascular risk factors).[19] Doses of radiation get smaller with new scanners, i.e. 1.5–7 mSv compared to 6–7 mSv of conventional coronary angiography, and CCT with doses <1 mSv is now possible.[16,20] Limitations of CCT are high image noise in obese patients and the need of a slow sinus rhythm that usually requires IV beta blockade. CCT angiography is considered appropriate in:[21]

- Patients with low or intermediate risk or pretest probability for CAD and stable disease or acute syndromes or positive imaging tests
- For evaluation of graft patency in symptomatic patients and stenting only in the main stem and with stents >3 mm.

CCT in high-risk patients and for general screening is not considered appropriate.

In asymptomatic patients with type 1 or type 2 diabetes, the use of CCT to screen for CAD did not reduce the composite rate of all-cause mortality, nonfatal MI, or unstable angina requiring hospitalization at 4 years.[22] In symptomatic patients with suspected CAD who required noninvasive testing, a strategy of initial CCT, as compared with functional testing (exercise electrocardiography, nuclear stress testing, or stress echocardiography), did not improve clinical outcomes over a median follow-up of 2 years (PROMISE trial).[23] The presence of coronary artery calcification does not, by itself, justify coronary angiography.[24]

The detection of pulmonary nodules at cardiac computed tomographic angiography results in a small relative reduction in lung cancer mortality of 8% at 3 years, and imaging of the entire thorax might be considered during tomographic imaging of the coronary arteries or coronary calcium, although the cost effectiveness of subsequent follow-up testing is questionable.[25,26]

Positron emission tomography has high sensitivity for detection of ischaemia and myocardial viability and perhaps characterization of atherosclerotic plaques. Disadvantages are the high cost and lack of clinical verification studies for its prognostic ability. Furthermore, in clinical practice, the use of positron emission tomography may not offer additional information on myocardial viability, compared to conventional methods.[27]

Coronary angiography is indicated for diagnostic and risk stratification purposes (see Table 30.5 and discussion on risk stratification) in patients with:

- Significant angina
- High-risk clinical characteristics or non-invasive testing criteria
- LV dysfunction (LVEF <45%) or CCF
- Aborted sudden death or VT/VF
- Inconclusive non-invasive testing
- Previous CABG or PCI with recurrent symptoms or at high risk of restenosis of a prognostically important site.

Serious complications of coronary angiography, such as death, MI, or stroke, and aortic dissection or aortic valve avulsion, had been previously reported in the order of 0.1%[28] but are probably even less in modern catheter labs. For coronary lesion assessment, see section on risk stratification.

Table 30.2 Initial diagnosis and assessment

ACCF/AHA 2012 GL on stable IHD. Clinical evaluation	
History and physical examination of patients with chest pain.	I-C
Patients should be categorized as stable or unstable of high, moderate or low risk.	I-C
Resting ECG in patients without an obvious, myocardial cause of chest pain.	I-B
ESC 2013 GL on stable CAD. Non-invasive investigations	
Blood tests in assessment of patients with known or suspected SCAD in order to optimize medical therapy	
If evaluation suggests clinical instability or ACS, repeated measurements of troponin preferably using high sensitivity or ultrasensitive assays to rule out myocardial necrosis.	I-A
Full blood count including haemoglobin and white cell count.	I-B
Screening for potential T2DM with HbA1c and fasting plasma glucose. An OGTT is added if HbA1c and fasting plasma glucose are inconclusive.	I-B
Creatinine measurement and estimation of renal function (creatinine clearance).	I-B
Fasting lipid profile (including LDL)[a].	I-C
Annual control of lipids, glucose metabolism, and creatinine in all patients with known SCAD.	I-C
Assessment of thyroid function if indicated by clinical suspicion of thyroid disorder.	I-C
Liver function tests early after beginning statin therapy.	I-C
Creatine kinase measurement in patients taking statins and complaining of symptoms suggestive of myopathy.	I-C
BNP/NT-proBNP measurements in patients with suspected heart failure.	IIa-C
Resting electrocardiogram for initial diagnostic assessment of stable coronary artery disease	
A resting ECG at presentation.	I-C
A resting ECG during or immediately after an episode of chest pain suspected to indicate clinical instability.	I-C
Echocardiography	
A resting transthoracic echocardiogram for: a) exclusion of alternative causes of angina; b) identification of regional wall motion abnormalities; c) measurement of LVEF for risk stratification; d) evaluation of diastolic function.	I-B
Ultrasound of the carotid arteries performed by adequately trained clinicians to detect increased intima-media thickness and/or plaque in patients with suspected SCAD without known atherosclerotic disease.	IIa-C
Ambulatory electrocardiogram monitoring for initial diagnostic assessment of stable coronary artery disease	
Patients with SCAD and suspected arrhythmia.	I-C
Patients with suspected vasospastic angina.	IIa-C
Chest X-ray for initial diagnostic assessment of SCAD	
Patients with atypical presentation or suspicion of pulmonary disease.	I-C
Patients with suspected heart failure.	IIa-C

[a] For details please refer to dyslipidaemia guidelines.

ACS, acute coronary syndrome; BNP, B-type natriuretic peptide; HbA1c, glycated haemoglobin; OGTT, oral glucose tolerance test; LDL, low density lipoprotein; NT-proBNP, N-terminal pro B-type natriuretic peptide; SCAD, stable coronary artery disease; T2DM, type 2 diabetes mellitus.

ACCF/AHA/ACP/AATS/PCNA/SCAI/STS 2012 Guideline for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol*. 2012;**60**:e44–e164 with permission from Elsevier.

ESC 2013 guidelines on the management of stable coronary artery disease. *Eur Heart J*. 2013;**34**:2949–3003, with permission from Oxford University Press.

Table 30.3 Pretest probability of coronary artery disease in symptomatic patients according to age and sex*

ACCF/AHA 2012 GL on stable CAD

	Non-anginal chest pain		Atypical angina		Typical angina	
Age (y)	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
30–39	4	2	34	12	76	26
40–49	13	3	51	22	87	55
50–59	20	7	65	31	93	73
60–69	27	14	72	51	94	86

ESC 2013 GL on stable CAD

	Typical angina		Atypical angina		Non-anginal pain	
Age (y)	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
30–39	59[b]	28[b]	29[b]	10[a]	18[b]	5[a]
40–49	69[c]	37[b]	38[b]	14[a]	25[b]	8[a]
50–59	77[c]	47[b]	49[b]	20[b]	34[b]	12[a]
60–69	84[c]	58[b]	59[b]	28[b]	44[b]	17[b]
70–79	89[d]	68[c]	69[c]	37[b]	54[b]	24[b]
>80	93[d]	76[c]	78[c]	47[b]	65[b]	32[b]

* Each value represents the per cent with significant CAD on catheterization.
Probabilities of obstructive coronary disease shown reflect the estimates for patients aged 35, 45, 55, 65, 75, and 85 years.
[a] Groups have a pretest probability <15% and hence can be managed without further testing.
[b] Groups have a pretest probability of 15–65%. They could have an exercise ECG if feasible as the initial test. However, if local expertise and availability permit a non-invasive imaging based test for ischaemia, this would be preferable, given the superior diagnostic capabilities of such tests. In young patients, radiation issues should be considered.
[c] Groups have PTPs between 66 and 85% and hence should have a non-invasive imaging functional test for making a diagnosis of SCAD.
[d] Groups have PTP >85% and one can assume that SCAD is present. They need risk stratification only.
Reprinted from the Journal of the *American College of Cardiology*, Vol **60**, Issue 24, Fihn, Stephen D, *et al*., and the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons, 2012 ACCF/AHA/ACCF/AHA/ACP/AATS/PCNA/SCAI/STS 2012 Guideline for the diagnosis and management of
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Table 30.4 Sensitivity and specificity of non-invasive stress tests for the diagnosis of coronary artery disease

ESC 2013 GL on stable CAD

	Sensitivity (%)	Specificity (%)
Exercise ECG[a]	45–50	85–90
Exercise echocardiography	80–85	80–88
Exercise stress SPECT	73–92	63–87
Dobutamine stress echocardiography	79–83	82–86
Dobutamine stress MRI[b]	79–88	81–91
Vasodilator stress echocardiography	72–79	92–95
Vasodilator stress SPECT	90–91	75–84
Vasodilator stress MRI[b]	67–94	61–85
Coronary CTA[c]	95–99	64–83
Vasodilator stress PET	81–97	74–91

[a] Results without/with minimal referral bias.
[b] Results obtained in populations with medium-to-high prevalence of disease without compensation for referral bias.
[c] Results obtained in populations with low-to-medium prevalence of disease.
2013 ESC Guidelines on the management of stable coronary artery disease. ***Eur Heart J***. 2013;**34**:2949–3003, by permission of Oxford University Press.

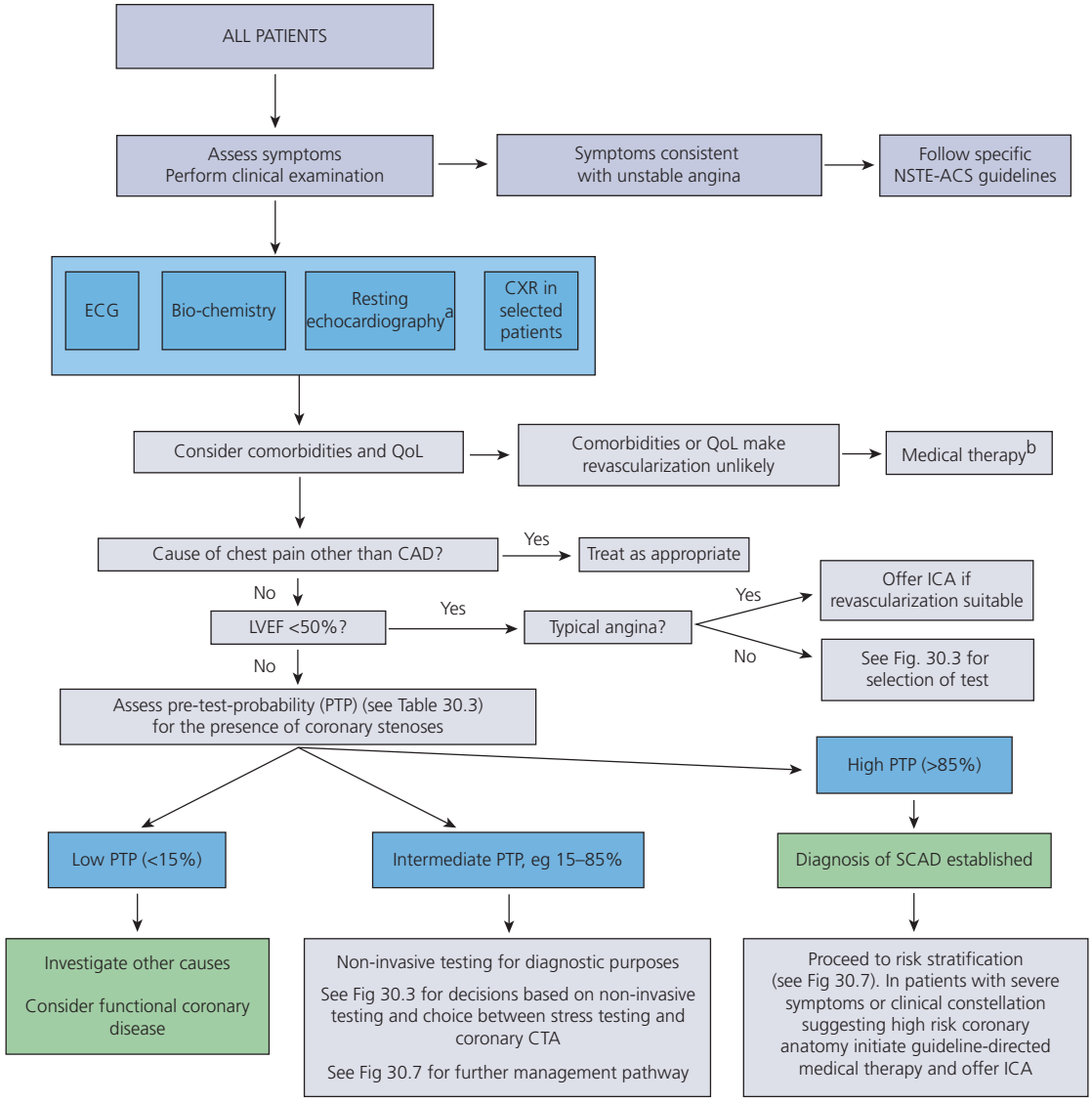


Figure 30.1 ESC 2013 GL on stable CAD. Initial diagnostic management of patients with suspected SCAD.

CAD, coronary artery disease; CTA, computed tomography angiography; CXR, chest X-ray; ECG, electrocardiogram; ICA, invasive coronary angiography; LVEF, left ventricular ejection fraction; PTP, pre-test probability; SCAD, stable coronary artery disease.

[a] May be omitted in very young and healthy patients with a high suspicion of an extracardiac cause of chest pain and in multimorbid patients in whom the echo result has no consequence for further patient management.

[b] If diagnosis of SCAD is doubtful, establishing a diagnosis using pharmacologic stress imaging prior to treatment may be reasonable.

ESC 2013 guidelines on the management of stable coronary artery disease. *Eur Heart J*. 2013;**34**:2949–3003, with permission from Oxford University Press.

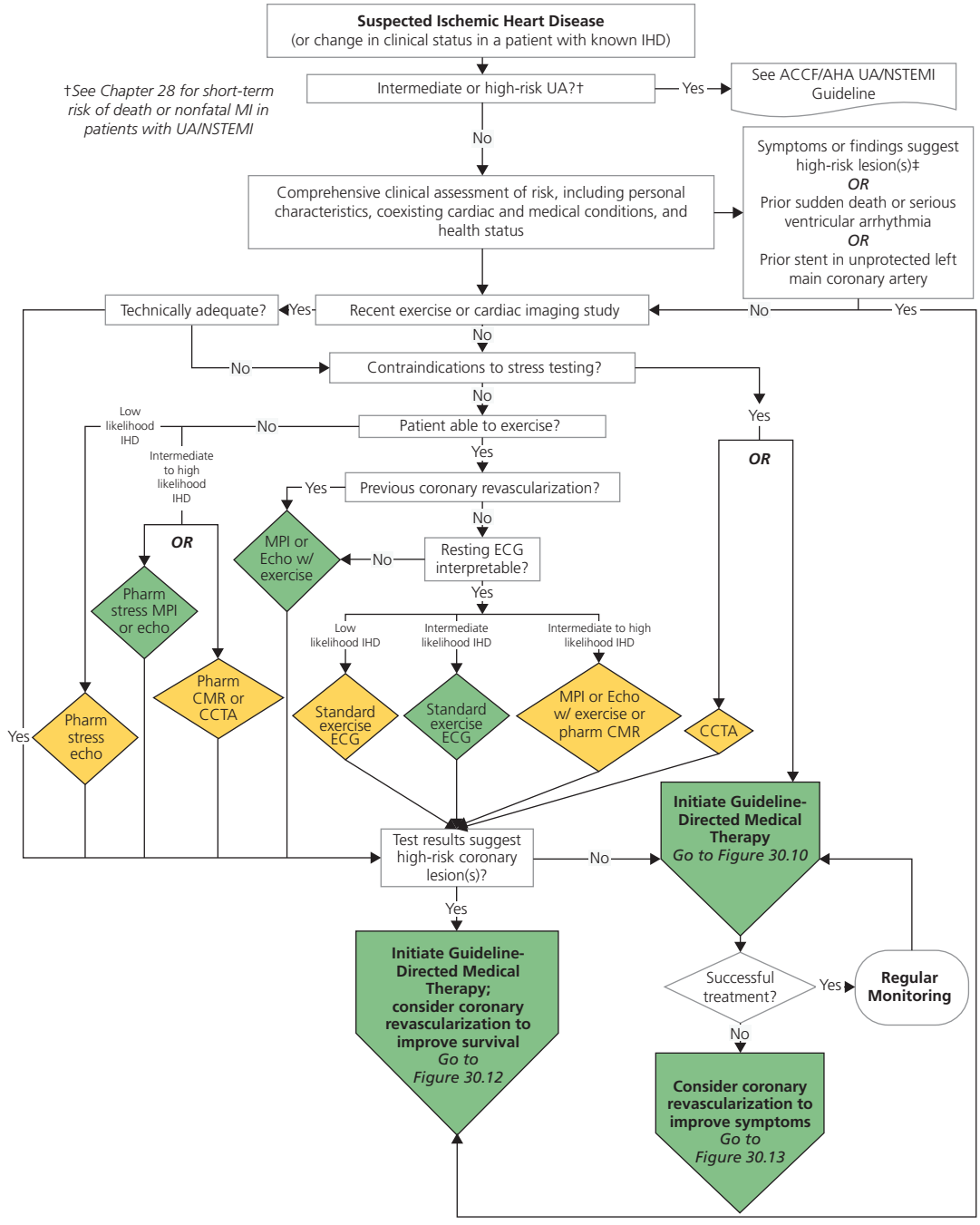


Figure 30.2 ACCF/AHA 2012 GL on stable IHD. Diagnosis of patients with suspected IHD.

Colours correspond to the class of recommendations in the ACCF/AHA (i.e. green is for Class I, yellow for IIa). The algorithms do not represent a comprehensive list of recommendations (see full guideline text for all recommendations). †See Chapter 28 on UA/NSTEMI for short-term risk of death or nonfatal MI in patients with UA/NSTEMI.

+ CCTA is reasonable only for patients with intermediate probability of IHD. CCTA indicates computed coronary tomography angiography; CMR, cardiac magnetic resonance; ECG, electrocardiogram; Echo, echocardiography; IHD, ischaemic heart disease; MI, myocardial infarction; MPI, myocardial perfusion imaging; Pharm, pharmacological; UA, unstable angina; and UA/NSTEMI, unstable angina/non–ST elevation myocardial infarction.

ACCF/AHA/ACP/AATS/PCNA/SCAI/STS 2012 Guideline for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol*. 2012;**60**:e44–e164 with permission from Elsevier.

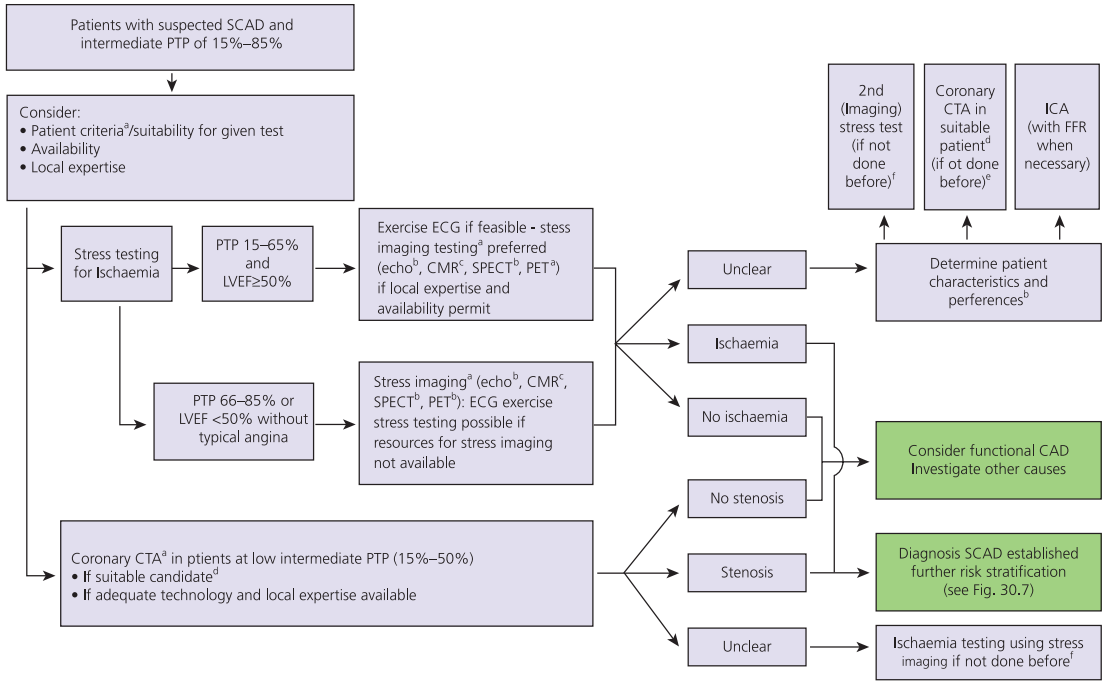


Figure 30.3 ESC 2013 GL on stable CAD. Non-invasive testing in patients with suspected SCAD and an intermediate pre-test probability.

CAD, coronary artery disease; CTA, computed tomography angiography; CMR, cardiac magnetic resonance; ECG, electrocardiogram; ICA, invasive coronary angiography; LVEF, left ventricular ejection fraction; PET, positron emission tomography; PTP, pre-test probability; SCAD, stable coronary artery disease; SPECT, single photon emission computed tomography.

[a] Consider age of patient versus radiation exposure.

[b] In patients unable to exercise use echo or SPECT/PET with pharmacologic stress instead.

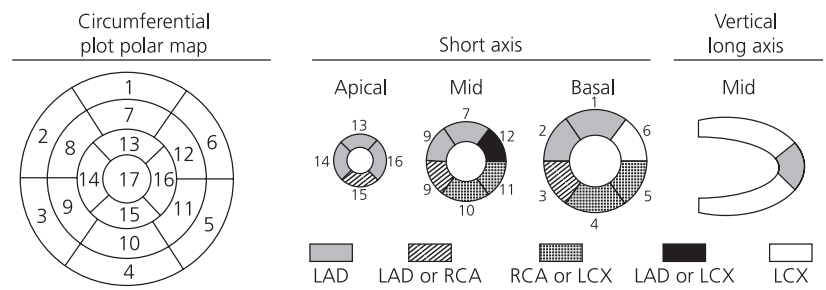
[c] CMR is only performed using pharmacologic stress.

[d] Patient characteristics should make a fully diagnostic coronary CTA scan highly probable; consider result to be unclear in patients with severe diffuse or focal calcification.

[e] Proceed as in lower left coronary CTA box.

[f] Proceed as in stress testing for ischaemia box.

ESC 2013 Guidelines on the management of stable coronary artery disease. *Eur Heart J*. 2013;**34**:2949–3003, with permission from Oxford University Press.



1. Basal anterior
2. Basal anteroseptal
3. Basal inferoseptal
4. Basal inferior
5. Basal inferolateral
6. Basal anterolateral
7. Mid-anterior
8. Mid-anteroseptal
9. Mid-inferoseptal
10. Mid-inferior
11. Mid-inferolateral
12. Mid-anterolateral
13. Apical anterior
14. Apical septal
15. Apical inferior
16. Apical lateral
17. Apex

Figure 30.4 Correspondence of left ventricular 17 myocardial segments with each coronary artery.

Pereztol-Valdés O, *et al*. Correspondence between left ventricular 17 myocardial segments and coronary arteries. *Eur Heart J*. 2005;**26**:2637–43, with permission from Oxford University Press.

Table 30.5 Diagnosis of stable CAD

Test	Exercise status		ECG interpretable		Pretest probability of IHD			
	Able	Unable	Yes	No	Low	Intermediate	High	
ACCF/AHA 2012 on stable CAD. Stress testing and advanced imaging for initial diagnosis in patients with suspected SIHD who require non-invasive testing								
Patients able to exercise*								
Exercise ECG	X		X			X		I-A
Exercise with nuclear MPI or echo	X			X		X	X	I-B
Exercise ECG	X		X		X			IIa-C
Exercise with nuclear MPI or echo	X		X			X	X	IIa-B
Pharmacological stress CMR	X			X		X	X	IIa-B
CCTA	X		Any		X			IIb-B
Exercise echo	X		X			X		IIb-C
Pharmacological stress with nuclear MPI, echo, or CMR	X		X		Any			III-C (no benefit)
Exercise stress with nuclear MPI	X		X		X			III-C (no benefit)
Patients unable to exercise								
Pharmacological stress with nuclear MPI or echo		X	Any			X	X	I-B
Pharmacological stress echo		X	Any		X			IIa-C
CCTA		X	Any		X	X		IIa-B
Pharmacological stress CMR		X	Any			X	X	IIa-B
Exercise ECG		X		X	Any			III-C (no benefit)
Other								
CCTA	Any		Any			X		IIa-C
If patient has any of the following: a) Continued symptoms with prior normal test, or b) Inconclusive exercise or pharmacological stress, or c) Unable to undergo stress with MPI or echo								
CAC score	Any		Any		X			IIb-C
ACC/AHA 2014 Update on Stable IHD.								
Coronary Angiography for Diagnosis of Coronary Artery Disease in Patients With Suspected SIHD								
Patients with unacceptable ischaemic symptoms despite GDMT and who are amenable to, and candidates for, coronary revascularization.								I-C
To define the extent and severity of CAD in patients whose clinical characteristics and results of non-invasive testing (exclusive of stress testing) indicate a high likelihood of severe IHD and who are amenable to, and candidates for, coronary revascularization.								IIa-C
Patients who cannot undergo diagnostic stress testing, or have indeterminate or non-diagnostic stress tests, when there is a high likelihood that the findings will result in important changes to therapy.								IIa-C
Patients with stress test results of acceptable quality that do not suggest the presence of CAD when clinical suspicion of CAD remains high and there is a high likelihood that the findings will result in important changes to therapy.								IIb-C
ESC 2013 GL on stable CAD. Non-invasive testing								
Performing an exercise electrocardiogram for initial diagnostic assessment of angina or evaluation of symptoms								
Exercise ECG as the initial test in patients with symptoms of angina and intermediate pre-test probability of CAD (Table 30.3, 15–65%), free of anti-ischaemic drugs, unless they cannot exercise or display ECG changes which make the ECG non-evaluable.								I-B

(*Continued*)

Table 30.5 Continued

Stress imaging as the initial test option if local expertise and availability permit.	I-B
Exercise ECG in patients on treatment to evaluate control of symptoms and ischaemia.	IIa-C
Exercise ECG in patients with ≥0.1 mV ST-depression on resting ECG or taking digitalis is not recommended.	III-C
Use of exercise or pharmacologic stress testing in combination with imaging	
An imaging stress test as the initial test if the pre-test probability is between 66 and 85% or if LVEF is <50% in patients without typical angina.	I-B
An imaging stress test in patients with resting ECG abnormalities which prevent accurate interpretation of ECG changes during stress.	I-B
Exercise stress testing is recommended rather than pharmacologic testing whenever possible.	I-C
An imaging stress test in symptomatic patients with prior revascularization (PCI or CABG).	IIa-B
An imaging stress test to assess the functional severity of intermediate lesions on coronary arteriography.	IIa-B
Use of coronary computed tomography angiography (CTA) for the diagnosis of stable coronary artery disease	
CTA as an alternative to stress imaging techniques for ruling out SCAD in patients within the lower range of intermediate PTP for SCAD in whom good image quality can be expected.	IIa-C
CTA in patients within the lower range of intermediate PTP for SCAD after a non-conclusive exercise ECG or stress imaging test or who have contraindications to stress testing if fully diagnostic image quality of coronary CTA can be expected.	IIa-C
Coronary calcium detection by CT is not recommended to identify individuals with coronary artery stenosis.	III-C
CTA is not recommended in patients with prior coronary revascularization.	III-C
CTA is not recommended as a 'screening' test in asymptomatic individuals without clinical suspicion of coronary artery disease.	III-C

ESC 2014 GL on revascularization.

Indications for diagnostic testing in patients with suspected CAD and stable symptoms

	Asymptomatic[a]	Symptomatic		
		Probability of significant disease[b]		
		Low (<15%)	Intermediate (15–85%)	High (>85%)
Anatomical detection of CAD				
Invasive angiography	III-A	III-A	IIb-A	I-A
CT angiography[c,d]	III-B	III-C	IIa-A	III-B
Functional test				
Stress echo	III-A	III-A	I-A	III-A
Nuclear imaging	III-A	III-A	I-A	III-A
Stress MRI	III-B	III-C	I-A	III-B
PET perfusion	III-B	III-C	I-A	III-B
Combined or hybrid imaging test				
	III-C	III-C	IIa-B	III-B

* Patients are candidates for exercise testing if they are capable of performing at least moderate physical functioning (i.e. moderate household, yard, or recreational work and most activities of daily living) and have no disabling co-morbidity. Patients should be able to achieve 85% of age-predicted maximum heart rate.
CAC indicates coronary artery calcium; CAD, coronary artery disease; CCTA, cardiac computed tomography angiography; CMR, cardiac magnetic resonance imaging; CT, computed tomography; ECG, electrocardiogram; echo, echocardiography; IHD, ischaemic heart disease; MPI, myocardial perfusion imaging; MRI, magnetic resonance imaging; PET, positron emission tomography; SIHD, stable ischaemic heart disease.
a: Screening for silent (asymptomatic) myocardial ischaemia may be considered in selected high-risk patients, such as those with diabetes mellitus.
b: Pre-test probability of CAD as assessed using the criteria in Table 30.3.
c: This refers to CT angiography, not calcium scoring.
d: CT is considered to perform best in the lower range of pre-test probability (15–50%).
ACCF/AHA/ACP/AATS/PCNA/SCAI/STS 2012 Guideline for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol*. 2012;**60**:e44–e164 with permission from Elsevier.
ACC/AHA/AATS/PCNA/SCAI/STS 2014 Focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease. J *Am Coll Cardiol*. 2014;**64**:1929–1949 with permission from Elsevier.
ESC 2013 Guidelines on the management of stable coronary artery disease. *Eur Heart J*. 2013;**34**:2949–3003, with permission from Oxford University Press.
ESC/EACTS 2014 Guidelines on myocardial revascularization. *Eur Heart J*. 2014;**35**:2541–619 with permission from Oxford University Press.

Differential diagnosis

Cardiac causes of angina-like pain

Apart from epicardial coronary artery stenosis, other cardiac conditions that may cause myocardial ischaemia are:

- **Aortic stenosis, hypertension** and **LV hypertrophy** (reduced coronary blood flow)
- **Microvascular coronary dysfunction**. It has been attributed to endothelial dysfunction and carries adverse prognosis. More common in women (WISE study)[29]
- **Abnormal cardiac nociception**. Increased perception of pain centrally mediated or due to changed sensitivity of chemical and mechanical atrial and ventricular receptors
- **Coronary artery spasm** (smooth muscle dysregulation probably due to inflammation)
- **Congenital coronary abnormalities** Myocardial bridging involves a segment of a coronary artery, usually the LAD, embedded within the myocardium in a way that arterial compression occurs with systole.[30] With intense symptoms and documented ischaemia, CABG may be required. The value of stenting is debated. Fistulas, anomalous origins of coronary arteries, compression by the PA as may happen with ASD are other relevant anomalies (see Chapter 2).
- **Syndrome X** refers to exercise-induced angina-like symptoms in the context of ischaemic changes on treadmill stress testing and normal coronary arteries on angiography.[31] The exact cause is not known, but microvascular disease and endothelial dysfunction due to inflammation, hypercholesterolaemia, smoking, and obesity have been proposed. Insulin resistance, hormonal dysfunction, and psychological factors may also play a role. Microvascular coronary dysfunction is highly prevalent among high-risk individuals and associated with an adverse prognosis regardless of sex.[32,33] Coronary reactivity testing may be helpful in establishing the diagnosis of coronary spasm, microvascular dysfunction, or abnormal cardiac nociception. Acetylcholine (intracoronary incremental doses of 2, 20, 100, and 200 micrograms over a period of 3 min) or ergonovine (20–60 micrograms over a period of 2–5 min)[34,35] may be used (Table 30.6). A positive response to acetylcholine or ergonovine spasm provocation testing is defined as transient occlusion (>90% narrowing) of a coronary artery with signs and symptoms of myocardial ischaemia (angina/ST changes),[36] or distal, diffuse epicardial spasm.[35] Provocation tests are safe with an incidence of transient VT/VF or bradyarrhythmias of up to 6.8% which is comparable to 7% during spontaneous angina events.[34,35] Arrhythmic complications are more often with acetylcholine than with ergonovine.[34] Adenosine stress perfusion using MRI is also a promising modality for the detection of transmural coronary flow distribution (endocardial less than epicardial) due to microvascular coronary dysfunction.[32] The index of microvascular resistance (IMR) is calculated as the distal coronary pressure at maximal hyperaemic divided by the inverse of the hypaeremic mean transit time.[37] Approximately 20% of patients presenting to the cardiac catheterization laboratory with angina have no angiographic evidence of coronary artery disease. In a recent study, an explanation for their angina could not be found in 23% of them. Endothelial dysfunction (a decrease in luminal diameter of >20% after intracoronary acetylcholine), microvascular impairment (an index of microcirculatory resistance ≥ 25), FFR ≤ 0.80, and a myocardial bridge were present in 44%, 21%, 5%, and 58% of patients, respectively.[38]
- **Prinzmetal's angina** refers to chest pain at rest, associated with ST elevation, and was thought to be due to coronary artery spasm (Table 30.6).

Table 30.6 Syndrome X, microvascular, and vasospastic angina

ACCF/AHA 2012 GL on UA/NSTEMI. Cardiovascular 'syndrome X'	
Nitrates, beta blockers, and calcium channel blockers, alone or in combination.	I-B
Risk factor reduction.	I-B
Intracoronary ultrasound to assess the extent of atherosclerosis and rule out missed obstructive lesions.	IIb-B
Coronary angiography and provocative testing with acetylcholine, adenosine, or methacholine and 24 h ambulatory ECG.	IIb-C
Invasive physiological assessment (i.e. coronary flow reserve measurement) if coronary angiography does not reveal a cause of chest discomfort.	IIb-C
Imipramine or aminophylline for continued pain despite implementation of Class I measures.	IIb-C
Transcutaneous electrical nerve stimulation and spinal cord stimulation for continued pain, despite the implementation of Class I measures may be considered for patients with syndrome X.	IIb-B
Medical therapy with nitrates, beta blockers, and calcium channel blockers for patients with non-cardiac chest pain is not recommended.	III-C

(*Continued*)

Table 30.6 Continued

ESC 2013 GL on stable CAD	
Investigation in patients with suspected coronary microvascular disease	
Exercise or dobutamine echocardiography in order to establish whether regional wall motion abnormalities occur in conjunction with angina and ST-changes.	IIa-C
Transthoracic Doppler echocardiography of the LAD with measurement of diastolic coronary flow following adenosine and at rest for non-invasive coronary flow reserve.	IIb-C
Intracoronary acetylcholine and adenosine with Doppler measurements during coronary arteriography, if the arteriogram is visually normal, to assess endothelium dependent and non-endothelium microvascular/epicardial vasospasm.	IIb-C
Diagnostic tests in suspected vasospastic angina	
ECG during angina if possible.	I-C
Coronary arteriography in patients with characteristic episodic chest pain and ST segment changes that resolve with nitrates and/or calcium antagonists to determine the extent of underlying coronary disease (level of evidence B).	I-C
Ambulatory ST segment monitoring to identify ST deviation.	IIa-C
Intracoronary provocative testing to diagnose the site and mode of spasm in patients with no obstructive lesions.	IIa-C

AHA/ACC 2014 Guideline for the management of patients with non-ST-elevation acute coronary syndromes. *J Am Coll Cardiol*. 2014;**64**:e139–228, with permission from Elsevier.
ESC 2013 Guidelines on the management of stable coronary artery disease. *Eur Heart J*. 2013;**34**:2949–3003, with permission from Oxford University Press.

Non-cardiac causes of angina-like pain

- **Oesophageal reflux**, oesophagitis, and abnormal oesophageal motility have similar distribution with cardiac pain but are not related to exercise. These findings are common in patients presenting with chest pain, but not necessarily the causative factor.
- **Duodenal ulcer** and **gall bladder pain**.
- **Pericardial pain**. Retrosternal or epigastric, precipitated by inspiration and relieved by sitting forward. May radiate to left shoulder.
- **Aortic dissection**. Tearing pain radiating to the back. Aortic aneurysms may also produce chronic pain.
- **Costochondritis**. Tenderness on palpation.
- **Pulmonary embolism** is usually associated with sudden onset of shortness of breath, rather than pain.

A full list of conditions that may cause chest pain are presented in Table 30.7.

Table 30.7 Causes of chest pain

Cardiovascular
Acute coronary syndrome
Aortic stenosis
Hypertension
Aortic dissection
Myocarditis
Pericarditis
Hypertrophic cardiomyopathy

(*Continued*)

Table 30.7 Continued

Musculoskeletal
Cervical disc disease
Costochondritis
Fibrositis
Herpes zoster (before the rash)
Neuropathic pain
Rib fracture
Pulmonary
Pneumonia
Pulmonary embolism
Tension pneumothorax
Pleuritis
Gastrointestinal
Cholecystitis
Cholangitis
Peptic ulcer
Gastro-oesophageal reflux
Oesophageal spasm
Boerhaave syndrome (oesophageal rupture with mediastinitis)
Pancreatitis
Psychiatric
Hyperventilation
Affective disorders (depression)
Anxiety disorder/panic attack
Somatization and psychogenic pain disorder
Thought disorders (fixed delusions)

Risk stratification

Risk stratification is essential for the choice of appropriate mode of therapy (Table 30.8, and Figures 30.5, 30.6, and 30.7). The major clinical and angiographic predictors of survival of patients with CAD are:

- LV function
- Anatomical extent and severity of coronary atherosclerosis
- Severity of documented ischaemia
- Severity of angina.

Table 30.8 Risk stratification

ACCF/AHA 2012 on stable IHD

Resting imaging to assess cardiac structure and function	
Doppler echocardiography in patients with known or suspected IHD and a prior MI, pathological Q waves, symptoms or signs suggestive of heart failure, complex ventricular arrhythmias, or an undiagnosed heart murmur.	I-B
Echocardiography in hypertension or diabetes mellitus and abnormal ECG.	IIb-C
Measurement of LV function with radionuclide imaging in patients with a prior MI or pathological Q waves, provided there is no need to evaluate symptoms or signs suggestive of heart failure, complex ventricular arrhythmias, or an undiagnosed heart murmur.	IIb-C
Echocardiography, radionuclide imaging, CMR, and cardiac computed tomography are not recommended for routine assessment of LV function in patients with a normal ECG, no history of MI, no symptoms or signs suggestive of heart failure, and no complex ventricular arrhythmias.	III-C
Routine reassessment (<1 year) of LV function with echocardiography, radionuclide imaging, CMR, or cardiac computed tomography in patients with no change in clinical status and for whom no change in therapy is contemplated.	III-C

ACCF/AHA 2012 GL on stable IHD. Stress testing and advanced imaging for patients with known stable IHD who require non-invasive testing for risk assessment

Test	**Exercise status**		**ECG interpretable**			**Additional considerations**
	Able	**Unable**	**Yes**	**No**		
Patients able to exercise *						
Exercise ECG	X		X		I-B	
Exercise with nuclear MPI or echo	X			X	I-B	Abnormalities other than LBBB or ventricular pacing
Exercise with nuclear MPI or echo	X		X		IIa-B	
Pharmacological stress CMR	X			X	IIa-B	
CCTA	X			X	IIb-B	
Pharmacological stress imaging (nuclear MPI, echo, CMR) or CCTA	X		X		III-C (no benefit)	
Patients unable to exercise						
Pharmacological stress with nuclear MPI or echo		X	Any		I-B	
Pharmacological stress CMR		X	Any		IIa-B	
CCTA		X	Any		IIa-C	Without prior stress test
Regardless of patient's ability to exercise						
Pharmacological stress with nuclear MPI or echo	Any			X	I-B	LBBB present
Exercise/pharmacological stress with nuclear MPI, echo, or CMR	Any		Any		I-B	Known coronary stenosis of unclear physiological significance being considered for revascularization
CCTA	Any		Any		IIa-C	Indeterminate result from functional testing
CCTA	Any		Any		IIb-C	Unable to undergo stress imaging or as alternative to coronary catheterization when functional testing indicates moderate to high risk and angiographic coronary anatomy is unknown
Requests to perform multiple cardiac imaging or stress studies at the same time	Any		Any		III-C (no benefit)	

(*Continued*)

Table 30.8 Continued

ACC/AHA 2012 on stable IHD. Non-invasive risk stratification	
High risk (>3% annual death or MI)	
1. Severe resting LV dysfunction (LVEF <35%) not readily explained by non-coronary causes	
2. Resting perfusion abnormalities ≥10% of the myocardium in patients without prior history or evidence of MI	
3. Stress ECG findings, including ≥2 mm of ST segment depression at low workload or persisting into recovery, exercise-induced ST segment elevation, or exercise-induced VT/VF	
4. Severe stress-induced LV dysfunction (peak exercise LVEF <45% or drop in LVEF with stress ≥10%)	
5. Stress-induced perfusion abnormalities encumbering ≥10% myocardium or stress segmental scores indicating multiple vascular territories with abnormalities	
6. Stress-induced LV dilation	
7. Inducible wall motion abnormality (involving >2 segments or two coronary beds)	
8. Wall motion abnormality developing at low dose of dobutamine (≤10 mg/kg/min) or at a low heart rate (<120 bpm)	
9. CAC score >400 Agaston units	
10. Multivessel obstructive CAD (≥70% stenosis) or left main stenosis (≥50% stenosis) on CCTA	
Intermediate risk (1–3% annual death or MI)	
1. Mild/moderate resting LV dysfunction (LVEF 35–49%) not readily explained by non-coronary causes	
2. Resting perfusion abnormalities in 5–9.9% of the myocardium in patients without a history or prior evidence of MI	
3. ≥1 mm of ST segment depression occurring with exertional symptoms	
4. Stress-induced perfusion abnormalities encumbering 5–9.9% of the myocardium or stress segmental scores (in multiple segments) indicating one vascular territory with abnormalities but without LV dilation	
5. Small wall motion abnormality, involving one to two segments and only one coronary bed	
6. CAC score 100–399 Agaston units	
7. One-vessel CAD with ≥70% stenosis or moderate CAD stenosis (50–69% stenosis) in ≥2 arteries on CCTA	
Low risk (<1% annual death or MI)	
1. Low-risk treadmill score (score ≥5) or no new ST segment changes or exercise-induced chest pain symptoms when achieving maximal levels of exercise	
2. Normal or small myocardial perfusion defect at rest or with stress encumbering <5% of the myocardium**	
3. Normal stress or no change of limited resting wall motion abnormalities during stress	
4. CAC score <100 Agaston units	
5. No coronary stenosis >50% on CCTA	
ESC 2013 GL on stable CAD. Non-invasive risk stratification	
Risk stratification by resting echocardiography quantification of ventricular function in stable coronary artery disease	
Resting echocardiography to quantify LV function.	I-C
Risk stratification using ischaemia testing	
Risk stratification based on clinical assessment and stress test performed for diagnosis of stable CAD.	I-B
Stress imaging in non-conclusive exercise ECG.	I-B
Stress ECG or preferably stress imaging after a significant change in symptom level.	I-B
Stress imaging after deterioration of symptoms if the site and extent of ischaemia would influence clinical decision making.	I-B
Pharmacological stress with echocardiography or SPECT in patients with LBBB.	IIa-B
Stress echocardiography or SPECT in patients with paced rhythm.	IIa-B
Testing in asymptomatic patients at risk for stable coronary artery disease for CV risk assessment	
Resting ECG in adults with hypertension or diabetes.	IIa-C
Resting ECG in adults without hypertension or diabetes.	IIb-C
In intermediate risk adults (see SCORE for definition of intermediate risk—www.heartscore.org) measurement of carotid intima-media thickness with screening for atherosclerotic plaques by carotid ultrasound, measurement of ankle–brachial index or measurement of coronary calcium using CT should be considered for CV risk assessment.	IIb-B
In adults with diabetes, ≥40 years, measurement of coronary calcium using CT may be considered for CV risk assessment.	IIb-B
In intermediate risk adults (see SCORE for definition of intermediate risk—www.heartscore.org) including sedentary adults considering starting a vigorous exercise programme), an exercise ECG, particularly when attention is paid to non-ECG markers such as exercise capacity.	IIa-B

(*Continued*)

Table 30.8 Continued

In asymptomatic adults with diabetes or asymptomatic adults with a strong family history of CAD or when previous risk assessment testing suggests high risk of CAD, such as a coronary artery calcium score of ≥400 stress imaging tests (MPI, stress echocardiography, perfusion CMR).	IIb-C
In low- or intermediate-risk (based on SCORE) asymptomatic adults stress imaging tests are not indicated.	III-C

* Patients are candidates for exercise testing if they are capable of performing at least moderate physical functioning (i.e. moderate household, yard, or recreational work and most activities of daily living) and have no disabling co-morbidity. Patients should be able to achieve 85% of age-predicted maximum heart rate.
CAC indicates coronary artery calcium; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance imaging; CT, computed tomography; CV, cardiovascular; ECG, electrocardiogram; echo, echocardiography; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; and MI, myocardial infarction; MPI, myocardial perfusion imaging; SCORE, systemic coronary risk evaluation.
** Although the published data are limited, patients with these findings will probably not be at low risk in the presence of either a high-risk treadmill score or severe resting LV dysfunction (LVEF ≤35%).
ACCF/AHA/ACP/AATS/PCNA/SCAI/STS 2012 Guideline for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol*. 2012;**60**:e44–e164 with permission from Elsevier.
ESC 2013 guidelines on the management of stable coronary artery disease. *Eur Heart J*. 2013;**34**:2949–3003, with permission from Oxford University Press.

Risk factor	Score contribution	Individual's score
Comorbidity*		
No	0	
Yes	86	
Diabetes		
No	0	
Yes	57	
Angina score		
Class I	0	
Class II	54	
Class III	91	
Duration of symptoms		
≥6 months	0	
<6 months	80	
Abnormal ventricular function		
No	0	
Yes	114	
ST depression or T wave inversion on resting electrocardiogram		
No	0	
Yes	34	
		Total =

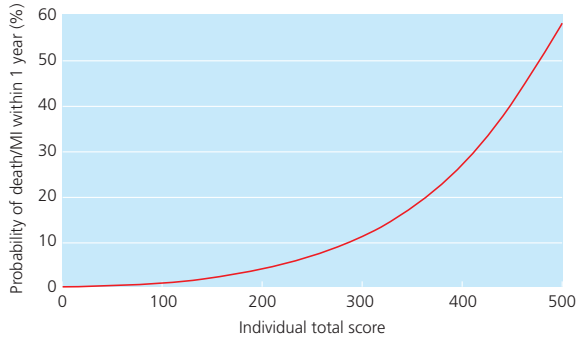


Figure 30.5 Top: Euro Heart score sheet to calculate risk score for patients presenting with stable angina (derived from 3779 patients with newly diagnosed stable IHD).

* one or more of previous cerebrovascular event; hepatic disease defined as chronic hepatitis or cirrhosis or other hepatic disease causing elevation of transaminases ≥3 times upper limit of normal; PVD defined as claudication either at rest or on exertion, amputation for arterial vascular insufficiency, vascular surgery (reconstruction or bypass) or angioplasty to the extremities, documented aortic aneurysm, or non-invasive evidence of impaired arterial flow; chronic renal failure defined as chronic dialysis or renal transplantation or serum creatinine >200 mmol/L; chronic respiratory disease defined as a diagnosis previously made by physician or patient receiving bronchodilators or FEV_1 <75%, arterial pO_2 <60%, or arterial pCO_2 >50% predicted in previous studies; chronic inflammatory conditions defined as a diagnosis of rheumatoid arthritis, systemic lupus erythematosus or other connective tissue disease, polymyalgia rheumatica, and so on; malignancy defined as a diagnosis of malignancy within a year of active malignancy. Right panel: risk of death or MI over 1 year after diagnosis of stable IHD, according to Euro Heart score. Plot to assign estimated probability of death or non-fatal MI within 1 year of presentation, according to a combination of clinical and investigative features in patients with stable angina. MI indicates myocardial infarction; FEV_1, forced expiratory volume; pO_2, partial pressure of oxygen; pCO_2, partial pressure of carbon dioxide; and PVD, peripheral vascular disease.
Daly CA, *et al*. Predicting prognosis in stable angina—results from the Euro heart survey of stable angina:prospective observational study. *BMJ*. 2006;**332**:262–7.

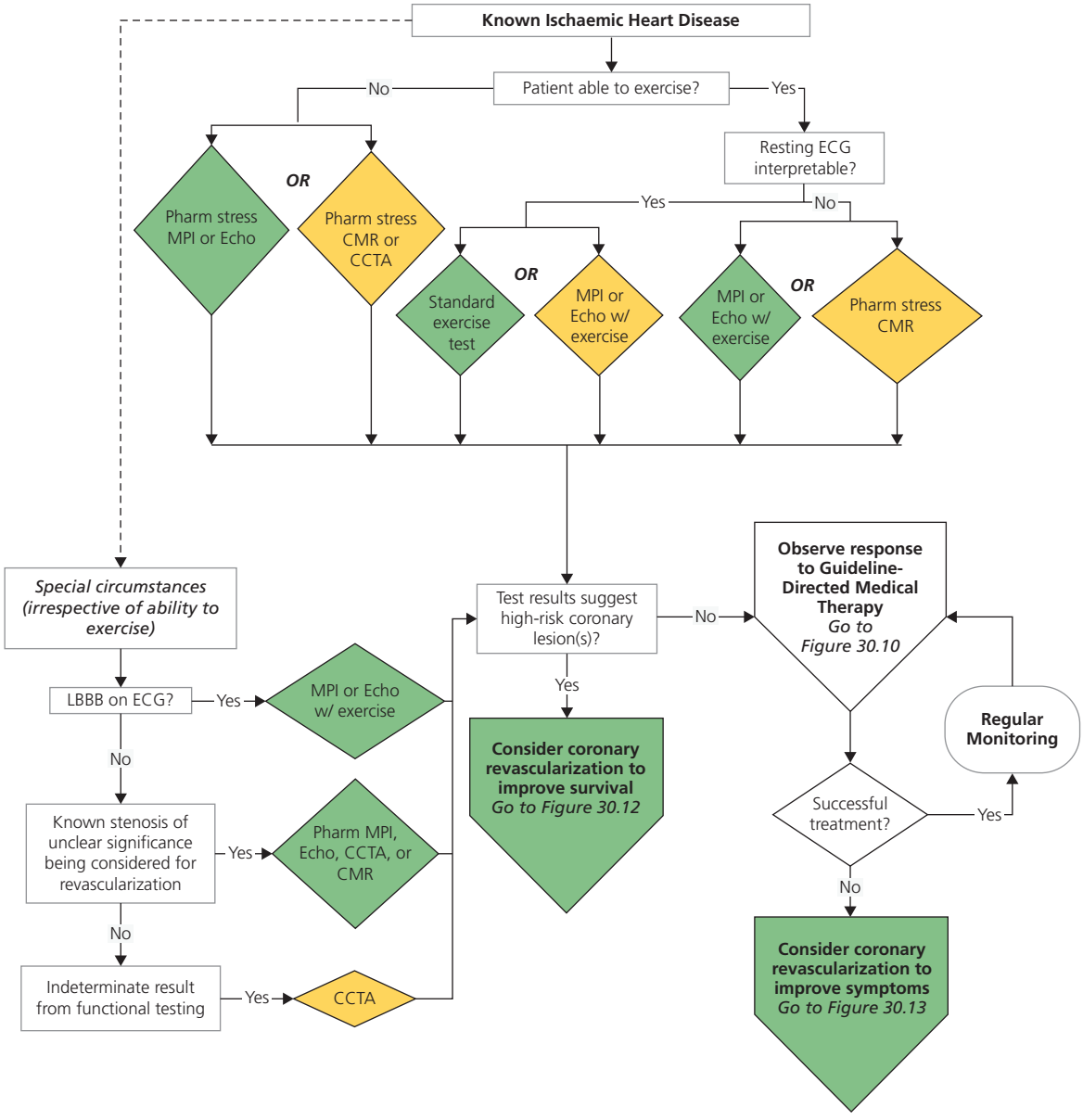


Figure 30.6 ACCF/AHA 2012 GL on stable IHD. Algorithm for risk assessment of patients with stable IHD.

* Colours correspond to the class of recommendations in the ACCF/AHA (i.e. green is for Class I, yellow for IIa). The algorithms do not represent a comprehensive list of recommendations (see full guideline text for all recommendations). CCTA indicates coronary computed tomography angiography; CMR, cardiac magnetic resonance; ECG, electrocardiogram; Echo, echocardiography; LBBB, left branch bundle block; MPI, myocardial perfusion imaging; and Pharm, pharmacological. ACCF/AHA/ACP/AATS/PCNA/SCAI/STS 2012 Guideline for the diagnosis and management of patients with stable ischemic heart disease. J Am Coll Cardiol. 2012;**60**:e44–e164 with permission from Elsevier.

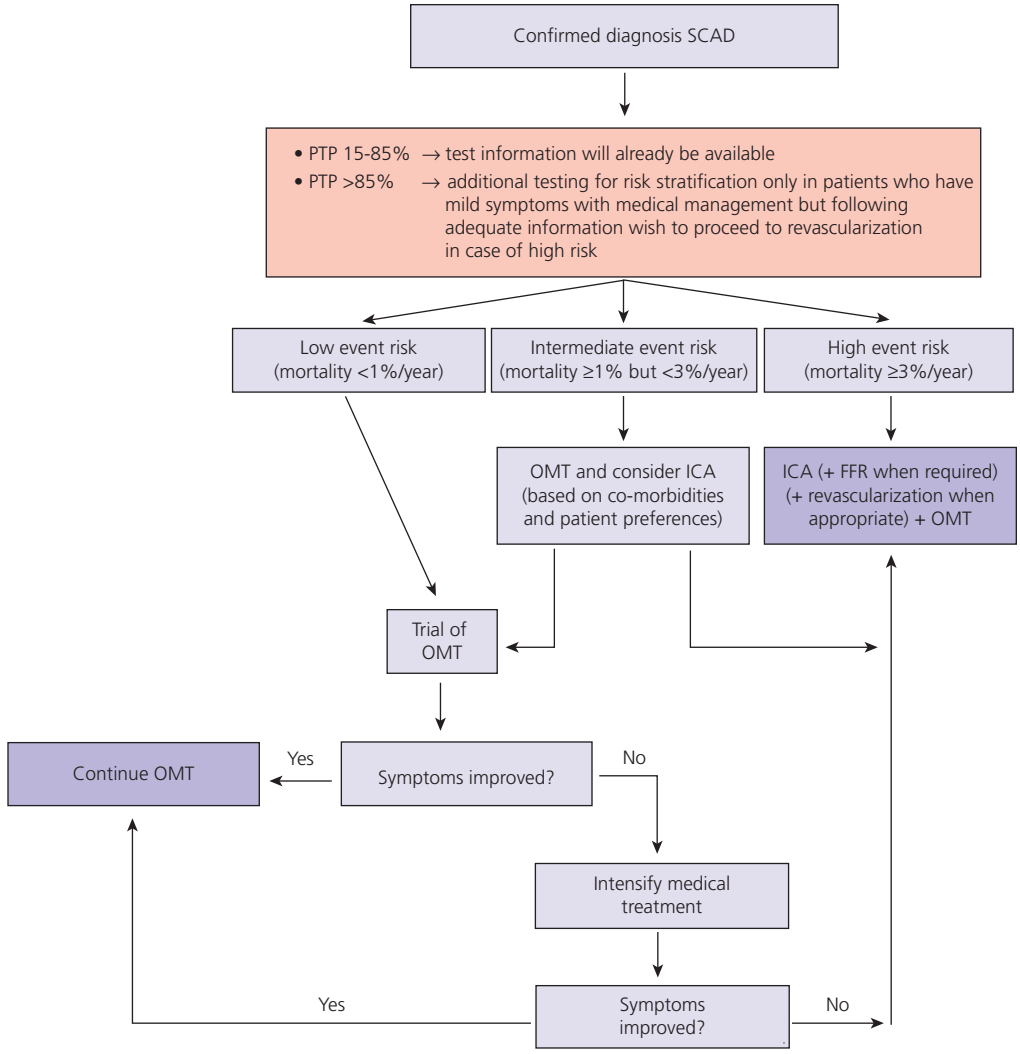


Figure 30.7 ESC 2013 GL on stable CAD. Management based on risk determination for prognosis in patients with chest pain and suspected SCAD.

ICA, invasive coronary angiography; OMT, optimal medical therapy; PTP, pre-test probability; SCAD, stable coronary artery disease.
ESC 2013 Guidelines on the management of stable coronary artery disease. *Eur Heart J.* 2013;**34**:2949–3003, with permission from Oxford University Press.

LV function and viability

Echocardiographic LVEF <50% is considered abnormal. LVEF <35% denotes patients at high risk and is an independent predictor of mortality. Dobutamine stress echocardiography, myocardial perfusion tests, cardiac magnetic resonance, and positron emission tomography are used for assessment of viability of apparently scarred ventricular tissue.[39] The demonstration of viable myocardium in patients with coronary artery disease and LV dysfunction has been traditionally considered as a prerequisite for potential revascularization.[39,40] Recent evidence failed to confirm the value of viability detection to guide revascularization (substudy of the STICH trial),[41] particularly in the presence of extensive scar and remodelling, and also probably because medical therapy may also restore the viable myocardium.[42]

Coronary anatomy indices

The extent of significant lesions on the coronary arteries has been correlated with long-term mortality,[43] and risk stratification can be based on coronary anatomy (Tables 30.9 and 30.10). The clinical importance of angiographic extensive coronary disease has been verified by subanalyses of the COURAGE and STICH trials.[44,45] Coronary stenoses are now considered haemodynamically significant when >50% diameter stenosis of the left main and >70% diameter stenosis of the other epicardial arteries.[2,46] However, both visual assessment and quantitative coronary angiography methods have limited accuracy for risk stratification purposes. The **SYNTAX score** is an angiographic grading tool, calculated as the sum of the points assigned to each lesion identified in the 16 segments of the coronary tree with >50% diameter narrowing in vessels with a diameter >1.5 mm (http://www.syntaxscore.com) (Figure 30.8). The **clinical SYNTAX score** (SYNTAX score II) combines the angiographic SYNTAX Score with a clinical risk score incorporating age, ejection fraction, and creatinine clearance. It is calculated as: Clinical SYNTAX score = SYNTAX score × [(Age/LVEF) + 1 point for each 10 mL creatinine clearance <60 mL.min/1.73 mm^2)]. It predicts major cardiac and cerebrovascular events and mortality better than angiographic score and has been proposed for use in patients with anticipated PCI.[47] Incorporating functional assessment by considering coronary lesions with **FFR** measurements <0.80 improves its clinical usefulness.[48]

The specificity of the **coronary calcium score** for obstructive coronary lesions is low. However, it has prognostic significance, and a calcium scoring system has been devised based on the X-ray attenuation coefficient, or CT number measured in Hounsfield units, and the area of calcium deposits. An Agatston score <100 indicates low risk and a score >300 high risk, and in acute coronary syndromes, target lesion calcification is associated with increased mortality and ischaemic complications.[49] Thus, it is useful for risk stratification, especially in asymptomatic subjects classified in intermediate Framingham risk range.[50–52] Coronary artery calcium density should also be considered. Coronary artery calcium volume is positively and independently associated with CHD and CVD risk, whereas calcium density, at any level of calcium volume, is inversely and significantly associated with CHD and CVD risk (MESA trial).[53] Of note, however, in the CONFIRM trial, a score of 0 did not rule out the presence of significant coronary disease, and in intermediate-risk populations calcium score did not add incremental prognostic information to that provided by clinical risk factors and the severity of CAD.[54]

Extent of ischaemia

In longitudinal studies, in patients with known or suspected coronary artery disease, detection of ischaemia predicts a significantly higher overall mortality, cardiac death, or MI, even in the absence of angina, whereas normal scintigraphy studies identify patients with a good prognosis at a low risk for future cardiac events.[55–57] Acute myocardial ischaemia is an established cause of polymorphic ventricular tachycardia or fibrillation and sudden cardiac death.[58] The majority of sudden deaths due to ischaemic heart disease are not associated with an acute MI, but transient acute ischaemia is an important trigger, preceding 35–80% of deaths due to a ventricular tachyarrhythmia.[59] However, although in the COURAGE nuclear substudy there was a suggestion of benefit by intervention in patients with substantial (>10%) ischaemia,[60] in another subanalysis of the COURAGE trial, anatomic burden of atherosclerosis was a consistent predictor of death, MI, and NSTE-ACS, whereas ischaemic burden was not.[44] In addition, imaging tests, such as exercise scintigraphy results, do not correlate well with angiographic findings, both in patients with and without angina, and they may not identify the culprit lesion(s) with certainty in the presence of multivessel disease.[61] In the DIAD trial on diabetics, the cardiac event rates were low and were not significantly reduced by myocardial perfusion imaging screening for myocardial ischaemia over 4.8 years.[62] The presence of extensive ischaemia may be useful in guiding therapy, but evidence is controversial. Studies considering CABG and PCI for revascularization with significant inducible ischaemia (>10% of LV myocardium) have produced conflicting results, with[63–66,] and without[67–69] survival benefit compared to medical therapy. In addition, no difference in the long-term survival of patients with restenosis who did and did not undergo revascularization has been detected.[70]

Fractional flow reserve has been found useful for guiding therapeutic strategies.[71] However, it shows modest concordance with imaging tests such as perfusion scintigraphy and dobutamine stress echocardiography, and quantitative coronary angiography particularly with 30% to 70% diameter stenoses.[72] Approximately one third of patients may show discordance between ≥50% diameter stenosis, especially of the left main stem, and FFR ≤0.8 thresholds of stenosis severity.[73] Thus, no single test can serve as a gold standard, particularly when equivocal or borderline results are produced.

Global coronary flow reserve, calculated by positron emission tomography as the ratio of stress to rest absolute myocardial blood flow (mL/min/g) for the whole left ventricle, is associated with outcomes, independently of angiographic CAD. In a recent study, only patients with low CFR appeared to benefit from revascularization, and only if the revascularization included coronary artery bypass grafting.[74]

Severity of angina was not a predictor of mortality in medically treated patients with left ventricular systolic dysfunction in a recent analysis of the STICH trial.

Table 30.9 Coronary angiography for risk stratification

ACCF/AHA 2012 GL on stable IHD	
Coronary angiography as an initial testing strategy to assess risk	
To assess cardiac risk in patients who have survived sudden cardiac death or potentially life-threatening ventricular arrhythmia.	I-B
Patients who develop symptoms and signs of heart failure should be evaluated to determine whether coronary angiography should be performed for risk assessment.	I-B
Coronary angiography to assess risk after initial work-up with non-invasive testing	
Coronary arteriography is recommended for patients whose clinical characteristics and results of non-invasive testing indicate a high likelihood of severe IHD and when the benefits are deemed to exceed risk.	I-C
Patients with LVEF <50% and moderate risk criteria on non-invasive testing with demonstrable ischaemia.	IIa-C
Inconclusive prognostic information after non-invasive testing or non-invasive testing is contraindicated or inadequate.	IIa-C
Unsatisfactory quality of life due to angina, LVEF >50%, and intermediate-risk criteria on non-invasive testing.	IIa-C
Patients who elect not to undergo revascularization or who are not candidates for revascularization because of co-morbidities or individual preferences.	III-B
LVEF >50% and low-risk criteria on non-invasive testing.	III-B
Low risk according to clinical criteria and no non-invasive risk testing.	III-C
Asymptomatic patients with no evidence of ischaemia on non-invasive testing.	III-C
ESC 2013 GL on stable CAD	
Risk stratification by invasive or non-invasive coronary arteriography in patients with stable coronary artery disease	
ICA (with FFR when necessary) for risk stratification in patients with severe stable angina (CCS 3) or with a clinical profile suggesting a high event risk, particularly if the symptoms are inadequately responding to medical treatment.	I-C
ICA (with FFR when necessary) for patients with mild or no symptoms with medical treatment in whom non-invasive risk stratification indicates a high event risk and revascularization is considered for improvement of prognosis.	I-C
ICA (with FFR when necessary) for risk stratification in patients with an inconclusive diagnosis on non-invasive testing or conflicting results from different non-invasive modalities.	IIa-C
If CTA is available, possible overestimation of stenosis severity should be considered in segments with severe calcification, especially in patients at high intermediate pretest probability.	IIa-C

If symptoms and/or ischaemia are markedly reduced/eliminated by OMT, then OMT may be continued; if not, catheterization should follow
CCS, Canadian Cardiovascular Society; CTA, computed tomography angiography; FFR, fractional flow reserve; ICA, invasive coronary angiography; OMT, optimal medical therapy.
ACCF/AHA/ACP/AATS/PCNA/SCAI/STS 2012 Guideline for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol*. 2012;**60**:e44–e164 with permission from Elsevier.
ESC 2013 guidelines on the management of stable coronary artery disease. *Eur Heart J*. 2013;**34**:2949–3003, with permission from Oxford University Press.

Table 30.10 Coronary artery disease prognostic index with medical therapy

Extent of CAD	Prognostic weight (0–100)	5-year survival rate (%)
1-vessel disease, 75%	23	93
>1-vessel disease, 50% to 74%	23	93
1-vessel disease, ≥ 95%	32	91
2-vessel disease	37	88
2-vessel disease, both 95%	42	86
1-vessel disease, ≥ 95% proximal LAD	48	83
2-vessel disease, ≥ 95% LAD	48	83
2-vessel disease, ≥ 95% proximal LAD	56	79
3-vessel disease	56	79
3-vessel disease, ≥ 95% in at least 1	63	73
3-vessel disease, 75% proximal LAD	67	67
3-vessel disease, ≥ 95% proximal LAD	74	59

Califf RM, *et al.* Task Force 5. Stratification of patients into high-, medium-, and low-risk subgroups for purposes of risk factor management. *J Am Coll Cardiol*. 1996;**27**:964–1047, with permission from Elsevier.

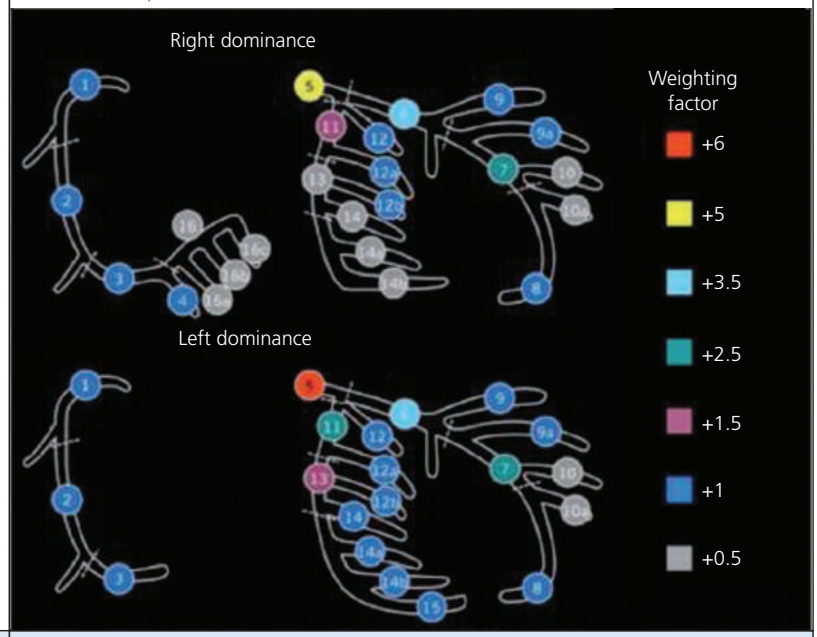
Steps	Variable assessed	Description
Step 1	Dominance	The weight of individual coronary segments varies according to coronary artery dominance (right or left). Co-dominance does not exist as an option in the SYNTAX score.
Step 2	Coronary segment	The diseased coronary segment directly affects the score as each coronary segment is assigned a weight, depending on its location, ranging from 0.5 (i.e. posterolateral branch) to 6 (i.e. left main in case of left dominance). 
Step 3	Diameter stenosis	The score of each diseased coronary segment is multiplied by 2 in case of a stenosis 50–99% and by 5 in case of total occlusion. In case of total occlusion, additional points will be added as follows: - Age >3 months or unknown +1 - Blunt stump +1 - Bridging +1 - First segment visible distally +1 per non visible segment - Side branch at the occlusion +1 if <1.5mm diameter +1 if both <1.5 and ≥1.5mm diameter +0 if ≥ 1.5mm diameter (i.e. bifurcation lesion)
Step 4	Trifurcation lesion	The presence of a trifurcation lesion adds additional points based on the number of diseased segments: - 1 segment +3 - 2 segments +4 - 3 segments +5 - 4 segments +6
Step 5	Bifurcation lesion	The presence of a bifurcation lesion adds additional points based on the type of bifurcation according to the Medina classification: - Medina 1.0.0 or 0.1.0 or 1.1.0: add 1 additional point - Medina 1.1.1 or 0.0.1 or 1.0.1 or 0.1.1: add 2 additional point Additionally, the presence of a bifurcation angle <70° adds 1 additional point.
Step 6	Aorto-ostial lesion	The presence of aorto-ostial lesion segments adds 1 additional point
Step 7	Severe tortuosity	The presence of severe tortuosity proximal of the diseased segment adds 2 additional points
Step 8	Lesion length	Lesion length >20mm adds 1 additional point
Step 9	Calcification	The presence of heavy calcification adds 2 additional points
Step 10	Thrombus	The presence of thrombus adds 1 additional point
Step 11	Diffuse disease/small vessels	The presence of diffusely diseased and narrowed segments distal to the lesion (i.e. when at least 75% of the length of the segment distal to the lesion has a vessel diameter of <2mm) adds 1 points per segment number

Figure 30.8 ESC/EACTS 2014 GL on revascularization. Guide to calculate the SYNTAX score.

ESC /EACTS 2014 Guidelines on myocardial revascularization. *Eur Heart J.* 2014;**35**:2541–619 with permission from Oxford University Press.

Therapy

Therapy of patients with CAD is aimed at alleviating ischaemia and affecting the natural history of the disease by improving endothelial function, stabilizing atherosclerotic plaques, and modifying risk factors.

Medical therapy

General measures

Lifestyle modification is essential for risk reduction and symptomatic relief (Tables 30.11 to 30.16 and Figures 30.9 to 30.11).

Smoking cessation and regular **physical activity** 30–60 min daily for at least 5 days a week are essential.[75,76] Women who smoke may have a 25% greater risk ratio of coronary artery disease than do male smokers, independent of other cardiovascular risk factors.[76] Mild physical activity is better than none, and additional benefits occur with more physical activity.[77] **Sedentary behavior** such as prolonged TV watching increases the risk of cardiovascular disease, diabetes, and all-cause mortality.[78] Loss of **weight** (aimed at a BMI 18.5–24.9 kg/m^2 and a waist circumference of <89 cm in women and <102 in men) is recommended, although BMI, waist circumference, and waist-to-hip ratio do not provide significant additional information about cardiovascular risk beyond that already provided by systolic blood pressure, diabetes, and lipids.[79,80] Reduction of calorie uptake and regular exercise are the best means to lose weight. Overweight is defined as BMI >25 kg/m^2, obesity class I as BMI >30 kg/m^2, obesity class II as BMI >35 kg/m^2, and extreme obesity—class III as BMI ≥40 kg/m^2.[79] Although several drugs are currently approved to treat obesity, only the lipase inhibitor ***orlistat***, the serotonin-2C receptor agonist ***lorcaserin***, the combination of ***phentermine-topiramate***, and, recently, the glucagon-like peptide-1 agonist ***liraglutide*** are FDA-approved for long-term (12 months) use.[81,82]

Recommended **diet** is low-fat Mediterranean diet with high fibre, fruits and vegetables, olive oil, and fish content. This reduces total mortality, as well as mortality from cardiovascular disease and cancer, and the incidence of parkinsonism and Alzheimer's.[83,84] Dietary intake of monounsaturated fatty acids (MUFA) as virgin olive oil, n-3 polyunsaturated fatty acids (n-3 PUFA) as fish oil, and most probably n-6 PUFA, such as linoleic acid in sunflower oil and nuts, is inversely associated with CHD risk.[85] Consumption of **plant seeds**, including whole grains, nuts, legumes, cocoa products, and coffee, also reduces cardiovascular risk and has been associated with decreased mortality.[86,87] However, recent data refute any established benefit of capsule supplementation of **omega-3 fatty acids**.[88–90] Vitamins B (that lower homocysteine), however, do not reduce risk in patients with a previous cardiovascular event.[91] **Plant sterols (phytosterols)** supplements reduce cholesterol absorption by competitive inhibition and transcriptional induction of genes implicated in cholesterol metabolism, but concerns have been raised that they may be atherogenic, although no association between cardiovascular disease and serum sterol concentration was detected in a recent meta-analysis,[92] **Moderate alcohol intake** (1–2 drinks per day for women and up to 2–3 drinks per day for men) reduces cardiovascular risk.[93,94] but episodic heavy drinking (≥ 6 alcoholic drinks) increases the risk of MI, particularly in older individuals,[94] and more than 2 drinks a day in middle-age increases the risk of stroke.[95] **Flavanols** are theoretically beneficial, but their role is not clinically established.[96] Moderate coffee consumption (3-5 cups a day) lowers the risk of cardiovascular disease, whereas heavy coffee consumption is not associated with increased risk.[97]

Influenza vaccine annually is indicated for all patients with CAD.[98]

Blood pressure should be <140/90 mmHg (and probably <130/80 mmHg in the presence of diabetes or chronic renal disease, see Chapter 25).

In **diabetics**, intensive glycaemic control reduces the risk of a coronary event by 15%, but without affecting mortality,[99] and at a risk of increased major hypoglycaemia. Thus, a **HbA$_{1c}$** <7% is recommended,[100] but changes in lifestyle and dietary measures, rather than strict adherence to HbA$_{1c}$ reduction are emphasized.[101] Ideally, and especially in young patients, preprandial and postprandial glucose should be maintained at <130 mg/dL and <180 mg/dL, respectively.[102] **Metformin** has a low side-effect profile (in patients with GFR >45 ml/min/1.73 m^2) and proven efficacy for risk reduction (UKPDS).[103] **Acarbose**, an alpha-glucosidase inhibitor that blocks the absorption of carbohydrate, has also been demonstrated to delay diabetes mellitus and reduce cardiovascular events.[104] Incretin-based therapies such as selective inhibitors dipeptidyl peptidase 4 (**DPP-4**) inhibitors, and glucagon-like peptide-1 (**GLP-1**), enhance insulin secretion and inhibit glucagon suppression and may be used as a second-line therapy for glycaemic control.[105] The DPP-4 inhibitors saxagliptin and alogliptin were shown not to increase the rates of major adverse cardiovascular events in patients at risk of or after an ACS, respectively, although the rate of hospitalization for heart failure may be increased.[106,107] GLP-1 receptor agonists may be cardioprotective,[105] and a once-weekly injection may avoid gastrointestinal side-effects. Second-generation **sulfonylureas** may also reduce the risk of cardiovascular events.[103] **Thiazolidinediones** may increase the risk of heart failure and should not be used in the presence of impaired LV function. Pioglitazone is safer than rosiglitazone in this respect,[108,109] and achieves greater increases in HDL and reductions in glycated haemoglobin and triglycerides compared to glimepiride, with a resultant slower progression of atherosclerosis,[110] but concerns about association with bladder cancer have emerged. Rosiglitazone may also increase

the risk of MI, although this is rather debatable.[111,112] An analysis of data from BARI 2D trial did not detect an association of rosiglitazone treatment with an increase in major ischaemic cardiovascular events among patients with type 2 diabetes mellitus and established coronary artery disease.[113] Thiazolidinediones may also increase the risk of long bone fractures. Glycaemic control with **insulin** may also reduce cardiovascular risk,[103] but early addition of insulin confers no benefit in patients with prediabetes (for definition, see Chapter 25) or patients whose type 2 diabetes is well controlled on diet or medication.[114]

Antiplatelet agents

Aspirin (75–162 mg/d) should be continued indefinitely, unless contraindicated. In high-risk patients, it reduces arterial thrombosis by 25% by inhibiting platelet cyclo-oxygenase-1 and decreasing synthesis of thromboxane A_2 (see also Chapter 28). After CABG, aspirin (100–325 mg/d) should be continued indefinitely (ACCF/AHA 2011 GL on CABG, I-A). Doses higher than 100 mg are no longer recommended following stent implantation. Although aspirin is necessary for secondary prevention, its value for primary prevention is controversial, because although effective for preventing CAD, it is also associated with excess extracranial bleeding.[115,116] In a recent trial, once-daily, enteric-coated 100 mg of aspirin significantly reduced the incidence of non-fatal MI, but not the risk of the composite outcome of cardiovascular death, non-fatal stroke, and non-fatal myocardial infarction, among Japanese patients 60 years or older with hypertension, dyslipidaemia, or diabetes.[115] The American College of Chest Physicians advocates its use for primary prevention in patients without established CAD,[117] whereas the ESC discourages it.[118] However, the ESC Working Group on Thrombosis recommends low-dose aspirin for primary prevention in patients at high risk of death, MI, or stroke (≥2 per 100 subject-years).[119] The AHA/ACC and the American Diabetes Association recommend aspirin (75–162 mg, IIa-B/C) for primary prevention in diabetics who are at increased CVD risk (10-year risk of CVD events over 10%) and who are not at increased risk for bleeding (based on a history of previous gastrointestinal bleeding or peptic ulcer disease or concurrent use of other medications that increase bleeding risk, such as NSAIDs or warfarin). They also consider its use in diabetics at intermediate risk (IIb-B/C).[120,82] In a recent report (May 2014), the FDA advised against its use for primary prevention.

Clopidogrel (75 mg/d) may replace aspirin if aspirin is absolutely contraindicated. In patients receiving a bare-metal stent, clopidogrel should be given for a minimum of 1 month, and ideally up to 12 months, unless the patient is at increased risk of bleeding; in this case, it should be given for a minimum of 2 weeks (see also Chapter 28). In patients receiving DES for a non-ACS indication, clopidogrel 75 mg daily should be added to aspirin and given for 6–12 months if patients are not at high risk of bleeding. However, the optimum duration of antiplatelet therapy following stenting is not established (see Practical aspects of PCI).

Cholesterol-lowering drugs

Statins inhibit the enzyme HMG-CoA reductase that facilitates the production of cholesterol in the liver, and reduce mortality and cardiovascular events both in patients with established CAD and persons at risk.[121–124] The reduction of major cardiac events is proportional to the reduction of LDL cholesterol, and statins in patients with CAD or at high cardiovascular risk aim at LDL <100 mg/dL (or ideally <70 mg/dL) (ESC 2012 GL on CVD prevention; Table 30.16).[125] The ESC guidelines recommend the intensity of therapy to be adjusted to the level of 10-year total fatal atherosclerotic cardiovascular disease risk, as estimated by the SCORE (Systemic Coronary Risk Estimation) system. The 2013 ACC/AHA guidelines on cholesterol treatment have failed to identify enough evidence to support continued use of specific LDL or HDL treatment targets (Figure 30.11 and Table 30.16).[123] They recommend statin therapy in:

1. patients with clinically evident atherosclerotic cardiovascular disease
2. individuals with LDL ≥190 mg/dL (4.9 mmol/L)
3. individuals aged 40–75 years with type 1 or type 2 diabetes and LDL ≥70 mg/dL (1.8 mmol/L)
4. individuals aged 40–75 years with a predicted 10-year risk of ≥7.5% according to a newly developed risk prediction algorithm and LDL ≥ 70 mg/dL (1.8 mmol/L).

The 10-year risk algorithm is based on data from the three NHLBI studies: Atherosclerosis Risk in Community (ARIC), Cardiovascular Health Study (CHS), and Coronary Artery Risk Development in Young Adults (CARDIA). (http://my.americanheart.org/cvriskcalculator). These guidelines are rather controversial. The main criticism is that the proposed algorithm did not use more contemporary data, has not been tested in clinical trials, and may overestimate risk.[126,127] In addition, the guidelines do not provide recommendations for patients not included in the 4 categories previously described. It has also been estimated that in the US they would increase the number of adults eligible for statin therapy by 12.8 million, with the increase seen mostly among older adults without cardiovascular disease.[128] There has been some evidence that patients who achieve an LDL-C level <50 mg/dL are at lower cardiovascular disease risk than are those achieving an LDL-C level 75 to <100 mg/dL, but clear attribution of this to high-dose statin therapy could not be ascertained.[129]

LDL-C levels are calculated by the Friedwald equation (*LDL-C = total cholesterol – HDL-C – triglycerides/5*), that underestimates LDL when triglycerides are ≥150mg/dL.[130]

If triglycerides are >200 mg/dL, elimination of sugar and trans fats intake as well as weight reduction and regular exercise may achieve reductions of up to 50%. Tests of apolipoprotein B and A-I, lipoprotein(a), or lipoprotein-associated phospholipase A2 do not add significant improvement in CVD prediction.[131]

Although **lipoprotein(a) (Lp(a))** is one of the most atherogenic lipoproteins and appears to predict cardiovascular risk[132] there is a lack of standardized measurement procedures, and no evidence that lowering Lp(a) reduces hard cardiovascular endpoints.[133] *Darapladib*, a selective oral inhibitor of lipoprotein-associated phospholipase A2 (LpPLA2), did not significantly reduce the risk for the primary composite endpoint of cardiovascular death, myocardial infarction, or stroke in patients with stable coronary heart disease.[134] However, there has been some observational evidence that lipoprotein apheresis in high-risk patients with progressive cardiovascular disease and isolated Lp(a)-hyperlipoproteinaemia (mean LDL 99 mg/dL, mean Lp(a) 105 mg/dL) may lower the rate of cardiovascular events.[135]

There is a causal effect of **triglycerides** on CAD risk,[136,137] but a causal role for **HDL-C**, though possible, remains less certain, especially in patients taking statins.[138] Low **HDL** levels can be caused by genetic abnormalities, haematologic malignancies, liver disease, acute inflammatory states, and drugs such as anabolic steroids, atypical antipsychotics, antiretroviral therapy, beta blockers, and immunosuppressive agents.[139] They are treated with lifestyle changes, since niacin or inhibitors of cholesterol ester transfer protein did not improve cardiovascular outcomes, despite significantly increasing the HDL cholesterol level.[140–142]

Statins may be **lipophilic** (lovastatin, simvastatin, atorvastatin) or **hydrophilic** (pravastatin, rosuvastatin). Hydrophilic statins may have fewer side effects due to less muscle cell penetration and lower dependence on the cytochrome P450 enzyme, but differences between the two groups by means of clinical outcomes are not established. Furthermore, lipophilic statins cross the blood-brain barrier and might be protective against neurogenerative disorders, such as Parkinson disease.[143] All statins decrease mitochondrial function, attenuate energy production, and alter muscle protein degradation, and may thus produce statin-associated ***myopathy***.[144] Rhabdomyolysis refers to additional renal impairment and/or myoglobinuria. Myopathy with significant elevation of serum creatine kinase (>10 of upper limit of normal-ULN) is a rare but serious side effect of statins, affecting 1 in 1000 to 1 in 10 000 people on standard statin doses. Statin-associated muscle symptoms and CK levels cover a broader range of clinical presentations, usually with normal or minimally elevated CK levels (< 4 ULN), with a prevalence of 7–29% in registries and observational studies. All statins may result in elevated CK levels but simvastatin has been particularly associated with myopathy,[145] and the FDA has warned against its use in high doses (80 mg od-9/6/2011). CYP3A4 inhibitors *ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, nefazodone, and especially itraconazole, HIV protease inhibitors (such as lopinavir, ritonavir, atazanavir, darunavir, and fosamprenavir), and hepatitis C virus protease inhibitors (such as boceprevir and telaprevir)* may significantly increase statin (especially lipophilic such as lovastatin and simvastatin) exposure, and result in rhabdomyolysis. According to an FDA Drug Safety Communication (1 March 2012), the concomitant administration of lovastatin and simvastatin with HIV protease inhibitors or HCV protease inhibitors is contraindicated. Atorvastatin should be restricted to 20 mg od, rosuvastatin to 10 mg, and pravastatin does not need dosage modification, whereas no data are available for fluvastatin, in patients taking HIV or HCV protease inhibitors. Ciclosporin and, rarely, calcium antagonists, digoxin, sildenafil, and excessive consumption of grapefruit or cranberry juice may also increase the risk of myopathy. Additional risk factors for myopathy are age (>80 years), female sex, hypothyroidism, diabetes, renal and hepatic function impairment, preexisting myopathies, major surgery, and vitamin D deficiency that by itself can cause musculoskeletal pain.[146] Interruption of statins for 2–6 weeks and resumption of another statin with lower or intermittent doses and ezetimibe may be needed. When it is difficult to determine whether a patient's symptoms are attributable to statin, the 'n-of-1 trial' approach may be used, i.e. the patient is assigned to statin therapy or placebo, up to three times each, for up to 3 weeks.[147] Mild elevations in ***serum aminotransferases*** arise in up to 3% of treated patients, usually but not invariably without concomitant γGT elevation, but clinically apparent drug-induced liver injury is rare. In the US Drug Induced Liver Injury Network Registry, among 1188 cases of drug-induced liver injury, 22 cases were attributed to a statin with a latency to onset of 34 days to 10 years (median 155 days) since starting therapy. Nine patients presented with cholestatic hepatitis and 12 patients presented with hepatocellular injury, of which six had an autoimmune phenotype. Nine patients were hospitalized, four developed evidence of hepatic failure, and one with pre-existing alcoholic liver disease died. All commonly used statins were implicated.[148] Statin therapy (as well as niacin) is associated with a slightly increased risk of development of ***diabetes***, especially in high doses, but the risk is low, both in absolute terms and when compared with the reduction in coronary events.[149,150] A recent study using the Mendelian randomization principle provided evidence that inhibition of HMGCoA is associated with increased body mass index, leading to increased insulin resistance and increased diabetes.[151] The proposed mechanism is that augmented uptake of cholesterol (caused by statins) in pancreatic β cells lowers insulin production. Patients with familial hypercholesterolaemia have low incidence of type 2 diabetes mellitus, due to their genetically determined low production of the LDL cholesterol receptor.[152]

Statins should not be stopped in high risk primary and secondary prevention patients, but screening of individuals with evidence of metabolic syndrome is reasonable. There is no increased risk of developing cognitive defects, such as memory loss, but available evidence is limited.[153] In another retrospective observational analysis of databases, an increased risk of ***acute kidney injury*** was found with high potency statins (≥10 mg rosuvastatin, ≥20 mg atorvastatin, and ≥40 mg simvastatin) in the first 120 days after initiation of treatment,[154] but such a relationship was refuted in a subsequent meta-analysis.[155] There is no increased risk of cancer with statins,[150] and these agents may actually reduce the risk of cancer in heart transplant recipients.[156] Statin exposure following ischaemic stroke is not associated with intracranial haemorrhage,[157] and statins can reduce stroke risk,[158] but avoiding statins should be considered for patients with a history of intracranial haemorrhage, particularly those cases with a lobar location.[159] Some worsening in energy and exertional fatigue, especially in women, may be seen.[160] In the **elderly** (≥80 years) statins should be used for secondary only prevention and at the lowest doses.[161]

Fibrates added to statin have not been found to reduce cardiovascular events (ACCORD trial),[162] and, according to new guidelines by the AHA, treatment with fibrates is indicated only for cholesterol levels >500 mg/dL.[163] The combination (especially with gemfibrosil) increases the risk of myopathy and fibrates increase homocysteine levels that may be prothrombotic; in addition, the ability of fibrates to increase HDL may be attenuated in patients with type-2 diabetes. Combinations of a statin with a fibrate might still be considered in high-risk individuals such as diabetics with a high triglyceride/low HDL-C pattern.[124,164]

The addition of **ezetimibe**, an inhibitor of NPC1L1, a protein that transports dietary cholesterol from the gut into intestinal enterocytes, to statins has not been found to affect intima media thickness of the carotid and femoral arteries (ENHANCE trial).[165] However, mutations that inactivate NPC1L1 have been associated with a reduced risk of CAD,[166] and compared with atorvastatin monotherapy, the combination of statin plus ezetimibe results in greater coronary plaque regression.[167] In the large IMPROVE-IT trial, adding ezetimibe to statin therapy in patients with an acute coronary event reduced the risk of MI and stroke by 1-2% without affecting cardiovascular mortality.[168]

The addition of **niacin (nicotinic acid)** to statins is not beneficial (AIM-HIGH, and HPS2-THRIVE trials), despite significant improvements in HDL cholesterol and triglyceride levels,[140,141] and niacin may have significant adverse events.

A monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9 **(PCSK9) (alirocumab or evolocumab)** significantly reduces LDL and Lp(a) levels in patients not responding to or intolerant of high-intensity statins and ezetimibe.[169] In patients on maximum doses of statins, addition of alirocumab 150 mg subcutaneously every two weeks for 78 weeks, or evolocumab 140 mg subcutaneously every two weeks or 420 mg monthly, resulted in approximately 50% reductions in composite cardiovascular events at 12 to 18 months.[170,171] PCSK9 inhibitors can be given alone or in combination with statins, and side effects are similar to those of statins with the exception of neurocognitive effects such as amnesia and confusional state (0.9-1.2% vs 0.3-0.5%), and probably myalgia. In another trial in a population of high cardiovascular risk patients with inadequately controlled LDL-C on maximally tolerated doses of statins, alirocumab given subcutaneously (75 mg every 2 weeks) produced significantly greater reductions in LDL-C compared to ezetimibe, without any difference in side effects after 52 weeks therapy.[172] The FDA approved alirocumab and evolocuman for secondary prevention in high-risk patients who cannot control their cholesterol with statins in 2015. **Familial hypercholesterolaemia** is discussed in Chapter 27 and its diagnosis and management in Chapter 28.

Other drugs

Beta blockers should be given in patients with a past MI, acute coronary syndrome, or LV dysfunction in the context of coronary artery disease, unless contraindicated (severe asthma, sick sinus syndrome, AV block). Metoprolol and bisoprolol have been shown to reduce adverse effects in stable patients.[173] However, they may not confer a survival benefit in patients with CAD without prior MI or in patients with a remote MI (>1 year).[174,175]

ACE inhibitors should be given indefinitely in patients with LVEF <40%, hypertension, diabetes, or chronic kidney disease. **Angiotensin II receptor blockers** may be used in patients intolerant of ACE inhibitors. However, ACEIs and ARBs are not beneficial in stable patients with CAD in the absence of mentioned co-morbidities and, especially, heart failure.[176] Aldosterone blockers are recommended in all patients with LVEF <40% and diabetes or heart failure, but without renal dysfunction or hyperkalaemia.

Calcium channel blockers If beta blocker treatment is unsuccessful or contraindicated. Long-acting non-dihydropyridines can be used, instead of beta blockers. When dihydropyridines are used, they should be combined preferably with a beta blocker.

Nitrates are useful for immediate angina relief. Short-acting nitrates are preferred. They may be also considered for long-acting therapy if beta blocker treatment is unsuccessful or contraindicated but with adequate nitrate-free interval to decrease nitrate tolerance. However, prolonged exposure to nitrates induces endothelial dysfunction and oxidative stress, and long-term therapy may worsen the prognosis of patients with CAD or vasospastic angina.[177–179]

Ranolazine For chronic angina relief, usually in addition to, or instead of, beta blockers. Ranolazine is a sodium ion channel inhibitor that does not affect heart rate or blood pressure. It does not affect the incidence of cardiac

mortality or MI (MERLIN-TIMI 36). Initial evidence suggesting that it may suppress reentrant and CAD-induced VF needs to be verified.[180]

Ivabradine has been found promising in heart failure (see Chapter 31) but in patients with stable CAD did not improve outcomes (SIGNIFY trial).[181]

Nicorandil is an anti-ischaemic and cardioprotective agent that as adjunct therapy may reduce major coronary events in stable patients.[182]

Vorapaxar, an inhibitor of the protease-activated receptor PAR-1 through which thrombin activates platelets, reduced the risk of cardiovascular death or ischaemic events in patients with stable atherosclerosis (a history of myocardial infarction, ischaemic stroke, or peripheral arterial disease) who were receiving standard therapy, but also increased the risk of moderate or severe bleeding, including intracranial haemorrhage.[183] Subsequently, reduction of late stent thrombosis and ischaemic stroke in patients without prior stroke were reported.[184,185] Vorapaxar also has been found effective for long-term secondary prevention in patients with diabetes and a prior MI in the absence of a prior stroke or TIA.[186] The FDA approved voraxapar for secondary prevention in patients with a history of MI or peripheral arterial disease but not a previous stroke or TIA, in May 2014.

Proton pump inhibitors are given in patients on dual antiplatelet therapy and at high risk of GI bleed (advanced age, warfarin, steroids, NSAIDs, peptic ulcer). Routine use is not recommended (ACC/AHA 2011 on PCI, III-C). Co-administration of PPIs with clopidogrel is discussed in Chapter 28.

NSAIDs (both non-selective and selective COX-2 inhibitors that spare COX-1 in the gut) are associated with an increased thrombotic risk, probably due to transient platelet COX-1 inhibition as opposed to aspirin that in low doses is a relatively selective and persistent inhibitor of COX-1.[187] Previous studies had shown that diclofenac, and probably ibuprofen, confer the highest risk, with naproxen being the safest agent.[188,189] However, a recent study on postmenopausal women enrolled in the Women's Health Initiative detected an increased risk for non-selective agents with COX-2>COX-1 inhibition such as naproxen, whereas there was no risk elevation for agents with non-selective COX-1>COX-2 inhibition, such as ibuprofen.[190] However, ibuprofen may also interfere with the antiplatelet effect of low dose aspirin.[187] Since the withdrawal of COX-2 inhibitor rofecoxib due to increased incidence of MIs, concerns have also been raised about celecoxib that inhibits neointimal formation, and thus theoretically stent restenosis, but has been associated with a higher thrombotic risk.[191] Thus, in high risk patients on aspirin who need an NSAID, a non-selective agent, perhaps other than ibuprofen, might be selected for the shortest possible time.[187]

Hormone therapy with estrogen plus progestin, or oestrogen alone, should not be given, and the value of antioxidant vitamin supplements (vitamins E, C, or beta carotene) or folic acid, with or without B6 and B12, is not proven.

Chelation therapy (ethylenediamine tetraacetic acid or EDTA) is not indicated and may be harmful because of its potential to cause hypocalcaemia. All patients should be screened for **depression**, particularly following an ACS. Specific guidelines on CAD prevention have been published by ACC/AHA and ESC.

In **syndrome X**, nitrates, beta blockers, and calcium channel blockers may be used but with variable success (Table 30.13). Nicorandil, aminophylline, and imipramine may also be tried.

Table 30.11 ACCF/AHA 2012 GL and 2014 update on stable IHD. Treatment of patients with stable IHD (SIHD)

Patient education	
Patients should have an individualized education plan to optimize care and promote wellness, including:	
a. Education on the importance of medication adherence for managing symptoms and retarding disease progression.	I-C
b. An explanation of medication management and cardiovascular risk reduction strategies in a manner that respects the patient's level of understanding, reading comprehension, and ethnicity.	I-B
c. A comprehensive review of all therapeutic options.	I-B
d. A description of appropriate levels of exercise, with encouragement to maintain recommended levels of daily physical activity.	I-C
e. Introduction to self-monitoring skills.	I-C
f. Information on how to recognize worsening cardiovascular symptoms and take appropriate action.	I-C
Patients should be educated about the following lifestyle elements that could influence prognosis: weight control; maintenance of a body mass index of 18.5–24.9 kg/m^2 and maintenance of a waist circumference <102 cm (40 inches) in men and <88 cm (35 inches) in women (less for certain racial groups); lipid management; blood pressure control; smoking cessation and avoidance of exposure to second-hand smoke; individualized medical, nutrition, and lifestyle changes for patients with diabetes mellitus to supplement diabetes treatment goals and education.	I-C
It is reasonable to educate patients about:	
a. Adherence to a diet that is low in saturated fat, cholesterol, and trans fat; high in fresh fruits, whole grains, and vegetables; and reduced in sodium intake, with cultural and ethnic preferences incorporated.	I-B
b. Common symptoms of stress and depression to minimize stress-related angina symptoms.	I-C
c. Comprehensive behavioural approaches for the management of stress and depression.	I-C
d. Evaluation and treatment of major depressive disorder when indicated.	I-B
Risk factor modification	
Lipid management	
Lifestyle modifications, including daily physical activity and weight management.	I-B
Reduced intake of saturated fats (to <7% of total calories), *trans* fatty acids (to <1% of total calories), and cholesterol (to <200 mg/d).	I-B
Moderate or high dose of a statin in the absence of contraindications or documented adverse effects.	I-A
In statin intolerance, low density lipoprotein cholesterol-lowering therapy with bile acid sequestrants,* niacin,† or both.	IIa-B
Blood pressure management	
Lifestyle modification: weight control; increased physical activity; alcohol moderation; sodium reduction; and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products.	I-B
In blood pressure ≥140/90 mmHg, antihypertensive drug therapy in addition to, or after a trial of, lifestyle modifications.	I-A
Medications used for treatment of high blood pressure should be based on specific patient characteristics and may include ACE inhibitors and/or beta blockers, with addition of other drugs, such as thiazide diuretics or calcium channel blockers, to achieve a goal blood pressure <140/90 mmHg.	I-B
Diabetes management	
A goal HbA_{1c} of ≤7% for patients with a short duration of diabetes mellitus and a long life expectancy.	IIa-B
A goal HbA_{1c} 7% to 9% for certain patients according to age, history of hypoglycaemia, presence of microvascular or macrovascular complications, or coexisting medical conditions.	IIa-C
Initiation of pharmacotherapy interventions to achieve target HbA_{1c}.	IIb-A
Therapy with rosiglitazone should not be initiated in patients with stable IHD.	III-C
Physical activity	
For all patients, 30–60 min of moderate-intensity aerobic activity, such as brisk walking, at least 5 days, and preferably 7 days, per week, supplemented by an increase in daily lifestyle activities (e.g. walking breaks at work, gardening, household work) to improve cardiorespiratory fitness and move patients out of the least-fit, least-active, high-risk cohort (bottom 20%).	I-B
Risk assessment with a physical activity history and/or an exercise test to guide prognosis and prescription.	I-B
Medically supervised programmes (cardiac rehabilitation) and physician-directed, home-based programmes for at-risk patients at first diagnosis.	I-A
Complementary resistance training at least 2 days per week.	IIa-C

(*Continued*)

Table 30.11 Continued

Weight management	
Body mass index and/or waist circumference should be assessed at every visit. Encourage weight maintenance or reduction through an appropriate balance of lifestyle physical activity, structured exercise, caloric intake, and formal behavioural programmes when indicated to maintain or achieve a body mass index between 18.5 and 24.9 kg/m^2 and a waist circumference <102 cm (40 inches) in men and <88 cm (35 inches) in women (less for certain racial groups).	I-B
Initial goal of weight loss therapy to reduce body weight by 5% to 10% from baseline. With success, further weight loss can be attempted if indicated.	I-C
Smoking cessation counselling	
Smoking cessation and avoidance of exposure to environmental tobacco smoke at work and home. Follow-up, referral to special programmes, and pharmacotherapy and a stepwise strategy for smoking cessation (Ask, Advise, Assess, Assist, Arrange, avoid).	I-B
Management of psychological factors	
Screening SIHD patients for depression and refer or treat when indicated.	IIa-B
Treatment of depression has not been shown to improve cardiovascular disease outcomes but might be reasonable for its other clinical benefits.	IIb-C
Alcohol consumption	
Non-pregnant women may have 1 drink (4 ounces of wine, 12 ounces of beer, or 1 ounce of spirits) a day and men 1 or 2 drinks a day, unless alcohol is contraindicated (such as in patients with a history of alcohol abuse or dependence or with liver disease).	IIb-C
Avoiding exposure to air pollution	
Avoid exposure to increased air pollution to reduce the risk of cardiovascular events.	IIa-C
Additional medical therapy to prevent MI and death	
Antiplatelet therapy	
Aspirin 75–162 mg daily indefinitely in the absence of contraindications.	I-A
Clopidogrel when aspirin is contraindicated.	I-B
Aspirin 75–162 mg daily and clopidogrel 75 mg daily in certain high-risk patients.	IIb-B
Dipyridamole is not recommended as antiplatelet therapy in stable IHD.	III-B
Beta blocker therapy	
Beta blockers for 3 years in all patients with normal LV function after MI or ACS.	I-B
Beta blockers in all patients with LVEF ≤40% with heart failure or prior MI, unless contraindicated. (Use should be limited to carvedilol, metoprolol succinate, or bisoprolol, which have been shown to reduce risk of death.)	I-A
Beta blockers as chronic therapy for all other patients with coronary or other vascular disease	IIb-C
Renin–angiotensin–aldosterone blocker therapy	
ACE inhibitors in all patients with hypertension, diabetes mellitus, LV ejection fraction ≤40%, or chronic kidney disease, unless contraindicated.	I-A
ARBs for patients with hypertension, diabetes mellitus, LV systolic dysfunction, or chronic kidney disease and have indications for, but are intolerant of, ACE inhibitors.	I-A
ACE inhibitor in patients with both SIHD and other vascular disease.	IIa-B
ARBs in other patients who are ACE inhibitor intolerant.	IIa-C
Influenza vaccination	
Annual influenza vaccine for patients with SIHD.	I-B
Additional therapy to reduce risk of MI and death	
Oestrogen therapy in post-menopausal women with SIHD.	III-A
Vitamin C, vitamin E, and beta carotene supplementation.	III-A
Treatment of elevated homocysteine with folate or vitamins B6 and B12.	III-A
Chelation therapy	III-C
Treatment with garlic, coenzyme Q10, selenium, or chromium.	III-C

(*Continued*)

Table 30.11 Continued

Medical therapy for relief of symptoms	
Use of anti-ischaemic medications	
Beta blockers as initial therapy for relief of symptoms.	I-B
Calcium channel blockers or long-acting nitrates when beta blockers are contraindicated or cause unacceptable side effects.	I-B
Calcium channel blockers or long-acting nitrates, in combination with beta blockers, when initial treatment with beta blockers is unsuccessful.	I-B
Sublingual nitroglycerin or nitroglycerin spray for immediate relief of angina.	I-B
Long-acting non-dihydropyridine calcium channel blocker (verapamil or diltiazem) instead of a beta blocker as initial therapy.	IIa-B
Ranolazine as a substitute for beta blockers if initial treatment with beta blockers leads to unacceptable side effects or is ineffective or if initial treatment with beta blockers is contraindicated	IIa-B
Ranolazine in combination with beta blockers when initial treatment with beta blockers is not successful in patients with SIHD.	IIa-A
Alternative therapies for relief of symptoms in patients with refractory angina	
Enhanced external counterpulsation for relief of refractory angina.	IIb-B
Spinal cord stimulation for relief of refractory angina.	IIb-C
Transmyocardial revascularization for relief of refractory angina.	IIb-B
Acupuncture for the purpose of improving symptoms or reducing cardiovascular risk.	III-C

* The use of bile acid sequestrant is relatively contraindicated when triglycerides are ≥200 mg/dL and is contraindicated when triglycerides are ≥500 mg/dL.
† Dietary supplement niacin must not be used as a substitute for prescription of niacin.
ACCF/AHA/ACP/AATS/PCNA/SCAI/STS 2012 Guideline for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol*. 2012;**60**:e44–e164 with permission from Elsevier.

Table 30.12 ESC 2012 GL on CVD prevention. Recommendations for prevention and therapy of stable CAD

Recommendations on diet
A healthy diet has the following characteristics:
Saturated fatty acids to account for <10% of total energy intake through replacement by polyunsaturated fatty acids.
Trans-unsaturated fatty acids: as little as possible, preferably no intake from processed food and <1% of total energy intake from natural origin.
<5 g of salt per day.
30–45 g of fibre per day, from wholegrain products, fruits, and vegetables.
200 g of fruit per day (2–3 servings).
200 g of vegetables per day (2–3 servings).
Fish at least twice a week, one of which to be oily fish.
Consumption of alcoholic beverages should be limited to two glasses per day (20 g/day of alcohol) for men and one glass per day (10 g/day of alcohol) for women.
Energy intake should be limited to the amount of energy needed to maintain (or obtain) a healthy weight, i.e. a BMI <25 kg/m^2.
In general, when following the rules for a healthy diet, no dietary supplements are needed.
The 'Five As' for a smoking cessation strategy
A-SK: Systematically inquire about smoking status at every opportunity.
A-DVISE: Unequivocally urge all smokers to quit.
A-SSESS: Determine the person's degree of addiction and readiness to quit.
A-SSIST: Agree on a smoking cessation strategy, including setting a quit date, behavioural counselling, and pharmacological support.
A-RRANGE: Arrange a schedule of follow-up.

(*Continued*)

Table 30.12 Continued

Recommendations regarding physical activity	
Healthy adults of all ages should spend 2.5–5 h a week on physical activity or aerobic exercise training of at least moderate intensity or 1–2.5 h a week on vigorous intense exercise. Sedentary subjects should start light-intensity exercise programmes.	I-A, Strong
Physical activity/aerobic exercise training should be performed in multiple bouts, each lasting ≥10 min and evenly spread throughout the week, i.e. on 4–5 days a week.	IIa-A, Strong
Patients with previous acute myocardial infarction, CABG, PCI, stable angina pectoris, or stable chronic heart failure should undergo moderate to vigorous intensity aerobic exercise training ≥3 times a week and 30 min per session. Sedentary patients should start light-intensity exercise programmes after adequate exercise-related risk stratification.	I-A, Strong
Body weight	
Weight reduction in overweight and obese people	I-A

ACS: acute coronary syndrome; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; LDL, low-density lipoprotein.
ESC 2012 Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2012;**33**:1635–701, with permission from Oxford University Press.

Table 30.13 ESC 2013 GL on stable IHD. Pharmacological therapy

General considerations	
Optimal medical treatment indicates at least one drug for angina/ischaemia relief plus drugs for event prevention.	I-C
Educate patients about the disease, risk factors and treatment strategy and review the patient's response soon after starting therapy.	I-C
Angina/ischaemia relief	
Short-acting nitrates.	I-B
First-line treatment with beta blockers and/or calcium channel blockers to control heart rate and symptoms.	I-A
For second-line treatment, add long-acting nitrates or ivabradine or nicorandil or ranolazine, according to heart rate, blood pressure, and tolerance.	IIa-B
For second-line treatment, trimetazidine.	IIb-B
According to co-morbidities use second-line therapies as first line.	I-C
In asymptomatic patients with large areas of ischaemia (>10%) beta blockers.	IIa-C
Calcium channel blockers and nitrates in vasospastic angina. Beta blockers avoided	IIa-B
Event prevention	
Low-dose aspirin daily in all patients	I-A
Clopidogrel as an alternative in case of aspirin intolerance.	I-B
Statins in all patients.	I-A
ACE inhibitors (or ARBs) if presence of other conditions	I-A
Treatment in patients with microvascular angina	
All patients receive secondary prevention medications including aspirin and statins.	I-B
Beta blockers as first line treatment.	I-B
Calcium antagonists if beta blockers ineffective or not tolerated.	I-B
ACE inhibitors or nicorandil in patients with refractory symptoms.	IIb-B
Xanthine derivatives or neurostimulatory techniques in patients with symptoms refractory to the above listed drugs.	IIb-B

ESC 2013 Guidelines on the management of stable coronary artery disease. *Eur Heart J.* 2013;**34**:2949–3003, with permission from Oxford University Press.

Table 30.14 ESC 2013 GL on stable CAD. Major side-effects, contra-indications, drug–drug interactions (DDI), and precautions of anti-ischaemic drugs

Drug class	Side effects[a]	Contraindications	DDI	Precautions
Short-acting and long-acting nitrates	Headache Flushing Hypotension Syncope and postural hypotension Reflex tachycardia Methaemoglobinaemia	Hypertrophic obstructive cardiomyopathy	PDE5 inhibitors (sildenafil or similar agents) α-adrenergic blockers CCBs	-
Beta blockers[b]	Fatigue, depression Bradycardia Heart block Bronchospasm Peripheral vasoconstriction Postural hypotension Impotence Hypoglycaemia/mask hypoglycaemia signs	Low heart rate or heart conduction disorder Cardiogenic shock Asthma COPD caution; may use cardioselective beta blockers if fully treated by inhaled steroids and long-acting beta agonists Severe peripheral vascular disease Decompensated heart failure Vasospastic angina	Heart-rate lowering CCB Sinus-node or AV conduction depressors	Diabetics COPD
CCBs: heart-rate lowering	Bradycardia Heart conduction defect Low ejection fraction Constipation Gingival hyperplasia	Low heart rate or heart rhythm disorder Sick sinus syndrome Congestive heart failure Low BP	Cardiodepressant (beta blockers, flecainide) CYP3A4 substrates	-
CCBs: dihydropyridines	Headache Ankle swelling Fatigue Flushing Reflex tachycardia	Cardiogenic shock Severe aortic stenosis Obstructive cardiomyopathy	CYP3A4 substrates	-
Ivabradine	Visual disturbances Headache, dizziness Bradycardia Atrial fibrillation Heart block	Low heart rate or heart rhythm disorder Allergy Severe hepatic disease	QTc prolonging drugs Macrolide antibiotics Anti-HIV Anti-fungal	Age >75 years Severe renal failure
Nicorandil	Headache Flushing Dizziness, weakness Nausea Hypotension Oral, anal, gastrointestinal ulceration	Cardiogenic shock Heart failure Low blood pressure	PDE5 inhibitors (sildenafil or similar agents)	-
Trimetazidine	Gastric discomfort Nausea Headache Movement disorders	Allergy Parkinson disease Tremors and movement disorders Severe renal impairment	None reported	Moderate renal impairment Elderly
Ranolazine	Dizziness Constipation Nausea QT prolongation	Liver cirrhosis	CYP450 substrates (digoxin, simvastatin, cyclosporine) QTc prolonging drugs	-
Allopurinol	Rash Gastric discomfort	Hypersensitivity	Mercaptopurine/ azathioprine	Severe renal failure

AV, atrioventricular; CCBs, calcium channel blockers; COPD, chronic obstructive pulmonary disease; DDI, Drug-Drug Interactions; HIV, Human Immunodeficiency Virus; PDE5, phosphodiesterase type 5.

[a] Very frequent or frequent; may vary according to specific drugs within the therapeutic class.

[b] Atenolol, metoprolol CR, bisoprolol, carvedilol.

ESC 2013 Guidelines on the management of stable coronary artery disease. *Eur Heart J*. 2013;**34**:2949–3003, with permission from Oxford University Press.

Table 30.15 ESC 2013 GL on diabetes

Management of patients with stable and unstable coronary artery disease and diabetes	
Patients with CVD investigated for disorders of glucose metabolism.	I-A
ACE-I or ARBs to reduce the risk for cardiovascular events.	I-A
Statin to reduce the risk for cardiovascular events.	I-A
Aspirin to reduce the risk for cardiovascular events.	I-A
Platelet P2Y12 receptor inhibition in patients with DM and ACS in addition to aspirin.	I-A
Beta-blockers considered to reduce mortality and morbidity in patients with DM and ACS.	IIa-B
Insulin-based glycaemic control in hyperglycaemia (>10 mmol/L or >180 mg/dL) with the target adapted to possible comorbidities.	IIa-C
Glycaemic control that may be accomplished by different glucose-lowering agents in patients with DM and ACS.	IIa-B

ACE-I, angiotensin converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blockers; CAD, coronary artery disease; CVD, cardiovascular disease; DM, diabetes mellitus.
ESC 2013 Guidelines on diabetes, pre-diabetes and cardiovascular diseases. *Eur Heart J.* 2013:**34**:3035–87, with permission from Oxford University Press.

Table 30.16 Treatment of dyslipidaemias

ESC/EAS 2011 GL on dyslipidaemias (adopted by the ESC 2013 GL on stable CAD). Lipid analyses as treatment target in the prevention of CVD	
LDL-C is recommended as target for treatment.	I-A
TC should be considered as treatment target if other analyses are not available.	IIa-A
TG should be analysed during the treatment of dyslipidaemias with high TG levels.	IIa-B
Non-HDL-C should be considered as a secondary target in combined hyperlipidaemias, diabetes, the MetS, or CKD.	IIa-B
Apo B should be considered as a secondary treatment target.	IIa-B
HDL-C is not recommended as a target for treatment.	III-C
The ratios apo B/apo AI and non-HDL-C/HDL-C are not recommended as targets for treatment.	III-C
ESC 2012 GL on CVD prevention. Recommendations on management of hyperlipidaemia	
The recommended target levels are <5 mmol/L (less than ~190 mg/dL) for total plasma cholesterol and <3 mmol/L (less than ~115 mg/DL) for LDL cholesterol for subjects at low or moderate risk.	I-A
In patients at high CVD risk, an LDL cholesterol goal <2.5 mmol/L (less than ~ 100 mg/dL) is recommended.	I-A
In patients at very high CVD risk, the recommended LDL cholesterol target is <1.8 mmol/L (less than ~ 70 mg/dL) or a ≥50% LDL cholesterol reduction when the target level cannot be reached.	I-A
All patients with familial hypercholesterolaemia must be recognized as high-risk patients and be treated with lipid-lowering therapy.	I-A
In patients with an ACS, statin treatment in high doses has to be initiated while the patients are in hospital.	I-A
Prevention on non-haemorrhagic stroke: treatment with statins must be started in all patients with established atherosclerotic disease and in patients at high risk for developing CVD. Treatment with statins must be started in patients with a history of non-cardioembolic ischaemic stroke.	I-A
Occlusive arterial disease of the lower limbs and carotid artery disease are CHD risk-equivalent conditions and lipid-lowering therapy is recommended.	I-A
Statins should be considered as the first-line drugs in transplant patients with dyslipidaemia.	IIa-B
Chronic kidney disease (stages 2–5, i.e. GFR <90 mL/min/1.73 m^2) is acknowledged as a CHD risk-equivalent and the LDL cholesterol target in these patients should be adapted to the degree of renal failure.	IIa-C

(*Continued*)

Table 30.16 Continued

ESC/EAS 2011 GL on dyslipidaemias (adopted by the ESC 2013 GL on stable CAD). Impact of lifestyle changes on lipid levels

	Magnitude of the effect	Level of evidence
Lifestyle interventions to reduce TC and LDL-C levels		
Reduce dietary saturated fat	+++	A
Reduce dietary trans fat	+++	A
Increase dietary fibre	++	A
Reduce dietary cholesterol	++	B
Utilize functional foods enriched with phytosterols	+++	A
Reduce excessive body weight	+	B
Utilize soy protein products	+	B
Increase habitual physical activity	+	A
Utilize red yeast rice supplements	+	B
Utilize polycosanol supplements	–	B
Lifestyle interventions to reduce TG levels		
Reduce excessive body weight	+++	A
Reduce alcohol intake	+++	A
Reduce intake of mono- and disaccharides	+++	A
Increase habitual physical activity	++	A
Reduce total amount of dietary carbohydrate	++	A
Utilize supplements of n-3 polyunsaturated fat	++	A
Replace saturated fat with mono- or polyunsaturated fat	+	B
Lifestyle interventions to increase HDL-C levels		
Reduce dietary trans fat	+++	A
Increase habitual physical activity	+++	A
Reduce excessive body weight	++	A
Reduce dietary carbohydrates and replace them with unsaturated fat	++	A
Use alcohol with moderation	++	B
Among carbohydrate-rich foods, prefer those with low glycaemic index and high fibre content	+	C
Quit smoking	+	B
Reduce intake of mono- and disaccharides	+	C

ESC/EAS 2011 GL on dyslipidaemias (adopted by the ESC 2013 GL on stable CAD). Monitoring lipids and enzymes in patients on lipid-lowering therapy

Testing lipids

How often should lipids be tested?

Before starting lipid-lowering drug treatment, at least two measurements should be made, with an interval of 1–12 weeks, with the exception of conditions where immediate drug treatment is suggested, such as in ACS.

How often should patients' lipids be tested after starting lipid-lowering treatment?

8 (± 4) weeks after starting drug treatment.

8 (± 4) weeks after adjustments to treatment until within the target range.

How often should cholesterol or lipids be tested once a patient has reached target or optimal cholesterol?

Annually (unless there are adherence problems or another specific reason for more frequent reviews).

(*Continued*)

Table 30.16 Continued

Monitoring liver and muscle enzymes
How often should liver enzymes (ALT) be routinely measured in patients taking lipid-lowering drugs?
Before treatment.
8 weeks after starting drug treatment or after any dose increase.
Annually thereafter if liver enzymes are <3 × ULN.
What if liver enzymes become raised in a person taking lipid-lowering drugs?
If <3 × ULN:
Continue therapy.
Recheck liver enzymes in 4–6 weeks.
If values rise to ≥3 × ULN:
Stop statin or reduce dose; recheck liver enzymes within 4–6 weeks.
Cautious reintroduction of therapy may be considered after ALT has returned to normal.
How often should CK be measured in patients taking lipid-lowering drugs?
Pre-treatment
Before starting treatment.
If baseline CK level >5 × ULN, do not start drug therapy; recheck.
Monitoring
Routine monitoring of CK is not necessary.
Check CK if patient develops myalgia.
Increase alertness regarding myopathy and CK elevation in patients at risk, such as elderly patients, concomitant interfering therapy, multiple medications, liver or renal disease.
What if CK becomes raised in a person taking lipid-lowering drugs?
If >5 × ULN:
Stop treatment; check renal function, and monitor CK every 2 weeks.
Consider the possibility of transient CK elevation for other reasons, such as muscle exertion.
Consider secondary causes of myopathy if CK remains elevated.
If ≤5 × ULN:
If no muscle symptoms, continue statin (patients should be alerted to report symptoms; consider further checks of CK).
If muscle symptoms, monitor symptoms and CK regularly.

ACC/AHA 2013 GL on treatment of cholesterol. Secondary causes of hyperlipidaemia most commonly encountered in clinical practice

Secondary cause	Elevated LDL-C	Elevated triglycerides
Diet	Saturated or *trans* fats, weight gain, anorexia	Weight gain, very low-fat diets, high intake of refined carbohydrates, excessive alcohol intake
Drugs	Diuretics, cyclosporine, glucocorticoids, amiodarone	Oral oestrogens, glucocorticoids, bile acid sequestrants, protease inhibitors, retinoic acid, anabolic steroids, sirolimus, raloxifene, tamoxifen, beta blockers (not carvedilol), thiazides
Diseases	Biliary obstruction, nephrotic syndrome	Nephrotic syndrome, chronic renal failure, lipodystrophies
Disorders and altered states of metabolism	Hypothyroidism, obesity, pregnancy	Diabetes (poorly controlled), hypothyroidism, obesity, pregnancy

*Cholesterol and triglycerides rise progressively throughout pregnancy; treatment with statins, niacin, and ezetimibe are contraindicated during pregnancy and lactation.

(*Continued*)

Table 30.16 Continued

ACC/AHA 2013 GL on treatment of cholesterol. Recommendations for treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults—statin treatment	
Treatment targets	
No recommendations for or against specific LDL–C or non-HDL–C targets	
Secondary prevention	
High-intensity statin therapy in women and men ≤75 years with clinical ASCVD*. In case of side-effects, use moderate-intensity therapy.	I-A
High- or moderate-intensity statin therapy in individuals >75 years with clinical ASCVD.	IIa-B
Primary prevention in individuals ≥21 years of age with LDL–C ≥190 mg/dL	
Evaluation for secondary causes of hyperlipidaemia.	I-B
Maximum tolerated statin therapy.	I-B
Intensification of therapy to achieve at least a 50% LDL-C reduction.	IIa-B
Addition of a non-statin after achievement of maximum intensity statin therapy.	IIb-C
Primary prevention in individuals with diabetes mellitus and LDL-C 70–189 mg/dL	
Moderate-intensity statin therapy for adults 40–75 years.	I-A
High-intensity statin therapy for adults 40–75 years with a ≥7.5% estimated 10-year ASCVD risk**.	IIa-B
Individualize and discuss with patient the option of statin therapy in adults <40 or >75 years.	IIa-C
Primary prevention in individuals without diabetes mellitus and with LDL-C 70–189 mg/dL	
Estimate 10-year ASCVD* risk to guide initiation of statin therapy.	I-B
Moderate- to high-intensity statin therapy for adults 40–75 years with a risk ≥7.5%.	I-A
Moderate intensity statin for adults 40–75 years with a risk 5–7%.	IIa-B
Individualize and discuss with patient the option of statin therapy in adults 40–75 years.	IIa-C
Individualize and discuss with patient the option of statin therapy in adults not in a statin benefit group.	IIb-C
Heart failure and haemodialysis	
No recommendation for initiation or discontinuation of statin in patients with NYHA class II-IV heart failure or maintenance haemodialysis.	

ACC/AHA 2013 GL on treatment of cholesterol. High-, moderate- and low-intensity statin therapy		
High-intensity statin therapy	**Moderate-intensity statin therapy**	**Low-intensity statin therapy**
Daily dose lowers LDL-C on average, by approximately ≥50%	Daily dose lowers LDL-C on average, by approximately 30% to <50%	Daily dose lowers LDL-C on average, by approximately <30%
Atorvastatin (40)–80 mg Rosuvastatin 20 *(40)* mg	Atorvastatin 10 *(20)* mg Rosuvastatin *(5)* 10 mg Simvastatin 20–40 mg Pravastatin 40 *(80)* mg Lovastatin 40 mg *Fluvastatin XL 80 mg* Fluvastatin 40 mg bid *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* Pravastatin 10–20 mg Lovastatin 20 mg *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

ACC/AHA 2013 GL on treatment of cholesterol. Statin safety recommendations	
Characteristics predisposing individuals to statin adverse effects Multiple or serious co-morbidities, including impaired renal or hepatic function History of previous statin intolerance or muscle disorders Unexplained ALT elevations >3 times ULN Concomitant use of drugs affecting statin metabolism >75 years of age History of haemorrhagic stroke Asian ancestry	I-B

(*Continued*)

Table 30.16 Continued

CK measurement	
Muscle pain, tenderness, stiffness, cramping, weakness, generalized fatigue	IIa-C
Muscle disease, family history of statin intolerance, drugs that increase the risk of myopathy	IIa-C
Routinely	III-A
If muscle symptoms develop	
Establish initiation of symptoms before or after statin therapy	IIa-B
In severe symptoms discontinue statins and evaluate CK, creatinine, urinalysis for myoglobinuria	IIa-B
In mild to moderate symptoms	
Discontinue the statin until evaluation of symptoms	IIa-B
Investigate for hypothyroidism, renal or hepatic dysfunction, polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, primary muscle diseases	
If symptoms resolve give the original or lower dose to establish causal relationship. In this case use a low dose of a different statin and increase as tolerated	
If after 2 months symptoms or CK do not resolve completely, consider other causes and if established, resume statin therapy	
Hepatic transaminases measurement	
Baseline before initiating treatment	I-B
Hepatotoxicity symptoms (fatigue or weakness, loss of appetite, abdominal pain, dark-coloured urine or yellowing of the skin or sclera)	IIa-C
Diabetes screening	
Dietary measures, physical activity, and smoking cessation, but no statin discontinuation if diabetes develops	I-B
Decrease statin dose when **LDL-C <40 mg/dL** (two measurements)	IIb-C
Caution with statin therapy in >75 years, drugs interfering with metabolism, for transplantation or HIV	IIa-C
If **confusional state or memory impairment** develop evaluate the patient for systemic and neuropsychiatric causes in addition to the possibility of statin side effects	IIb-C
Simvastatin in doses ≥**80 mg** daily	III-C
ACC/AHA 2013 GL on treatment of cholesterol. Monitoring, optimizing, and insufficient response to statin therapy	
Monitoring statin therapy	
Fasting lipids 4–12 weeks after initiation or dose adjustment and then every 3–12 months	I-A
Optimizing statin therapy	
Maximum tolerated dose used if high- or moderate intensity recommended but not tolerated	I-B
Insufficient response to statin therapy	
In insufficient response or intolerance: Reinforce medication adherence Reinforce adherence to intensive lifestyle changes Exclude secondary causes of hyperlipidaemia	I-A
Focus on the intensity of the statin therapy	IIa-B
As an aid to monitoring: High-intensity statin therapy generally results in an average LDL-C reduction of ≥50% Moderate-intensity statin therapy generally results in an average LDL-C reduction of 30 to <50% LDL–C levels and % reduction to be used only to assess response to therapy and adherence. Not to be used as performance standards.	
In individuals at higher ASCVD risk and a less than anticipated therapeutic response despite maximum tolerated intensity, addition of a non-statin cholesterol-lowering drug(s) may be considered if the risk reduction benefits outweigh the potential for adverse effects	IIb-C
Higher-risk individuals include: Clinical ASCVD and <75 years Baseline LDL–C ≥190 mg/dL 40–75 years and diabetes mellitus	

(*Continued*)

Table 30.16 Continued

In individuals who are candidates for statin treatment but are in complete statin intolerance, use non-statin cholesterol-lowering drugs that have been shown to reduce ASCVD events in RCTs if the risk-reduction benefits outweigh the potential for adverse effects.	IIa-B
ACC/AHA 2013 GL on treatment of cholesterol. Non-statin safety recommendations	
Safety of niacin	
Baseline hepatic transaminases, fasting blood glucose or haemoglobin A1c, and uric acid obtained before treatment, during up-titration, and every 6 months	I-B
Niacin should not be used if: Hepatic transaminase are >2–3 times ULN Persistent severe cutaneous symptoms, persistent hyperglycaemia, acute gout or unexplained abdominal pain or gastrointestinal symptoms occur New-onset atrial fibrillation or weight loss occurs	III-B
In adverse effects from niacin, the risk/benefit ratio should be reconsidered before reinitiating niacin therapy	I-B
To reduce the frequency and severity of adverse cutaneous symptoms: Start niacin at a low dose and titrate to a higher dose over a period of weeks Take niacin with food or premedicating with aspirin 325 mg 30 min before niacin dosing to alleviate flushing symptoms If an extended-release preparation is used, increase the dose from 500 mg to a maximum of 2000 mg/day over 4–8 weeks If immediate-release niacin is chosen, start at a dose of 100 mg tds and up-titrate to 1 g tds or 1.5 g bd	IIa-C
Safety of bile acid sequestrants	
Fasting triglycerides ≥300 mg/dL or type III hyperlipoproteinaemia, because severe triglyceride elevations might occur (fasting lipid obtained before, 3 months after initiation, and every 6–12 months)	III-B
Triglycerides 250–299 mg/dL. Evaluate fasting lipids in 4–6 weeks and discontinue if triglycerides exceed 400 mg/dL	IIa-C
Safety of cholesterol-absorption inhibitors	
Hepatic transaminases before initiating ezetimibe. When coadministered with a statin, monitor transaminases as clinically indicated, and discontinue ezetimibe if persistent ALT elevations >3 times ULN	IIa-B
Safety of fibrates	
Gemfibrozil not in patients on statin therapy (increased risk for muscle symptoms and rhabdomyolysis)	III-B
Fenofibrate with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering (when >500 mg/dL) outweigh the risk	IIb-C
Creatinine and eGFR before fenofibrate initiation, in 3 months, and every 6 months thereafter	I-B
Fenofibrate should not be used in moderate or severe renal impairment (eGFR <30 mL/min/1.73 m^2)	III-B
If eGFR is 30–59 mL/min/1.73 m^2, fenofibrate should not exceed 54 mg/day	III-B
If, during follow-up, the eGFR decreases persistently to ≤30 mL/min/1.73 m^2, fenofibrate should be discontinued	III-B
Safety of omega-3 fatty acids	
If EPA and/or DHA are used for severe hypertriglyceridaemia, (≥500 mg/dL), evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding	IIa-B

A downloadable spreadsheet enabling estimation of 10-year and lifetime risk for ASCVD and a web-based calculator are available at http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/science-andquality/practice-guidelines-and-quality-standards/2013-prevention-guideline-tools.aspx.
* Clinical atherosclerotic cardiovascular disease (ASCVD) includes acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin.
** The Pooled Cohort Equations are used to estimate 10-year ASCVDrisk in individuals with and without diabetes.
ACS, acute coronary syndrome; ALT, alanine aminotransferase; Apo, apolipoprotein; CHD, coronary heart disease; CK, creatine phospholkinase; CKD, chronic kidney disease; CVD, cardiovascular disease; GFR, glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low density lipoprotein cholesterol; MetS, metabolic syndrome; TC, total cholesterol; TG, triglyceride; ULN, upper limit of normal.
ESC/EAS 2011 Guidelines for the management of dyslipidaemias. *Eur Heart J*. 2011;**32**:1769–818, with permission from Oxford University Press.
ESC 2012 Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2012;**33**:1635–701, with permission from Oxford University Press.
ACC/AHA 2013 Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. *J Am Coll Cardiol*. 2013;**63**:2889–934 with permission from Elsevier.

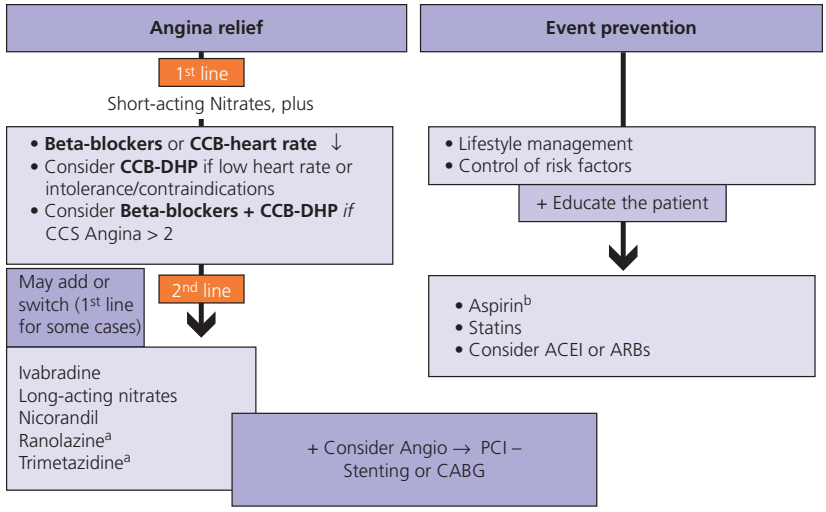


Figure 30.9 ESC 2013 GL on stable CAD. Medical management of patients with stable coronary artery disease

[a] Data for diabetics.

[b] If intolerance, consider clopidogrel.

ACCF indicates American College of Cardiology Foundation; ACEI, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin receptor blocker; ASA, aspirin; ATP III, Adult Treatment Panel 3; BP, blood pressure; CABG, coronary artery bypass graft; CCB, calcium channel blocker; CCS, Canadian Cardiovascular Society; CKD, chronic kidney disease; DHP, dihydropyridine; HDL-C, high density lipoprotein cholesterol; JNC VII, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LDL-C, low density lipoprotein cholesterol; LV, left ventricular; MI, myocardial infarction; NHLBI, National Heart, Lung, and Blood Institute; NTG, nitroglycerin; PCI, percutaneous coronary intervention.

ESC 2013 Guidelines on the management of stable coronary artery disease. *Eur Heart J.* 2013;**34**:2949–3003, with permission from Oxford University Press.

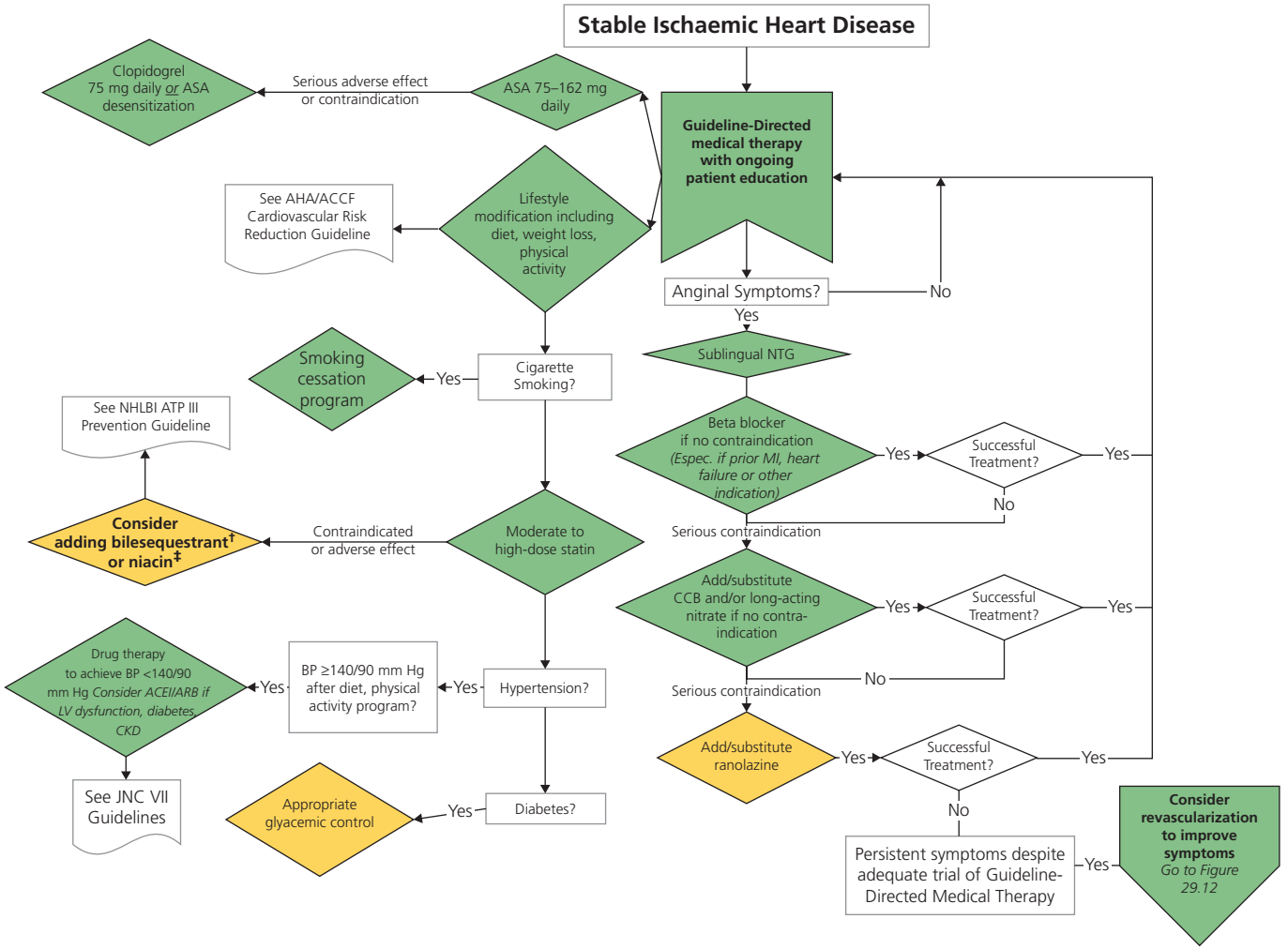


Figure 30.10 ACCF/AHA 2012 GL on stable IHD. Algorithm for guideline-directed medical therapy for patients with SIHD.*

* Colours correspond to the class of recommendations in the ACCF/AHA. The algorithms do not represent a comprehensive list of recommendations (see full guideline text for all recommendations).
† The use of bile acid sequestrant is relatively contraindicated when triglycerides are ≥200 mg/dL and is contraindicated when triglycerides are ≥500 mg/dL.
‡ Dietary supplement niacin must not be used as a substitute for prescription niacin.
ACCF indicates American College of Cardiology Foundation; ACEI, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin receptor blocker; ASA, aspirin, ATP III, Adult Treatment Panel 3; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; HDL-C, high density lipoprotein cholesterol; JNC VII, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LDL-C, low density lipoprotein cholesterol; LV, left ventricular; MI, myocardial infarction; NHLBI, National Heart, Lung, and Blood Institute; and NTG, nitroglycerin.
ACCF/AHA/ACP/AATS/PCNA/SCAI/STS 2012 Guideline for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol*. 2012;**60**:e44–e164 with permission from Elsevier.

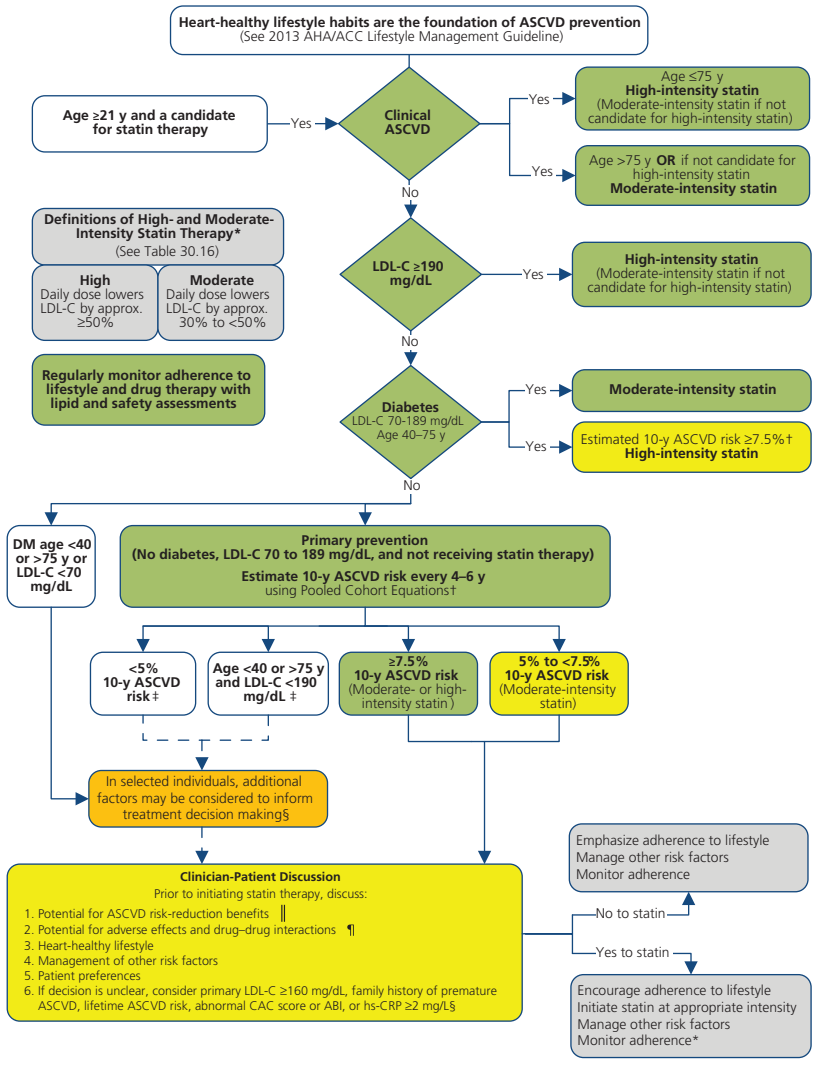


Figure 30.11 2013 ACC/AHA 2013 GL on cholesterol. Statin initiation recommendations to reduce atherosclerotic cardiovascular disease (ASCVD) risk I adults.

Colours correspond to the Classes of Recommendation (green I, yellow IIa, orange IIb).
Assessment of the potential for benefit and risk from statin therapy for ASCVD prevention provides the framework for clinical decision making, incorporating patient preferences.
* Per cent reduction in LDL-C can be used as an indication of response and adherence to therapy, but is not itself a treatment goal.
† The Pooled Cohort Equations can be used to estimate 10-year ASCVD risk in individuals with and without diabetes. The estimator within this application should be used to inform decision making in primary prevention patients not on a statin.
‡ Consider moderate-intensity statin as more appropriate in low-risk individuals.
§ For those in whom a risk assessment is uncertain, consider factors such as primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidaemias, family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative, hs-CRP ≥2 mg/L, CAC score ≥300 Agatston units, or ≥75th percentile for age, sex, and ethnicity (for additional information, see http://www.mesa-nhlbi.org/CACReference.aspx), ABI <0.9, or lifetime risk of ASCVD. Additional factors that may aid in individual risk assessment may be identified in the future.
‖ Potential ASCVD risk-reduction benefits. The absolute reduction in ASCVD events from moderate- or high-intensity statin therapy can be approximated by multiplying the estimated 10-year ASCVD risk by the anticipated relative-risk reduction from the intensity of statin initiated (~30% for moderate-intensity statin or ~45% for high-intensity statin therapy). The net ASCVD risk-reduction benefit is estimated from the number of potential ASCVD events prevented with a statin, compared to the number of potential excess adverse effects.
¶ Potential adverse effects. The excess risk of diabetes is the main consideration in ~0.1 excess cases per 100 individuals treated with a moderate-intensity statin for 1 year and ~0.3 excess cases per 100 individuals treated with a high-intensity statin for 1 year. In RCTs, both statin-treated and placebo-treated participants experienced the same rate of muscle symptoms. The actual rate of statin-related muscle symptoms in the clinical population is unclear. Muscle symptoms attributed to statin therapy should be evaluated.
ABI indicates ankle-brachial index; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; and RCT, randomized controlled trial.
ACC/AHA 2013 Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. *Circulation*. 2013;**129**:S1–S45 with permission from Wolters Kluwer.

Revascularization

Indications

Revascularization is appropriate in certain settings for prognostic or symptomatic relief (Tables 30.17 to 30.19, and Figures 30.1 to 30.3, 30.6, 30.7, and 30.12 to 30.16).

The earliest trials of coronary artery bypass grafting (CABG) vs medical therapy in patients with chronic stable angina were conducted in the 1970s and 1980s.[192–194] Symptomatic relief was better with CABG; however, no overall difference was observed in survival or freedom from MI with CABG vs medical therapy, except in patients with **left main disease (VA trial)**, **multivessel disease plus LV dysfunction but not overt heart failure (35% <LVEF <50%) (VA and CASS trials)**, and probably **proximal LAD disease in conjunction with multivessel disease and LVEF ≥50% (European trial)**. Thus, in high- and medium-risk patients CABG decreases mortality compared to medical therapy. In low-risk patients it is detrimental.[195,196] Despite major advances in medical therapy (especially aggressive lipid-lowering and antiplatelet therapy) and surgical techniques (including the use of the internal mammary artery), the overall conclusions from these trials and associated registry studies are probably considered valid today, but the potential benefit of revascularization may be of a lesser magnitude. The **MASS-II trial on patients with proximal multivessel coronary stenosis of more than 70% by visual assessment and documented ischaemia** compared 10-year survival of medically treated patients with those treated with PCI or CABG. Medical therapy was associated with a significantly higher incidence, 2.29-fold increased risk, of combined events of cardiac death, subsequent myocardial infarction, and additional revascularization compared to CABG,[197] although a recent analysis of MASS-II demonstrated similar results on the evolution of LVEF in patients with multivessel disease and preserved LVEF regardless of the method of treatment.[198] In the BARI 2D trial on diabetics, patients with extensive coronary artery disease had less cardiac death or MI when treated with CABG and optimum medical therapy than medical therapy alone.[199] Thus, CABG offers improved survival/MI/stroke rates in **diabetics with extensive coronary disease (total occlusions, proximal left coronary disease, and greater myocardial jeopardy) and reduced LV function (LVEF <50%, but not class III or IV heart failure—BARI 2D trial)**.[200]

The presence of **extensive ischaemia** is useful in identifying patients who would benefit from revascularization. Revascularization by CABG and PCI may offer a greater survival benefit than medical therapy in patients with significant inducible ischaemia (>10% of LV myocardium).[63–66] This, however, has not been verified in all studies.[67–69]

In patients with **ischaemic heart failure and LVEF <35%**, the value of CABG is now established.[201,202] In the STICHES trial, in patients with LVEF ≤35% (but not with left main stem significant stenosis or class II or greater angina), CABG reduced cardiovascular death, but not total mortality.[202] The presence of inducible ischaemia,[68] or the detection of myocardial viability by SPECT or dobutamine echocardiography,[41] did not identify patients who would benefit with CABG in this trial, although, considering crossovers and hospitalization for cardiovascular causes, favoured revascularization. The assessment of myocardial viability also did not identify patients with a survival benefit from CABG, as compared with medical therapy alone in both the STICH and the smaller Heart trial.[41,201] However, in patients with extensive disease and at least two of prognostic factors, such as presence of 3-vessel CAD, EF below the median (27%), and end-systolic volume index (ESVI) above the median (79 mL/m^2), CABG did reduce mortality compared to medical therapy alone.[45] In addition, in a 10-year follow-up of the STICH, CABG did reduce total as well as cardiac mortality over a 10-year follow-up (STICHES trial).[203]

In the absence of acute coronary syndrome or recent myocardial infarction, elective percutaneous coronary intervention with balloon, bare metal stents (BMS) or drug-eluting stents (DES) has not been shown to improve survival or decrease the risk of MI, compared to medical therapy alone, regardless of the use of stents, even in the presence of proven ischaemia.[204–207] The COURAGE trial enrolled 2287 patients with >70% coronary stenosis in at least one proximal epicardial coronary artery and evidence of myocardial ischaemia or angina. For the composite of death and non-fatal MI, no statistical difference was found between the two groups after a mean follow-up of 4.6 years. Rates of angina were consistently lower in the PCI group than in the medical therapy group during follow-up but were no longer statistically significant at 5 years. Rates of subsequent revascularization were also lower in the PCI group.[208] There was a trend for better survival in a subgroup of patients with substantial ischaemia (>10% myocardium).[60] In the FAME II trial, 888 patients with stable coronary artery disease and at least one stenosis with FFR ≤0.80 were randomly assigned to FFR-guided PCI plus the best available medical therapy or the best available medical therapy alone. In 2 years, the primary endpoint, a composite of death, myocardial infarction, or urgent revascularization, was met by 8.1% of patients in the PCI group and 19.5% in the medical-therapy group (hazard ratio, 0.39; p <0.001). The difference was driven by a lower rate of urgent revascularization in the PCI group than in the medical-therapy group (4% vs 16.3%; p <0.001).[209] Thus, lesions with **FFR <0.80** may be treated with PCI,[210] whereas coronary lesions with fractional flow reserve (FFR) >0.8 can be safely left on

medical therapy without intervention (DEFER, FAME, and FAME II trials). Routine FFR assessment of at least ambiguous lesions at time of diagnostic angiography should be considered,[71,211,212] although reservations have been raised.[213] In stable, low-risk patients, PCI may be beneficial by means of reducing a combined endpoint of mortality and incidence of an acute coronary syndrome, compared to medical therapy alone (JSAP trial).[214] PCI may be also beneficial in stable patients who had had an MI within the previous 3 months,[204] particularly with full revascularization in the presence of **post-MI residual ischaemia** (combined endpoint of cardiac death, non-fatal MI, and/or symptom-driven revascularization—SWISSI II trial).[215] In a retrospective analysis of the UK Central cardiac Audit database, elective chronic total coronary occlusion angioplasty improved long-term survival.[216] However, in the only randomized trial conducted so far (OAT), opening of an occluded artery beyond 24 h after the MI in patients without residual ischaemia does not decrease the risk of death, reinfarction rate, or development of LV failure.[217,218]

PCI vs CABG

In general, 5-year mortality is similar after CABG and PCI in most patient subgroups with multivessel disease.[219] There has been evidence that with the use of LIMA to LAD, CABG offers reduced mortality, myocardial infarctions, and reintervention, especially in diabetics, but at a higher risk of stroke comparable to PCI. [220–224] The ASCERT study recently reported results from the ACC PCI and STS CABG registries: among patients older than 65 years and with two- or three-vessel CAD that did not require emergency therapy, CABG offered a better survival compared to PCI (mortality rates 16.4% vs 20.7%, RR: 0.79, 95% CI: 0.76–0.82).[222] In a recent extensive analysis of Medicare beneficiaries, aged ≥66 years, multivessel CABG was associated with lower long-term mortality than multivessel PCI in the community setting. Patients with diabetes, heart failure, peripheral arterial disease, or tobacco use had the largest predicted differences in survival after CABG, whereas those with none of these factors had slightly better survival after PCI.[221] In the SYNTAX trial, 1800 patients with previously untreated left main stem or 3-vessel disease were randomly assigned to undergo CABG or PCI with DES.[224] Five-year all-cause mortality and stroke were not significantly different between CABG (11.4% and 3.7%, respectively) and PCI (13.9% and 2.4%, respectively). Major adverse cerebrovascular and cardiac rates were significantly increased with PCI in patients with intermediate SYNTAX Score, i.e. 23–32, (36.0% vs 25.8%, p = 0.008) or high, i.e. >33 SYNTAX Score (44.0% vs 26.8%, p <0.0001). Adverse rates were not significantly different for patients with a low (0–22) baseline SYNTAX Score. A higher rate of stroke in the CABG group was detected at the first year of follow-up. These results suggest that CABG remains the standard of care for patients with complex disease (intermediate or high SYNTAX Scores); however, PCI may be an acceptable alternative revascularization method to CABG when treating patients with less complex disease, but its superiority over medical therapy alone is not proven. The SYNTAX II Score may be a more useful guide for decision making between CABG and PCI in this respect.[225] In the BEST trial, 880 patients with multivessel CAD were randomized to CABG or second generation everolimus-eluting stents. No difference in mortality was detected, but at a follow-up of 4.6 years, there were significantly fewer spontaneous myocardial infarctions and repeat-revascularization procedures in the CABG group than in the PCI group.[226]

The large New York state registry of 60 000 patients has reported an advantage of CABG in the presence of **2-vessel disease with proximal LAD stenosis**.[227] Considering PCI with second generation everolimus-eluting stents, the risk of death was similar, and PCI compared to CABG was associated with a higher risk of myocardial infarction (among patients with incomplete revascularization) and repeat revascularization but a lower risk (62%) of stroke.[228] In patients with **isolated proximal LAD disease**, a meta-analysis of nine RCTs on 1210 patients including diabetics, showed no difference in mortality, but fewer repeat revascularizations after CABG,[229] and this was also verified by the New York registry.[230] PCI may now also be used instead of CABG for **isolated, unprotected left main stem lesions.**[231–233] (Table 30.17 and Figure 30.15).

CABG offers improved survival and reduced MIs in **diabetics with multivessel disease**, but at an increased risk of stroke,[199,221,234] although there has been indirect evidence that mortality is similar between CABG and PCI when using cobalt–chromium everolimus-eluting stents.[235] The BARI 2D trial in diabetics detected similar rates of 5-year cardiac mortality between revascularization with CABG or PCI plus intensive medical therapy (5.9%) and intensive medical therapy alone groups (5.7%; p = 0.38). Patients with extensive coronary disease and greater myocardial jeopardy had less cardiac death or MI when treated with CABG and optimum medical therapy than medical therapy alone.[199] In the FREEDOM trial, 1900 patients with diabetes were randomly assigned to undergo either CABG or PCI with DES.[234] After 5 years of follow-up, the 947 patients assigned to undergo CABG had significantly lower mortality (10.9% vs 16.3%) and fewer myocardial infarctions (6.0% vs 13.9%) than the 953 patients assigned to undergo PCI. However, patients in the CABG group had significantly more strokes (5.2% vs 2.4%), mostly because of strokes that occurred within 30 days after revascularization. Treatment effects between CABG and PCI were not different in patients treated with insulin who had a higher rate of major cardiac adverse events in both revascularization arms.[236] Diabetic patients with acute coronary syndrome and multivessel disease enrolled in the ACUITY trial had less bleeding and acute kidney injury, greater need for repeat revascularization procedures, and comparable rates of myocardial infarction, stroke, and death through 1-year follow-up when treated with PCI rather than CABG.[237] In the USA, patients undergoing CABG had better outcomes but at higher costs than those undergoing PCI over a period from 2004 to 2008.[238]

Thus, PCI is considered inappropriate for left main stenosis and additional CAD with intermediate to high CAD burden (multiple diffuse lesions, presence of chronic total occlusion, or high SYNTAX score), or triple-vessel CAD and high CAD burden, in the presence of diabetes.

Complete revascularization

The issue of **complete revascularization** is not settled in patients with stable coronary artery disease, as opposed to those with acute coronary syndromes.[239] Although a comprehensive meta-analysis of RCTs and observational studies indicated reduced mortality and MI with complete, as opposed to incomplete, revascularization,[240] this is not unequivocally established either for CABG,[241,242] or PCI.[243–245] In a recent study on asymptomatic patients (33% of them diabetic) who had been subjected to previous revascularization with CABG or PCI, the detection of inducible ischaemia on myocardial perfusion scintigraphy did not indicate a survival benefit from repeat revascularization.[246] Leaving stenosis with non-significant FFR ungrafted during CABG has not shown excess hazard over a 3-year follow-up.[247]

Summary of indications for revascularization

In the era of modern medical therapy the indications of revascularization are less well defined, and each case should be individualized. However, current recommendations by cardiology societies and experts can be summarized as:

No revascularization is indicated

1. Asymptomatic or mildly symptomatic patients without significant ischaemia on non-invasive testing.
2. Non-significant disease (significant is defined as lesions with >50% stenosis and ischaemia or >90% stenosis in two angiographic views or FFR ≤0.8).
3. Occluded vessel 24 h after MI and no significant residual ischaemia.

CABG is indicated

1. Left main disease, three-vessel disease and SYNTAX score ≥33.
2. Three-vessel disease, LVEF 35–50%, and diabetes.

PCI is indicated

1. One- or two-vessel disease without proximal LAD.
2. Two- or three-vessel disease and SYNTAX score ≤22.

In all other settings, the decision depends on patient individual risks due to co-morbidities and age.

Table 30.17 Revascularization in stable IHD

ACCF/AHA 2012 GL on stable IHD. Revascularization to improve survival compared with medical therapy		
UPLM or complex CAD		
CABG and PCI	Heart Team approach recommended	I-C
CABG and PCI	Calculation of the STS and SYNTAX scores	IIa-B
UPLM (≥50% diameter stenosis)		
CABG		I-B
PCI	When **both** of the following are present: ◆ Anatomical conditions associated with a low risk of PCI procedural complications and a high likelihood of good long-term outcome (e.g. a low SYNTAX score of ≤22, ostial or trunk left main CAD) ◆ Clinical characteristics that predict a significantly increased risk of adverse surgical outcomes (e.g. STS-predicted risk of operative mortality ≥5%)	IIa-B
	for UA/NSTEMI if not a CABG candidate	IIa-B
	for STEMI when distal coronary flow is TIMI flow grade <3 and PCI can be performed more rapidly and safely than CABG	IIa-C
UPLM (>50% diameter stenosis)		
PCI	When both of the following are present: ◆ Anatomical conditions associated with a low to intermediate risk of PCI procedural complications and intermediate to high likelihood of good long-term outcome (e.g. low-intermediate SYNTAX score of <33, bifurcation left main CAD) ◆ Clinical characteristics that predict an increased risk of adverse surgical outcomes (e.g. moderate-severe COPD, disability from prior stroke, or prior cardiac surgery; STS-predicted risk of operative mortality >2%)	IIb-B

(*Continued*)

Table 30.17 Continued

	In patients (versus performing CABG) with unfavourable anatomy for PCI and who are good candidates for CABG	III-B (harm)
3-vessel disease (≥70% diameter stenoses) with or without proximal LAD artery disease		
CABG		I-B
	Choose CABG over PCI in patients with complex 3-vessel CAD (e.g. SYNTAX >22) who are good candidates for CABG	IIa-b
	Use of LIMA in proximal LAD stenosis and extensive ischaemia	IIa-B
PCI	Of uncertain benefit	IIb-B
2-vessel disease (≥70% diameter stenoses) with proximal LAD artery disease		
CABG		I-B
	Use of LIMA in proximal LAD stenosis and extensive ischaemia	IIa-B
PCI	Of uncertain benefit	IIb-B
2-vessel disease (≥70% diameter stenoses) without proximal LAD artery disease		
CABG	With extensive ischaemia (e.g., high-risk criteria on stress testing, abnormal intracoronary haemodynamic evaluation, or 20% perfusion defect by myocardial perfusion stress imaging) or target vessels supplying a large area of viable myocardium	IIa-B
	Of uncertain benefit without extensive ischaemia and proximal LAD involvement	IIb-C
PCI	Of uncertain benefit	IIb-B
1-vessel proximal LAD artery disease (≥70% diameter stenosis)		
CABG	With LIMA for long-term benefit in the presence of extensive ischaemia	IIa-B
PCI	Of uncertain benefit	IIb-B
1-vessel disease (≥70% diameter stenosis) without proximal LAD artery involvement		
CABG	<70% diameter non–left main coronary artery stenosis, fractional flow reserve >0.80, no or only mild ischaemia on noninvasive testing	III-B (harm)
PCI	<70% diameter non–left main coronary artery stenosis, fractional flow reserve >0.80, no or only mild ischaemia on noninvasive testing	III-B (harm)
LV dysfunction		
CABG	LVEF 35–50% and multivessel CAD or proximal LAD coronary artery stenosis, when viable myocardium is present in the region of intended revascularization	IIa-B
	LVEF <35% without significant left main CAD whether or not viable myocardium is present.	IIb-B
PCI	Insufficient data	
Survivors of sudden cardiac death with presumed ischaemia-mediated VT and ≥70% stenosis of major artery		
CABG		I-B
PCI		I-C

(*Continued*)

Table 30.17 Continued

No anatomical or physiological criteria for revascularization		
CABG	(e.g. <70% diameter non-left main coronary artery stenosis, fractional flow reserve >0.80, no or only mild ischaemia on non-invasive testing)	III-B (Harm)
PCI		III-B (harm)
ACC/AHA 2012 on Stable IHD. Revascularization to improve symptoms with significant anatomic (>50% left main or >70% non–left main CAD) or physiological (FFR<0.80) coronary artery stenoses (similar recommendations have been provided by ACCF/AHA/SCAI 2011 on CABG and on PCI).		
≥1 significant stenoses amenable to revascularization and unacceptable angina despite GDMT	I–A I–A	CABG PCI
≥1 significant stenoses and unacceptable angina in whom GDMT cannot be implemented because of medication contraindications, adverse effects, or patient preferences	IIa–C IIa–C	CABG PCI
Previous CABG with ≥1 significant stenoses associated with ischaemia and unacceptable angina despite GDMT	IIa–C IIb–C	PCI CABG
Complex 3-vessel CAD (e.g., SYNTAX score >22) with or without involvement of the proximal LAD artery and a good candidate for CABG	IIa-B	CABG preferred over PCI
Viable ischaemic myocardium that is perfused by coronary arteries that are not amenable to grafting	Ib-B	TMR as an adjunct to CABG
No anatomic or physiologic criteria for revascularization	III-C Harm III-C Harm	CABG PCI

For one vessel CAD, full recommendation is: CABG or PCI to improve symptoms should not be performed in patients who do not meet anatomic (≥50% left main or ≥70% non–left main stenosis) or physiological (e.g., abnormal fractional flow reserve) criteria for revascularization.
CABG indicates coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; FFR, fractional flow reserve; GDMT, guideline-directed medical therapy; LAD, left anterior descending; LIMA, left internal mammary artery; LV, left ventricular; N/A, not applicable; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; STS, Society of Thoracic Surgeons; SYNTAX, Synergy between percutaneous coronary intervention with TAXUS and cardiac surgery; TIMI, Thrombolysis In Myocardial Infarction; TMR, transmyocardial laser revascularization; UA/NSTEMI, unstable angina/non–ST-elevation myocardial infarction; UPLM, unprotected left main; and VT, ventricular tachycardia.
ACCF/AHA/ACP/AATS/PCNA/SCAI/STS 2012 Guideline for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol*. 2012;**60**:e44–e164 with permission from Elsevier.

Table 30.18 ESC on revascularization in stable CAD

ESC 2013 GL on stable CAD. Revascularization of stable coronary artery disease patients on optimal medical therapy.*		
Indication (in asymptomatic patients, the decision will be guided by the extent of ischaemia on stress testing)	**To improve prognosis**	**To improve symptoms persistent on OMT**
A Heart Team approach to revascularization is recommended in patients with unprotected left main, 2–3 vessel disease, diabetes or comorbidities.	I-C	I-C
Left main >50% diameter stenosis (with documented ischaemia or FFR <0.80 for angiographic diameter stenoses 50–90%).	I-A	I-A
Any proximal LAD >50% diameter stenosis (with documented ischaemia or FFR <0.80 for angiographic diameter stenoses 50–90%).	I-A	I-A
2–3 vessel disease with impaired LV function/CHF.	I-B	IIa-B
Single remaining vessel (with documented ischaemia or FFR <0.80 for diameter stenoses >50%).	I-C	I-A
Proven large area of ischaemia (>10% LV as assessed by non-invasive test (SPECT, MRI, stress echocardiography).	I-B	I-B

(*Continued*)

Table 30.18 Continued

Any significant stenosis with limiting symptoms or not responsive/intolerant of OMT.	NA	I-A
Dyspnoea/cardiac heart failure with >10% ischaemia/viability as assessed by non-invasive test (SPECT, MRI, stress echocardiography), supplied by stenosis >50%.	IIb-B	IIa-B
No limiting symptoms with OMT in vessel other than left main or proximal LAD or single remaining vessel or vessel subtending area of ischaemia <10% of myocardium or with FFR ≥0.80.	III-A	III-C

ESC 2014 GL on revascularization. Type of revascularization (CABG or PCI) in patients with SCAD with suitable coronary anatomy for both procedures and low predicted surgical mortality		
Recommendations according to extent of CAD	**CABG**	**PCI**
One or two-vessel disease without proximal LAD stenosis	IIb-C	I-C
One-vessel disease with proximal LAD stenosis.	I-A	I-A
Two-vessel disease with proximal LAD stenosis.	I-B	I-C
Left main disease with a SYNTAX score ≤ 22.	I-B	I-B
Left main disease with a SYNTAX score 22–32.	I-B	IIa-B
Left main disease with a SYNTAX score > 32.	I-B	III-B
Three-vessel disease with a SYNTAX score ≤ 22.	I-A	I-B
Three-vessel disease with a SYNTAX score 23–32.	I-A	III-B
Three-vessel disease with a SYNTAX score > 32.	I-A	III-B

[a] Decision to be taken in a Heart Team meeting.
[b] Frailty defined by means of validated scores (Charlson, Barthel, Frailty scores)
*: similar recommendations were provided by the ESC 2014 GL on revascularization

CABG: coronary artery bypass graft; CAD: coronary artery disease; CHF: congestive heart failure; DES: drug eluting stent; FFR: fractional flow reserve; LAD: left anterior descending; LV: left ventricle; NA: not available; OMT: optimal medical treatment; PCI: percutaneous coronary intervention; SCAD: stable coronary artery disease.

ESC 2013 Guidelines on the management of stable coronary artery disease. *Eur Heart J.* 2013;**34**:2949–3003, with permission from Oxford University Press.
ESC /EACTS 2014 Guidelines on myocardial revascularization. *Eur Heart J.* 2014;**35**:2541–619 with permission from Oxford University Press.

Table 30.19 Revascularization in special patient subsets

ESC 2014 GL on revascularization. Revascularization in patients with diabetes	
Multivessel CAD and/or evidence of ischaemia, to reduce cardiac adverse events.	I-B
Multivessel CAD and an acceptable surgical risk, CABG is recommended over PCI.	I-A
Multivessel CAD and SYNTAX score <22, PCI as alternative to CABG.	IIa-B*
New-generation DES are recommended over BMS.	I-A
Bilateral mammary artery grafting should be considered.	IIa-B
In patients on metformin, renal function should be carefully monitored for 2 to 3 days after coronary angiography/PCI.	I-C
ACCF/AHA GL 2011 on CABG. Renal dysfunction	
Off-pump CABG in patients with preoperative renal dysfunction (creatinine clearance <60 mL/min).	IIb-B
Maintenance of a perioperative haematocrit >19% and mean arterial pressure > 60 mm Hg in patients undergoing on-pump CABG.	IIb-C
Delay of surgery after coronary angiography until the effect of radiographic contrast material on renal function is assessed.	IIb-B
The effectiveness of pharmacological agents to provide renal protection during cardiac surgery is uncertain	IIb-B

*: IIb-B by the ESC 2014 GL on Diabetes. Other recommendations are similar.
BMS: bare-metal stent; DES: drug-eluting stent.
ESC/EACTS Guidelines on myocardial revascularization, ESC /EACTS 2014 Guidelines on myocardial revascularization. *Eur Heart J.* 2014;**35**:2541–619 with permission from Oxford University Press.
ACCF/AHA 2011 Guideline for coronary artery bypass graft surgery. *J Am Coll Cardiol.* 2011;**58**:e123–e210 with permission from Elsevier.

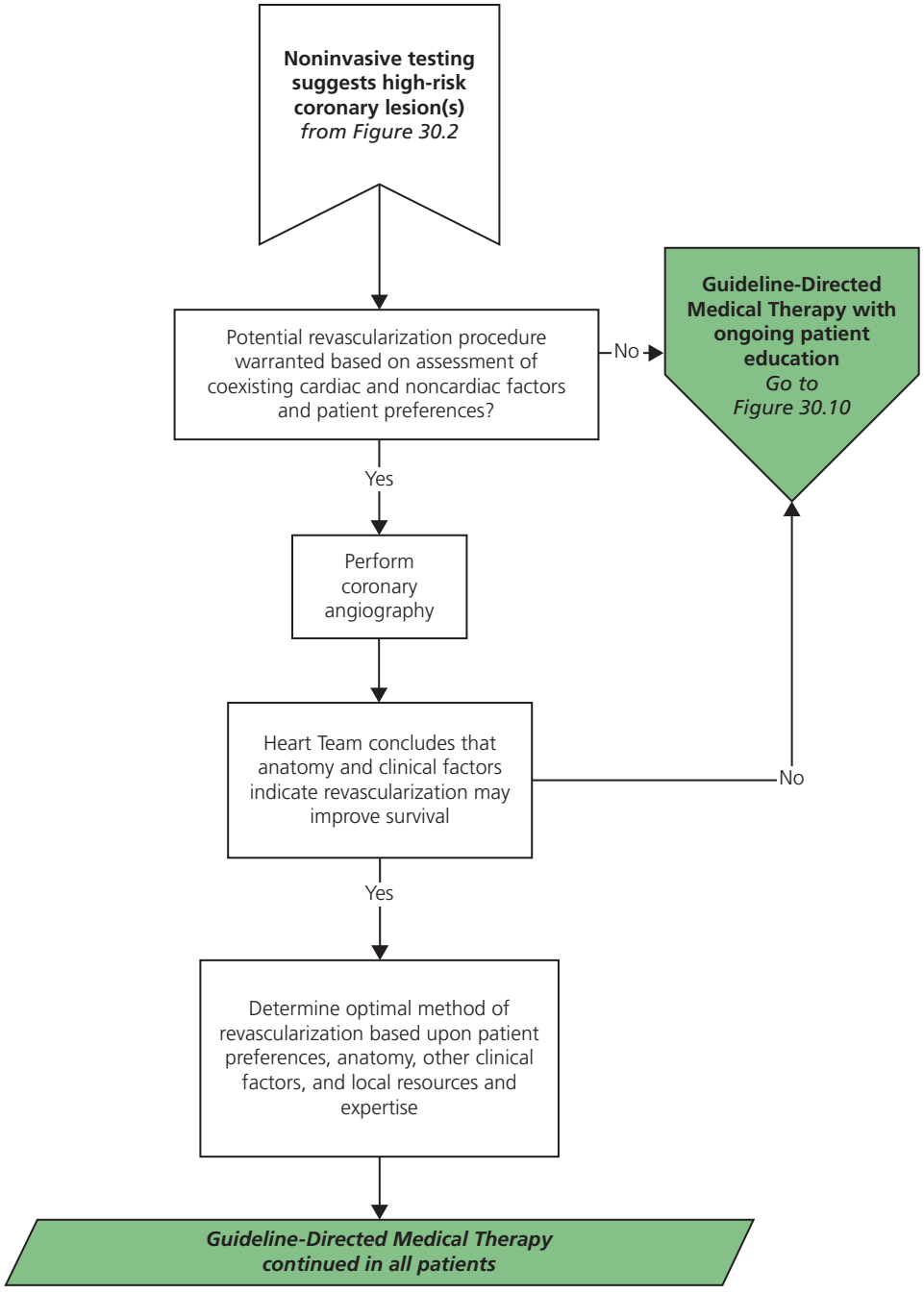


Figure 30.12 ACC/AHA GL 2012 on stable IHD. Algorithm for revascularization to improve survival of patients with SIHD.*

* Colours correspond to the class of recommendations in the ACCF/AHA (i.e. green is for Class I, yellow for IIa). The algorithms do not represent a comprehensive list of recommendations (see full guideline text for all recommendations).
ACCF/AHA/ACP/AATS/PCNA/SCAI/STS 2012 Guideline for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol*. 2012;**60**:e44–e164 with permission from Elsevier.

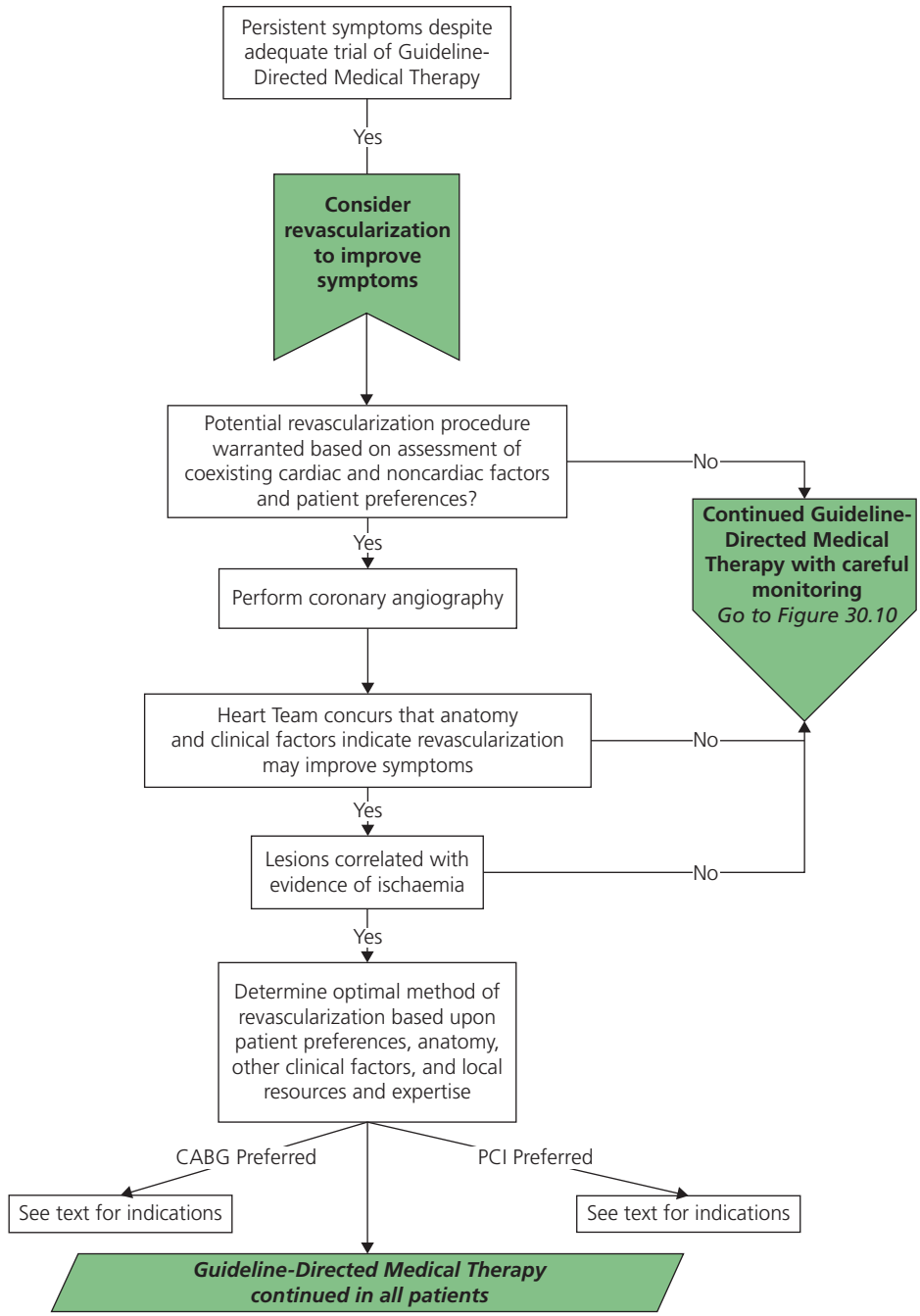


Figure 30.13 ACC/AHA 2012 GL on stable IHD. Algorithm for revascularization to improve symptoms of patients with SIHD.*

* Colours correspond to the class of recommendations in the ACCF/AHA. The algorithms do not represent a comprehensive list of recommendations (see full guideline text for all recommendations).
ACCF/AHA/ACP/AATS/PCNA/SCAI/STS 2012 Guideline for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol*. 2012;**60**:e44–e164 with permission from Elsevier.

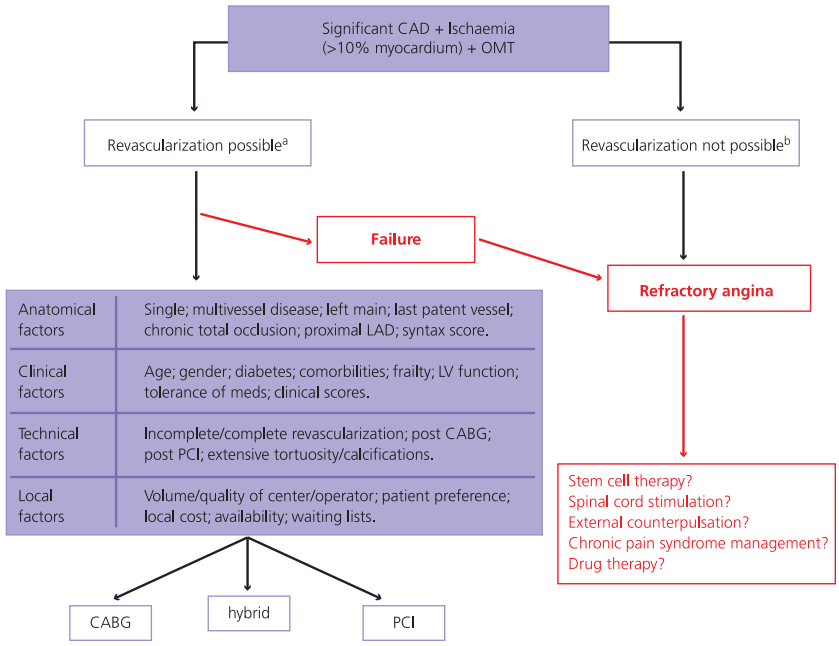


Figure 30.14 ESC GL on stable CAD. Global strategy of intervention in stable coronary artery disease patients with demonstrated ischaemia.

CABG, coronary artery bypass graft; CAD, coronary artery disease; LAD, left anterior descending; LV, left ventricular; OMT, optimal medical treatment; PCI, percutaneous coronary intervention.

[a] Indication of revascularization for prognosis or symptoms.

[b] Not suitable for revascularization due to anatomy or clinical conditions.

ESC 2013 Guidelines on the management of stable coronary artery disease. *Eur Heart J*. 2013;**34**:2949–3003, with permission from Oxford University Press.

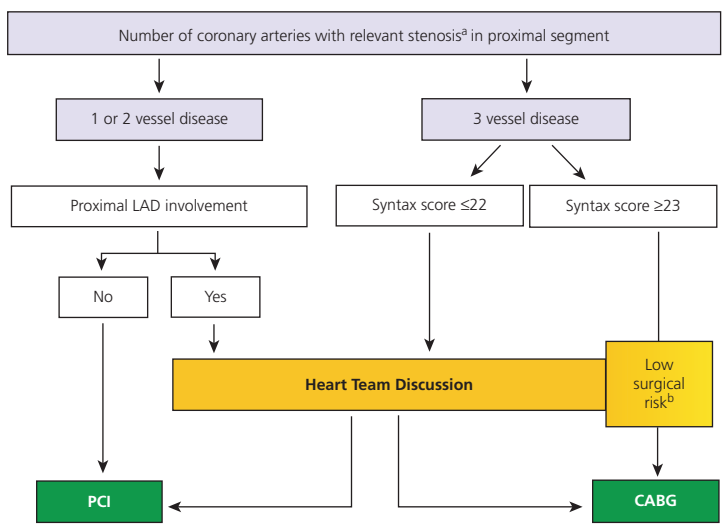


Figure 30.15 ESC GL on stable CAD. Percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) in stable coronary artery disease without left main coronary artery involvement.

CABG, coronary artery bypass graft; LAD, left anterior descending; PCI, percutaneous coronary intervention.

[a] >50% stenosis and proof of ischaemia, >90% stenosis in two angiographic views, or FFR <0.80.

[b] CABG is the preferred option in most patients unless patient co-morbidities or specificities deserve discussion by the heart team. According to local practice (time constraints, workload) direct transfer to CABG may be allowed in these low-risk patients, when formal discussion in a multidisciplinary team is not required.

ESC /EACTS 2014 Guidelines on myocardial revascularization. *Eur Heart J.* 2014;**35**:2541–619 with permission from Oxford University Press.

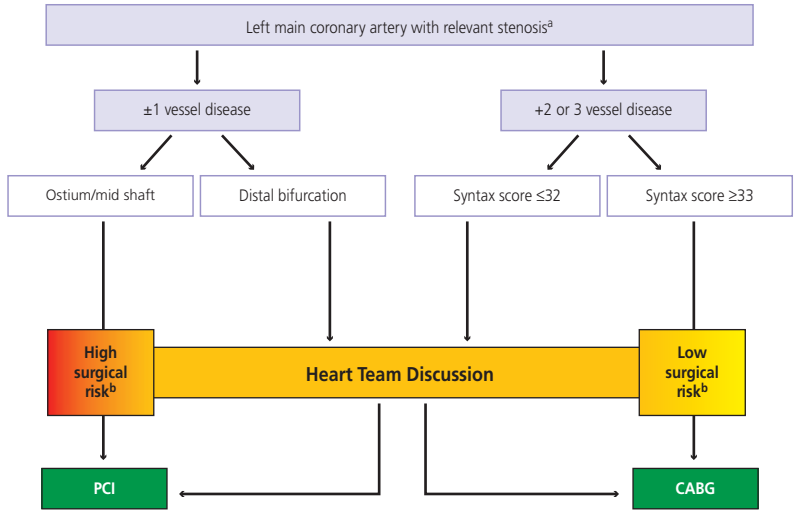


Figure 30.16 ESC GL on stable CAD. Percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) in stable coronary artery disease with left main coronary artery involvement.

CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

[a] 50% stenosis and proof of ischaemia, >70% stenosis in two angiographic views, or FFR <0.80.

[b] Preferred option in general. According to local practice (time constraints, workload) direct decision may be taken without formal multidisciplinary discussion, but preferably with locally agreed protocols.

ESC /EACTS 2014 Guidelines on myocardial revascularization. *Eur Heart J.* 2014;**35**:2541–619 with permission from Oxford University Press.

Surgical revascularization

CABG procedures carry a **3% peri-operative mortality risk, 0–10% risk of myocardial infarction, 5% risk of need for prolonged intubation, 2–6% risk of reoperation for bleeding, 1–4% risk of wound infection, 0.5–1% renal failure risk, 1.6% risk of stroke, and a 6% risk of residual cognitive defects** that may not be less even with beating heart procedures.[240,248,249]

The beneficial effects of CABG do not last beyond 10 years after surgery, presumably due to the limited longevity of used grafts (Table 30.20). At 12–18 months after CABG, vein graft occlusion or >75% stenosis occurs in 43% of patients and in 25% of vein graft used,[250] while, at 10 years, only about half of saphenous vein grafts are patent, and of those, only half are free of angiographic arteriosclerosis.[251] Vein graft failure is associated with repeat revascularization but not with death and/or MI.[252] Furthermore, grafting a coronary artery increases the risk of disease progression 3–6 times, especially in the right coronary artery.[253] Saphenous vein graft intimal hyperplasia is not reduced by the addition of clopidogrel to aspirin (CASCADE).[254] The use of the **left internal thoracic artery** to the LAD is superior to venous grafts, and the right internal thoracic artery is preferable to the radial to the best recipient vessel after the LAD.[251,255] The use of bilateral internal thoracic arteries is safe, even in diabetics, despite a trend for more deep wound infections,[256,257] and multiple arterial grafts improve survival compared to vein grafts.[258] Bilateral internal thoracic artery grafting should also be considered even in patients >65 years of age.[259] Anterior ischaemia in the presence of a patent anastomosed LIMA may suggest subclavian steal syndrome, i.e. proximal subclavian stenosis.[260] Bypassing **intermediate lesions** can result in more rapid progression of native vessel disease as well as accelerated graft failure, and FFR might be useful in identifying significant lesions that deserve bypass grafting.[247] A reduced risk of stroke with off-pump beating heart bypass surgery (**OPCAB**), that was suggested by a recent meta-analysis,[261] has not been verified in the largest randomized trials so far. Similar (CORONARY and GOPCABE trials)[262,263] or even worse outcomes (ROOBY trial)[264] with OPCAB have been reported, and the issue of less effective revascularization with this approach has been raised with a resultant worse long-term survival compared to on-pump surgery.[265] However, off-pump surgery may be protective against new-onset ventricular arrhythmias,[266] and might be preferable in high-risk patients. In patients with a patent LIMA to the LAD artery and ischaemia in the distribution of the right or left circumflex coronary arteries, it may be reasonable to recommend reoperative CABG to treat angina if medical therapy has failed and the coronary stenoses

are not amenable to PCI (ACCF/AHA 2011 on CABG, IIa-B). The European System for Cardiac Operative Risk Evaluation, **logistic EuroSCORE and EuroSCORE II** (http://www.euroscore.org) and the Society of Thoracic Surgeons **STS score** (http://riskcalc.sts.org) that is probably more accurate in high-risk patients are useful guides for calculation of the intraoperative risk. Details for management of antiplatelet therapy are discussed in Chapter 28. Aortocoronary **saphenous vein graft aneurysms** occur, with an approximate incidence of 0.07%, as a late complication of CABG. They are associated with significant morbidity and mortality since they grow with time, and percutaneous or surgical management is recommended.[267] The prevalence of **severe carotid disease** (> 80% stenosis of the internal carotid artery) among patients undergoing coronary artery bypass grafting is 6–12%,[268,269] but the optimum management of concomitant carotid disease of this population remains controversial. There is conflicting data, but it seems that a combined endarterectomy and CABG or staged carotid stenting followed by CABG is superior to staged endarterectomy followed by CABG at a later stage.[270,271] After CABG, patients should receive beta blockers (that should be started at least 24 h preop to reduce post-op AF; Tables 30.21 and 30.22), statins (ACCF/AHA 2011 on CABG I-A), and IV insulin to maintain a blood glucose <180 mg/dL while avoiding hypoglycaemia (ACCF/AHA 2011 on CABG I-B). The value of preoperative beta blockers in patients without a prior MI was questioned in a recent retrospective analysis of an STS database that was, however, based on rather outdated observational data.[272] Choice of the graft conduit and perioperative medication are presented in Table 30.22. Sexual activity is allowed 6–8 weeks after CABG (AHA/ESC, IIa-B) or non-coronary open heart surgery (AHA/ESC 2013 consensus document on sexual counselling, IIa-C).[273]

Table 30.20 ESC 2014 GL on revascularization. Graft patency after CABG

Graft	Patency at 1 year	Patency at 4–5 years	Patency at ≥10 years
SVG	75–95%	65–80%	32–71%
Radial artery	92–96%	90%	63-83%
Left IMA	>95%	90–95%	88–95%
Right IMA	>95%	>90%	65–90%

IMA, internal mammary artery; ND, no data.
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Table 30.21 ESC 2014 GL on revascularization. Recommendations for treatment of arrhythmias after revascularization

Beta-blockers to decrease the incidence of AF after CABG If no contraindications.	I-A
Pre-operative amiodarone as prophylactic therapy for patients at high-risk for AF.	IIa-A
Anticoagulation for new onset AF during/after PCI despite antiplatelet therapy.	IIa-C
Percutaneous LAA closure and antiplatelet therapy in AF and contraindication for long-term antiplatelet and anticoagulation therapy	IIb-B
Anticoagulation for at least 3 months with new-onset AF after CABG	IIa-C
Concomitant surgical occlusion/ removal of the LAA during CABG in AF	IIb-C
In survivors of out-of-hospital cardiac arrest, immediate coronary angiography and revascularization if appropriate	IIa-B
In patients with electrical storm, urgent coronary angiography and revascularization as required	IIa-C
In patients with CAD and LVEF >35%, testing for residual ischaemia and subsequent revascularization prior to primary ICD implantation. After revascularization, assessment for reverse LV remodelling up to 6 months prior to primary prophylactic ICD implantation.	IIa-B

ESC /EACTS 2014 Guidelines on myocardial revascularization. *Eur Heart J.* 2014;**35**:2541–619 with permission from Oxford University

Table 30.22 Technical aspects of CABG

ACCF/AHA 2011 GL on CABG	
The role of preoperative carotid artery noninvasive screening in CABG patients	
A multidisciplinary team approach (consisting of a cardiologist, cardiac surgeon, vascular surgeon, and neurologist) for patients with clinically significant carotid artery disease for whom CABG is planned.	I-C
Carotid artery duplex scanning in selected patients with high-risk features (i.e., age >65 years, left main coronary stenosis, peripheral artery disease, history of cerebrovascular disease [transient ischaemic attack, stroke, etc.], hypertension, smoking, and diabetes mellitus).	IIa-C
In previous transient ischaemic attack or stroke and a significant (50% to 99%) carotid artery stenosis, consider carotid revascularization in conjunction with CABG. The sequence and timing (simultaneous or staged) of carotid intervention and CABG should be determined by the patient's relative magnitudes of cerebral and myocardial dysfunction.	IIa-C
If there is no history of transient ischaemic attack or stroke, carotid revascularization may be considered in the presence of bilateral severe (70% to 99%) carotid stenoses or a unilateral severe carotid stenosis with a contralateral occlusion.	IIb-C
Patients with chronic obstructive pulmonary disease/respiratory insufficiency	
Preoperative intensive inspiratory muscle training is reasonable to reduce the incidence of pulmonary complications in patients at high risk for respiratory complications after CABG.	IIa-B
After CABG, noninvasive positive pressure ventilation may be reasonable to improve pulmonary mechanics and to reduce the need for reintubation.	IIb-B
High thoracic epidural analgesia may be considered to improve lung function after CABG.	IIb-B
Bypass graft conduit	
The left internal mammary artery (LIMA) should be used to bypass the LAD.	I-B
The right internal mammary artery to bypass the LAD when the LIMA is unavailable or unsuitable.	IIa-C
Use of a second internal mammary artery to graft the left circumflex or right coronary artery is reasonable.	IIa-B
Complete arterial revascularization in patients ≤ 60 years of age with few or no comorbidities.	IIb-C
Arterial grafting of the right coronary artery may be reasonable when a critical (≥90%) stenosis is present.	IIb-B
Contraindicated in <90% RCA stenosis.	III-C
Use of a radial artery graft may be reasonable when grafting left-sided coronary arteries with severe stenoses (>70%) and rightsided arteries with critical stenoses (≥90%).	IIb-B
Preoperative antiplatelet therapy	
Aspirin (100 mg to 325 mg daily) to CABG patients preoperatively.	I-B
In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least 5 days before surgery.	I-B
Prasugrel should be discontinued for at least 7 days	I-C
In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours.	I-B
In patients referred for CABG, short-acting intravenous glycoprotein IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2 to 4 hours before surgery and abciximab for at least 12 hours beforehand.	I-B
In patients referred for urgent CABG, it may be reasonable to perform surgery less than 5 days after clopidogrel or ticagrelor has been discontinued and less than 7 days after prasugrel has been discontinued.	IIb-C
Perioperative beta blockers and antiarrhythmic drugs	
Beta blockers should be administered for at least 24 hours before CABG, and should be reinstituted as soon as possible after CABG, to all patients without contraindications to reduce the incidence or clinical sequelae of postoperative AF.	I-B
Beta blockers should be prescribed to all CABG patients without contraindications at the time of hospital discharge.	I-C
Beta blockers in patients without contraindications, particularly in those with LVEF>30% for reducing the risk of in-hospital mortality and perioperative myocardial ischaemia	IIa-B
Intravenous administration of beta blockers in clinically stable patients unable to take oral medications is reasonable in the early postoperative period.	IIa-B
The effectiveness of preoperative beta blockers in reducing inhospital mortality rate in patients with LVEF less than 30% is uncertain.	IIb-B
Preoperative administration of amiodarone to reduce the incidence of postoperative AF is reasonable for patients at high risk for postoperative AF who have contraindications to beta blockers.	IIa-B
Digoxin and nondihydropyridine calcium channel blockers can be useful to control the ventricular rate in the setting of AF but are not indicated for prophylaxis.	IIa-B

(*Continued*)

Table 30.22 Continued

ESC 2014 GL on revascularization	
Procedural aspects of CABG	
Procedures in a hospital structure and by a team specialized in cardiac surgery, using written protocols.	I-B
Endoscopic vein harvesting to reduce the incidence of leg wound complications.	IIa-A
Routine skeletonized IMA dissection	IIa-B
Skeletonized IMA dissection in patients with diabetes or when bilateral IMAs are harvested.	I-B
Complete myocardial revascularization	I-B
Arterial grafting with IMA to the LAD	I-B
Bilateral IMA grafting in patients <70 years of age.	IIa-B
Use of the radial artery only for target vessels with high-degree stenosis.	I-B
Total arterial revascularization in patients with poor vein quality independently of age.	I-C
Total arterial revascularization in patients with reasonable life expectancy.	IIa-B
Minimization of aortic manipulation	I-B
Off-pump CABG for high-risk patients in high-volume off-pump centres.	IIa-B
Off-pump CABG and/or no-touch on-pump techniques on the ascending aorta in significant atherosclerotic disease of the ascending aorta	I-B
Minimally invasive CABG in isolated LAD lesions.	IIa-C
Electrocardiogram-triggered CT scans or epiaortic scanning of the ascending aorta in patients >70 years and/or with signs of extensive generalized atherosclerosis.	IIa-C
Routine intraoperative graft flow measurement	IIa-C
Carotid artery screening before CABG	
Doppler ultrasound scanning in patients undergoing CABG and with a history of stroke/TIA or carotid bruit	I-C
Doppler ultrasound in patients with multivessel CAD, PAD, or >70 years of age.	IIa-C
MRI, CT, or digital subtraction angiography if carotid artery stenosis by ultrasound is >70% and myocardial revascularization is contemplated.	IIb-C
Screening for carotid stenosis is not indicated in patients with unstable CAD requiring emergency CABG with no recent stroke/TIA.	III-B
Carotid artery revascularization in patients scheduled for CABG	
CEA or CAS should be performed by teams achieving a combined death/stroke rate at 30 days of: <3% in patients without previous neurological symptoms, <6% inpatients with previous neurological symptoms.	I-A
Individualize the indication for carotid revascularization after discussion by a multidisciplinary team including a neurologist.	I-C
The timing of the procedures (synchronous or staged) should be determined by local expertise and clinical presentation, targeting the most symptomatic territory first.	IIa-C
In patients with a <6-month history of TIA/stroke	
Carotid revascularization is recommended for 70–99% carotid stenosis	I-C
Carotid revascularization may be considered for 50–69% carotid stenosis depending on patient-specific factors and clinical presentation.	IIb-C
In patients with no previous TIA/stroke within 6 months	
Carotid revascularization may be considered in men with bilateral 70–99% carotid stenosis or 70–99% carotid stenosis and contralateral occlusion.	IIb-C
Carotid revascularization may be considered in men with 70–99% carotid stenosis and ipsilateral previous silent cerebral infarction.	IIb-C
Type of carotid artery revascularization	
Choice of CEA vs. CAS in patients undergoing CABG should be based on patient comorbidities, supra-aortic vessel anatomy, urgency for CABG and local expertise.	IIa-B
ASA immediately before and after carotid revascularization.	I-A
Dual antiplatelet therapy with ASA and clopidogrel for patients undergoing CAS for a duration of at least 1 month.	I-B

(*Continued*)

Table 30.22 Continued

CAS should be considered in patients with: • post-radiation or postsurgical stenosis • obesity, hostile neck, tracheostomy, laryngeal palsy • stenosis at different carotid levels or upper internal carotid artery stenosis • severe comorbidities contraindicating CEA.	IIa-C
ESC 2014 GL on revascularization	
Management of patients with associated CAD and peripheral arterial disease	
Postpone vascular surgery and first treat CAD, except when vascular surgery cannot be delayed due to a life- or limb-threatening condition	I-C
The choice between CABG and PCI should follow the general recommendations for revascularization	I-C
Prophylactic myocardial revascularization before high risk vascular surgery in stable patients if they have persistent signs of extensive ischaemia or are at high cardiac risk.*	IIb-B
Recommendations for training, proficiency, and operator/institutional competence in CABG	
Trainees should have performed at least 200 CABG procedures under supervision before being independent.	IIa-C
CABG should be performed with an annual institutional volume of at least 200 cases	IIa-C
Routine use of the internal mammary artery at a rate >90%	I-B
Routine reporting of CABG outcome data to national registries and/or the EACTS database	I-C

The term carotid artery stenosis refers to a stenosis of the extracranial portion of the internal carotid artery, and the degree of stenosis is according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria

*: High cardiac risk (reported cardiac risk often > 5%): 1) aortic and other major vascular surgery; 2) peripheral vascular surgery.

ASA, acetylsalicylic acid; CABG, coronary artery bypass grafting; CAS, carotid artery stenting; CEA, carotid endarterectomy; PAD, peripheral artery disease; TIA, transient ischaemic attack.

ACCF/AHA 2011 Guideline for coronary artery bypass graft surgery. *J Am Coll Cardiol*. 2011;**58**:e123–e210 with permission from Elsevier.

ESC /EACTS 2014 Guidelines on myocardial revascularization. *Eur Heart J*. 2014;**35**:2541–619 with permission from Oxford University Press.

Percutanous coronary intervention (PCI)—technical aspects

There are several potential reasons why PCI has failed to reduce mortality in stable, as opposed to unstable, CAD. Although MIs frequently occur at sites of mild-to-moderate stenoses,[274,275] post-mortem examinations have demonstrated that ruptured plaques that lead to thrombosis more likely occur within the segment of significant stenoses.[276,277] The majority of ruptured plaques and half of thin-cap fibroatheromas (i.e. vulnerable plaques) exhibit a >50% diameter stenosis.[278] Thus, subtotal occlusions of a vessel supplying non-infarcted myocardium, stenoses >90% that by definition represent vulnerable plaques,[279] significant complex lesions that are prone to develop total occlusions,[280] and stenoses with unequivocally reduced fractional flow reserve (<0.80),[281] may represent optimal targets for PCI. However, randomized studies of PCI vs medical therapy to support this view are missing, although observational studies on registries argue in favour of PCI.[282] Possible explanations for the failure of PCI to improve prognosis might be the limited number of patients with proven significant ischaemia enrolled in these trials, and adoption of complex, elaborate techniques that have not proved their usefulness but expose the patient to additional risk of iatrogenic MI (approximately 7% measured by CK-MB elevation)[283] that has prognostic significance, regardless of its extent.[284–286] PCI may reduce spontaneous MI compared to medical therapy, but at the expense of procedural MI that results in no difference in MI in total.[286] Recently, the Society for Cardiovascular Angiography and Interventions proposed a limit of 10-fold rise of CK-MB in order to define MI following revascularization.[287] The clinical relevance of this definition remains to be seen. Additionally, PCI is directed at the lesions that cause ischaemic symptoms and does not change the natural history of coronary atherosclerosis in which non-obstructive lesions might progress suddenly to high-grade stenoses or vessel occlusion. These sites might have been bypassed by a coronary graft. PCI is associated with greater freedom from angina compared with medical therapy, although this benefit is attenuated with the use of modern, evidence-based medications.[288] Approximately 12–38% of PCI performed on stable patients in the US may not fulfill the appropriateness criteria of ACC.[289,290]

General recommendations on PCI are presented in Tables 30.23, and 30.24. **The in-hospital mortality of PCI is estimated at approximately 1%, whereas periprocedural infarction (defined as an increase in biomarkers >3 times the 99th percentile upper reference limit) is 15%, ischemic stroke 0.1%, and emergency CABG is required in 0.1–0.4% of patients**.[248,291–293] In the National Cardiovascular Data Registry report, PCI in-hospital mortality was 1.27%, ranging from 0.65% in elective PCI to 4.81% in ST-segment elevation myocardial infarction patients.[293] Recent data indicate a mortality of 1.08% and an inverse relationship between complications and operator and institutional volume.[291]

Older age, extreme BMIs, multivessel disease, a lower ejection fraction, unstable haemodynamic state or shock, several co-morbidities (cerebrovascular disease, peripheral vascular disease, congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, and renal failure), and a history of coronary artery bypass graft surgery are risk factors that increase mortality.[294] Cardiac mortality after PCI has been reduced the last two decades (6.6% for 2003–2008, compared to 9.8% for 1991–1996), mainly due to reduction of myocardial infarctions and sudden death.[295]

BMS is superior to balloon, and **DES** is superior to BMS by decreasing target lesion revascularization, and in a propensity-matched comparison from the DAPT cohort, DES stent thrombosis was lower to that of BMS through 33 months.[296] Second-generation DES may also decrease mortality or the risk of MI compared to BMS.[297] First-generation DES have been associated with a higher stent thrombosis rate than BMS, but this is not true with second generation DES and modern dual antiplatelet therapy.[298] Early stent thrombosis (within the first 20 days) with second generation DES is 1% and thereafater 0.2–0.4% per year.[299] There is evidence for a safety advantage of second-generation drug-eluting stents, such as everolimus-eluting and biolimus-eluting stents, as compared with early-generation DES, as detected in long-term (>1 year) follow-up.[300] Third-generation DES such as biodegradable polymer do not result in reduced stent thrombosis or MI compared to platinum–chromium everolimus-eluting stents, thus indicating other stent characteristics such as strut thickness are important, regardless of the biodegradability of the polymer.[301–303] The permanent presence of a metallic foreign body within the artery following stenting may cause vascular inflammation, restenosis, thrombosis, and neoatherosclerosis and impair the physiological vasomotor function of the vessel and future potential of grafting the stented segment. **Bioresorbable scaffolds** have the potential to overcome these limitations and are under trial. However, there have been concerns about stent thrombosis higher than that of cobalt-chromium everolimus eluting stents, with reported rates of 0.9% to 2.1% in 6 months to one year follow-up (ABSORB II, ABSORB Japan, ABSORB China, ABSORB III, EVERBIO II, and TROFI II trials).[304–306]

Continuation of dual antiplatelet therapy beyond 1 year has not been found beneficial in randomized trials on both stable and unstable patients treated with first- and second-generation DES. Treatment with dual antiplatelet therapy beyond one year after drug-eluting stent implantation reduces myocardial infarction and stent thrombosis, although it may be associated with increased mortality because of an increased risk of non-cardiovascular mortality not offset by a reduction in cardiac mortality.[307,308] With second generation DES even 3–6 months of dual antiplatelet therapy may reduce bleeding without affecting major cardiac events compared to 12–24 months therapy.[309] These findings cannot be generalized.[310] The optimum duration of dual antiplatelet therapy after stenting is not established and should be individualized, depending on the type of stent used as well as comorbidities such as renal failure, and a history of previous myocardial infarction that affect the relative risk of adverse cardiac event and haemorrhage, and the DAPT score may be useful in this respect (see Chapter 28).

In-stent restenosis with new generation DES is approximately 10% and usually occurs within the first 6 months. The treatment of in-stent restenosis is challenging; drug-eluting balloons may be used, but everolimus-eluting DES, and probably drug-coated balloons, are the best options, especially for DES restenosis.[311,312] Interestingly, although restenosis is an independent predictor of long-term survival in patients undergoing coronary stenting, revascularization has not been found to offer any advantage on survival.[70]

In **coronary bifurcations**, stenting of both the main vessel and side branch in bifurcation lesions may increase MI and stent thrombosis risk, compared with stenting of the main vessel only.[313] The clinical significance of side branch occlusion is still debatable. Predictors of side branch occlusion are ostial side branch stenosis, length of side branch lesion, and ACS.[314] **Femoral artery pseudoaneurysms** following PCI may be treated with manual compression, especially if <2 cm, with a 1.7% risk of infection, rupture, or femoral vein thrombosis, but larger ones may require ultrasound-guided thrombin injection with a <1.4% rate of distal embolization.[315] The **radial access** offers lower vascular and bleeding complication rates, but at increased fluoroscopy times.[316] Although the risk of artery occlusion ranges from 0.8% to 30%, it is usually asymptomatic and transradial catheterization and intervention may be performed regardless of the results of the Allen test.[317] Experience and procedural volume are critical for this approach.[318] The clinical value of intravascular ultrasound (**IVUS**) guidance is debatable, especially when DES (as opposed to BMS) are used. There has been some evidence that it may reduce MI and stent thrombosis and MI, particularly in ACS and complex lesions.[319,320]

In patients with **chronic kidney disease**, DES are preferred.[321] **Contrast-induced nephropathy** is associated with a worse outcome.[322] Either an isomolar or a low-molecular-weight other than ioxaglate or iohexol contrast medium have been previously recommended, but subsequent studies on this issue have been contradictory to allow certain recommendations. *N*-acetylcysteine does not appear to be beneficial,[323] but it might be useful (1200 mg orally before PCI followed by 1200 mg daily during the next 48 h) when combined with a sodium bicarbonate infusion (500 mL in the first hour followed by an infusion of 100 mL/h in the next 5 hours (in total 1000 mL).[324] Another policy is to administer 250 mL of normal saline solution over 30 min and IV furosemide (0.5 mg/kg, up to a maximum of 50 mg) approximately 90 min before the coronary procedure, and perform the procedure when a urine output of >300 mL/h is achieved. Additional doses of furosemide (up to a maximal cumulative dose of 2.0 mg/kg) are given in cases where the urine output is <300 mL/h

during treatment, and matched hydration is continued for 4 h after the last contrast dose.[325] Statin loading with atorvastatin 80 mg within 24 h preprocedure[326] or rosuvastatin (10–40 mg)[327,328] may also reduce contrast-induced renal injury in statin-naïve patients.

There has been some evidence that concomitant **balloon counterpulsation** may improve long-term outcomes in high-risk patients undergoing PCI.[329,330] Although the use of **closure devices** is not recommended on a routine basis by the ACC/AHA/SCAI 2011 guideline on PCI, their use may decrease complications even after elective intervention.[331] However, in patients undergoing PCI, bleeding is associated with increased in-hospital mortality that is highest with non-access site bleeding.[332] The management of patients on **oral anticoagulants** who are subjected to PCI is discussed in detail in Chapter 28.

Coronary angiography or PCI can be performed in patients on oral anticoagulation (warfarin or NOAC) and with additional anticoagulation (UFH, LMWH, or bivalirudin), preferably through a radial access. For elective PCI, there is no need for additional anticoagulation if the INR is >2.5.[248] PCI should be performed by operators with a **workload** of at least 75 cases per year in an institution performing >400 and certainly ≥200 cases per year. On-site **surgical backup** is no more mandatory for elective PCI, provided there have been plans for rapid transport to a cardiac surgery operating room in a nearby hospital.[333,334] Rates of in-hospital mortality and emergency CABG for primary and non-primary PCI appear similar at centres with and without on-site surgery (CPORT and MASS COMM trials and VA CART Program).[335–338]

Table 30.23 Pharmacotherapy for PCI

ACCF/AHA 2011 GL for PCI. Antiplatelet and antithrombin pharmacotherapy at the time of PCI	
Oral antiplatelet agents	
Patients already on daily aspirin therapy, 81 mg to 325 mg before PCI.	I-B
Patients not on aspirin therapy, non-enteric aspirin 325 mg before PCI.	I-B
Loading dose of a $P2Y_{12}$ inhibitor with stenting.	I-A
Clopidogrel 600 mg loading dose	I-B
Prasugrel Contraindicated in patients with prior TIA/CVA Not recommended in patients >75 years of age Lower maintenance dose in persons weighting <60 kg	I-B III-B
Ticagrelor Issues of patient compliance may be especially important	I-B
GP IIb/IIIa inhibitors (abciximab, double-bolus eptifibatide, high-bolus dose tirofiban)	
No clopidogrel pre-treatment.	IIa-B
Clopidogrel pre-treatment.	IIb-B
Antithrombin agents	
UFH Dosing based on whether or not GPI was administered	I-C
Bivalirudin Lower bleeding rates associated with bivalirudin are mitigated when used concomitantly with a GPI	I-B
Enoxaparin An additional dose of 0.3 mg/kg IV enoxaparin should be administered at the time of PCI to patients who have received <2 therapeutic SC doses (e.g. 1 mg/kg) or received the last SC enoxaparin dose 8 to 12 h before PCI (I-B) Patients treated with SC enoxaparin within 12 h of PCI should not receive additional treatment with UFH during PCI ('stacking')	IIb-B III-B
Anti-Xa inhibitors	
Fondaparinux PCI should not be performed with fondaparinux as the sole antithrombin agent in patients treated with upstream fondaparinux. An additional anticoagulant with anti-IIa activity should be administered.	III-C (harm)

(*Continued*)

Table 30.23 Continued

ACCF/AHA 2012 GL on stable CAD. Dual antiplatelet therapy compliance and stent thrombosis	
PCI with coronary stenting (bare-metal stent or drug-eluting stent) should not be performed if the patient is not likely to be able to tolerate and comply with dual antiplatelet therapy for the appropriate duration of treatment based on the type of stent implanted.	III-B
ACCF/AHA 2011 GL on PCI and 2016 update on duration of DAPT. Postprocedural recommendations for patients undergoing PCI	
Aspirin	
After PCI, use of aspirin should be continued indefinitely.	I-A
In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg)	I-B-NR
P2Y12 inhibitors	
After BMS implantation, P2Y12 inhibitor (clopidogrel) for at least 1 month	I-A
After DES implantation, P2Y12 inhibitor (clopidogrel) for at least 6 months	I-B-NR
In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg)	I-B-NR
Further continuation of DAPT in patients treated for an MI that occurred 1 to 3 years earlier, who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g. prior bleeding on DAPT, coagulopathy, oral anticoagulant use).	IIb-A-SR
Continuation of DAPT with clopidogrel for longer than 1 month in patients treated with BMS or longer than 6 months in patients who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g. prior bleeding on DAPT, coagulopathy, oral anticoagulant use.	IIB-A-SR
Discontinuation of P2Y12 inhibitor after 3 months in patients who develop a high risk of bleeding (e.g. treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g. major intracranial surgery), or develop significant overt bleeding.	IIb-C-LD
In patients without prior history of ACS, coronary stent implantation, or recent (within 12 months) CABG, treatment with DAPT is not beneficial.	III-B-NR
PPIs	
PPIs should be used in patients with a history of prior GI bleeding who require DAPT.	I-C
Use of PPIs in patients with an increased risk of GI bleeding (e.g., advanced age, concomitant use of warfarin, steroids, NSAIDs, Helicobacter pylori infection) who require DAPT.	IIa-C
Routine use of a PPI is not recommended for patients at low risk of GI bleeding, who have much less potential to benefit from prophylactic therapy.	III-C
ESC 2014 GL on revascularization. Recommendations for antithrombotic treatment in stable CAD patients undergoing PCI	
Pretreatment with antiplatelet therapy	
Treatment with 600 mg clopidogrel preferably 2 hours or more before the elective procedure	I-A
Pretreatment with clopidogrel in patients with high probability for significant CAD	IIb-C
In patients on a maintenance dose of 75 mg clopidogrel, a new loading dose of 600 mg or more once the indication for PCI is confirmed	IIb-C
Antiplatelet therapy during PCI	
ASA before elective stenting	I-B
ASA oral loading dose of 150–300 mg (or 80–150 mg i.v.) if not pre-treated	I-C
GP IIb/IIIa antagonists should be considered only for bail-out	IIa-C
Antiplatelet therapy after stenting	
DAPT for at least 1 month after BMS implantation	I-A
DAPT for 6 months after DES implantation	I-B
Shorter DAPT duration (<6 months) after DES implantation in patients at high bleeding risk.	IIb-A

(*Continued*)

Table 30.23 Continued

Life-long single antiplatelet therapy, usually ASA	I-A
Instruction to patients about the importance of complying with antiplatelet therapy	I-C
DAPT for more than 6 months in patients at high ischaemic risk and low bleeding risk	IIb-C
Clopidogrel (600 mg loading dose or more, 75 mg daily maintenance dose) for elective stenting.	I-A
Anticoagulant therapy	
Unfractionated heparin 70–100 U/kg.	I-B
Bivalirudin (0.75 mg/kg bolus, followed by 1.75 mg/kg/hour for up to 4 hours after the procedure) in case of heparin-induced thrombocytopenia.	I-C
Bivalirudin (0.75 mg/kg bolus, followed by 1.75 mg/kg/hour during the procedure) in patients at high bleeding risk	IIa-A
Enoxaparin i.v. 0.5 mg/kg.	IIa-B
General recommendations on antiplatelet therapy	
A proton pump inhibitor in patients with a history of gastrointestinal haemorrhage or peptic ulcer, or multiple other risk factors (e.g. Helicobacter pylori infection, age 65 years, and concurrent use of anticoagulants, NSAIDs, or steroids).	I-A
Clopidogrel 75 mg od as an alternative in case of ASA intolerance in patients with stable CAD.	I-B
Platelet function testing or genetic testing may be considered in high-risk situations (e.g. history of stent thrombosis; compliance issue; suspicion of resistance; high bleeding risk).	IIb-C
Routine platelet function testing or genetic testing for clopidogrel or ASA not recommended	III-A
Treatment interruption	
Do not interrupt antiplatelet therapy within the recommended duration of treatment.	I-C
Cessation of ticagrelor or clopidogrel for 5 days, and for 7 days for prasugrel, if clinically feasible, before major surgery	IIa-C
Resume clopidogrel, ticagrelor or prasugrel after CABG as soon as considered safe.	Iia-C
Platelet function testing to guide antiplatelet therapy interruption rather than arbitrary use of a specified period of delay in patients undergoing CABG surgery.	IIa-C

ACT indicates activated clotting time; CVA, cerebrovascular accident; DAPT, dual antiplatelet therapy; GPI, glycoprotein IIb/IIIa inhibitor; IC, intracoronary; IV, intravenous; SC, subcutaneous; SIHD, stable ischaemic heart disease; TIA, transient ischaemic attack; and UFH, unfractionated heparin.
ACCF /AHA /SCAI 2011 Guideline for Percutaneous Coronary Intervention: *J Am Coll Cardiol*. 2011;**58**:2550–83, copyright with permission from Elsevier.
ACCF/AHA/ACP/AATS/PCNA/SCAI/STS 2012 Guideline for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol*. 2012;**60**:e44–e164.
ESC /EACTS 2014 Guidelines on myocardial revascularization. *Eur Heart J*. 2014;**35**:2541–619 with permission from Oxford University Press.
ESC 2013 Guidelines on the management of stable coronary artery disease. *Eur Heart J*. 2013;**34**:2949–3003, with permission from Oxford University Press.
2016 ACC/AHA Guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. *Circulation*. 2016; Mar 29. [Epub ahead of print].

Table 30.24 Technical aspects of PCI

ACCF/AHA/SCAI 2011 GL on PCI. Summary of Recommendations for preprocedural considerations and interventions in patients undergoing PCI		
Contrast-induced AKI		
Patients should be assessed for risk of contrast-induced AKI before PCI.		I-C
Patients undergoing cardiac catheterization with contrast media should receive adequate preparatory hydration.		I-B
In patients with CKD (creatinine clearance <60 mL/min), the volume of contrast media should be minimized.		I-B
Administration of N-acetylcysteine is not useful for the prevention of contrast-induced AKI.		III-A No Benefit
Anaphylactoid reactions		
Patients with prior evidence of an anaphylactoid reaction to contrast media should receive appropriate prophylaxis before repeat contrast administration.		I-B
In patients with a prior history of allergic reactions to shellfish or seafood, anaphylactoid prophylaxis for contrast reaction is not beneficial.		III-C No Benefit
Statins		
Administration of a high-dose statin is reasonable before PCI to reduce the risk of periprocedural MI.		IIa-a: Statin naive IIa-a: Chronic statin therapy
Bleeding risk		
All patients should be evaluated for risk of bleeding before PCI.		I-C
CKD		
In patients undergoing PCI, the glomerular filtration rate should be estimated and the dosage of renally cleared medications should he adjusted.		I-B
Aspirin		
Patients already on daily aspirin therapy should take 81 mg to 325 mg before PCI.		I-B
Patients not on aspirin therapy should be given nonenteric aspirin 325 mg before PCI.		I-B
ESC 2014 GL on revascularization. Prevention of contrast-induced nephropathy		
Patients undergoing coronary angiography or MDCT		
Patients should be assessed for risk of contrast-Induced AKI.		IIa-C
Patients with moderate-to-severe CKD		
Hydration with Isotonic saline is recommended (especially in patients with eGFR<40 mL/min/1.73 m^2)		I-A
Use of low-osmolar or Iso-osmolar contrast media is recommended.	<350 mL or <4 mL/kg or total contrast volume/GFR <3.4.	I-A
Short-term, high-dose statin therapy should be considered.	Rosuvastatin 40/20 mg or atorvastatin 80 mg or simvastatin 80 mg.	IIa-A
Iso-osmolar contrast media should be considered over low-osmolar contrast media		IIa-A
Volume of contrast media should be minimized.		IIa-B
Furosemide with matched hydration may be considered over standard hydration in patients at very high risk for CIN or in cases where prophylactic hydration before the procedure cannot be accomplished.	Initial 250 mL intravenous bolus of normal saline over 30 min (reduced to ≤150 mL in case of LV dysfunction) followed by an I.V. bolus (0.25–4.5 mg/kg) of furosemide. Hydration infusion rate has to be adjusted to replace the patient's urine output. When the rate of urine output is >300 mL/h, patients undergo the coronary procedure. Matched fluid replacement maintained during the procedure and for 4 hours post-treatment.	IIb-A
N-Acetylcysteine administration instead of standard hydration is not indicated.		III-A
Infusion of sodium bicarbonate 0.84% instead of standard hydration is not indicated.		III-A

(*Continued*)

Table 30.24 Continued

Severe CKD		
Prophylactic haemofiltration 6 hours before complex PCI may be considered.	Fluid replacement rate 1000 mL/h without negative loss and saline hydration continued for 24 hours after the procedure.	IIb-B
Prophylactic renal replacement therapy is not recommended as a preventive measure.		III-B
ACCF/AHA/SCAI 2011 GL on PCI		
Vascular access		
The use of radial artery access can be useful to decrease access site complications.		IIa-A
Adjunctive diagnostic/Therapeutic devices		
Fractional flow reserve is reasonable to assess angiographic intermediate coronary lesions (50% to 70% diameter stenosis) and can be useful for guiding revascularization decisions in patients with SIHD.		IIa-A
IVUS is reasonable for the assessment of angiographically indeterminant left main CAD.		IIa-B
IVUS and coronary angiography are reasonable 4 to 6 weeks and 1 year after cardiac transplantation to exclude donor CAD, detect rapidly progressive cardiac allograft vasculopathy, and provide prognostic information.		IIa-B
IVUS is reasonable to determine the mechanism of stent restenosis.		IIa-C
IVUS may be reasonable for the assessment of non–left main coronary arteries with angiographically intermediate coronary stenosis (50% to 70% diameter stenosis).		IIb-B
IVUS may be considered for guidance of coronary stent implantation, particularly in cases of left main coronary artery stenting.		IIb-B
IVUS may be reasonable to determine the mechanism of stent thrombosis.		IIb-C
Not recommended when PCI or CABG is not being contemplated		III-C
Rotational atherectomy is reasonable for fibrotic or heavily calcified lesions that might not be crossed by a balloon catheter or adequately dilated before stent implantation.		IIa-C
Rotational atherectomy should not be performed routinely for de novo lesions or in-stent restenosis.		III-A
Laser angioplasty might be considered for fibrotic or moderately calcified lesions that cannot be crossed or dilated with conventional balloon angioplasty.		IIb-C
Laser angioplasty should not be used routinely during PCI.		III-A
Cutting balloon angioplasty might be considered to avoid slippage-induced coronary artery trauma during PCI for in-stent restenosis or ostial lesions in side branches.		IIb-C
Cutting balloon angioplasty should not be used routinely during PCI.		III-A
Percutaneous haemodynamic support devices		
Elective insertion of an appropriate haemodynamic support device as an adjunct to PCI may be reasonable in carefully selected high-risk patients.		IIb-C
No-reflow pharmacological therapies		
Administration of an intracoronary vasodilator (adenosine, calcium channel blocker, or nitroprusside) is reasonable to treat PCI-related no-reflow that occurs during primary or elective PCI.		IIa-B
Chronic total occlusions		
PCI of a chronic total occlusion in patients with appropriate clinical indications and suitable anatomy is reasonable when performed by operators with appropriate expertise		IIa-B
Saphenous vein grafts		
Embolic protection devices should be used during saphenous vein graft PCI when technically feasible.		I-B
Platelet GP IIb/IIIa inhibitors are not beneficial as adjunctive therapy during saphenous vein graft PCI.		III-B
PCI is not recommended for chronic saphenous vein graft occlusions.		III-C
Bifurcation lesions		
Provisional side-branch stenting should be the initial approach in patients with bifurcation lesions when the side branch is not large and has only mild or moderate focal disease at the ostium.		I-A
It is reasonable to use elective double stenting in patients with complex bifurcation morphology involving a large side branch where the risk of side-branch occlusion is high and the likelihood of successful side-branch reaccess is low.		IIa-B
Aorto-ostial stenoses		
IVUS is reasonable for the assessment of angiographically indeterminant left main CAD.		IIa-B
Use of DES is reasonable when PCI is indicated in patients with an aorto-ostial stenosis.		IIa-B

(*Continued*)

Table 30.24 Continued

Coronary Stents	
DES in high risk of restenosis and the patient is likely to be able to tolerate and comply with prolonged DAPT.	
Elective PCI and STEMI	I-A
UA/NSTEMI	I-C
Balloon angioplasty or BMS in patients with high bleeding risk, inability to comply with 12 months of DAPT, or anticipated invasive or surgical procedures within the next 12 months.	I-B
PCI with coronary stenting should not be performed if the patient is not likely to be able to tolerate and comply with DAPT.	III-B
DES should not be implanted if the patient is not likely to be able to tolerate and comply with prolonged DAPT or this cannot be determined before stent implantation.	III-B
Restenosis	
Patients who develop clinical restenosis after balloon angioplasty should be treated with BMS or DES if anatomic factors are appropriate and if the patient is able to comply with and tolerate DAPT.	I-B
Patients who develop clinical restenosis after BMS should be treated with DES if anatomic factors are appropriate and the patient is able to comply with and tolerate DAPT.	I-A
Patients who develop clinical restenosis after DES may be considered for repeat PCI with balloon angioplasty, BMS, or DES containing the same drug or an alternative antiproliferative drug if anatomic factors are appropriate and the patient is able to comply with and tolerate DAPT.	IIb-C
Vascular closure devices	
Patients considered for vascular closure devices should undergo a femoral angiogram to ensure their anatomic suitability for deployment.	I-C
The use of vascular closure devices is reasonable for the purposes of achieving faster haemostasis and earlier ambulation compared with the use of manual compression.	IIa-B
The routine use of vascular closure devices is not recommended for the purpose of decreasing vascular complications, including bleeding.	III-B
Clopidogrel genetic testing	
Genetic testing might be considered to identify whether a patient at high risk for poor clinical outcomes is predisposed to inadequate platelet inhibition with clopidogrel.	IIb-C
When a patient predisposed to inadequate platelet inhibition with clopidogrel is identified by genetic testing, treatment with an alternate P2Y12 inhibitor (e.g., prasugrel or ticagrelor) might be considered.	IIb-C
Platelet function testing	
Platelet function testing may be considered in patients at high risk for poor clinical outcomes.	IIb-C
In patients treated with clopidogrel with high platelet reactivity, alternative agents, such as prasugrel or ticagrelor, might be considered.	IIb-C
ESC 2014 GL on revascularization	
Intracoronary diagnostic techniques	
FFR to identify haemodynamically relevant coronary lesion(s) when evidence of ischaemia is not available.	I-A
FFR-guided PCI in multivessel disease	IIa-B
IVUS to optimize stent implantation	IIa-B*
IVUS to assess severity and optimize treatment of unprotected left main lesions.	IIa-B
IVUS or OCT to assess mechanisms of stent failure.	IIa-C
OCT in selected patients to optimize stent implantation.	IIb-C
Treatment of specific lesion subsets	
DES for PCI of ostial lesions.	IIa-B
For PCI of bifurcation lesions, stent implantation in the main vessel only, followed by provisional balloon angioplasty with or without stenting of the side branch	IIa-A
Percutaneous recanalization of CTOs in expected ischaemia reduction in a corresponding myocardial territory and/or angina relief.	IIa-B
Retrograde recanalization of CTOs after a failed anterograde approach or as the primary approach	IIb-C

(*Continued*)

Table 30.24 Continued

ACCF/AHA/SCAI 2011 GL on PCI	
Operator and institutional competency and volume	
Elective/urgent PCI should be performed by operators with an acceptable annual volume (≥75 procedures) at high-volume centres (>400 procedures) with on-site cardiac surgery.	I-C
Elective/urgent PCI should be performed by operators and institutions whose current risk-adjusted outcomes statistics are comparable to those reported in contemporary national data registries.	I-C
Primary PCI for STEMI should be performed by experienced operators who perform more than 75 elective PCI procedures per year and, ideally, at least 11 PCI procedures for STEMI per year. Ideally, these procedures should be performed in institutions that perform more than 400 elective PCIs per year and more than 36 primary PCI procedures for STEMI per year.	I-C
It is reasonable that operators with acceptable volume (≥75 PCI procedures/ year) perform elective/urgent PCI at low-volume centres (200 to 400 PCI procedures/year) with on-site cardiac surgery.	IIa-C
It is reasonable that low-volume operators (<75 PCI procedures per year) perform elective/urgent PCI at high-volume centres (>400 PCI procedures per year) with on-site cardiac surgery. Ideally, operators with an annual procedure volume of fewer than 75 procedures per year should only work at institutions with an activity level of more than 600 procedures per year. Operators who perform fewer than 75 procedures per year should develop a defined mentoring relationship with a highly experienced operator who has an annual procedural volume of at least 150 procedures.	IIa-C
The benefit of primary PCI for STEMI patients eligible for fibrinolysis when performed by an operator who performs fewer than 75 procedures per year (<11 PCIs for STEMI per year) is not well established.	IIb-C
It is not recommended that elective/urgent PCI is performed by low-volume operators (<75 procedures per year) at low-volume centres (200 to 400 procedures per year) with or without on-site cardiac surgery. An institution with a volume of fewer than 200 procedures per year, unless in a region that is underserved because of geography, should carefully consider whether it should continue to offer this service.	III-C
PCI in hospitals without on-site surgical backup	
Primary PCI is reasonable in hospitals without on-site cardiac surgery, provided that appropriate planning for program development has been accomplished.	IIa-B
Elective PCI might be considered in hospitals without on-site cardiac surgery, provided that appropriate planning for program development has been accomplished and rigorous clinical and angiographic criteria are used for proper patient selection.	IIb-B
Primary or elective PCI should not be performed in hospitals without on-site cardiac surgery capabilities without a proven plan for rapid transport to a cardiac surgery operating room in a nearby hospital or without appropriate haemodynamic support capability for transfer.	III-C
ESC 2014 GL on revascularization	
Recommendations for training, proficiency, and operator/institutional competence in PCI	
Physicians training in interventional cardiology should complete formal training according to a 1–2 year curriculum at institutions with at least 800 PCIs per year and an established 24-hour/7-day service for the treatment of patients with ACS.	IIa-C
Trainees should have performed at least 200 PCI procedures as first or only operator with one-third of PCI procedures in emergency or ACS patients under supervision before becoming independent.	IIa-C
National Societies of the ESC should develop recommendations on annual operator and institutional PCI volume. This Task Force recommend:	IIa-C
◆ PCI for ACS should be performed by operators with an annual volume of at least 75 procedures at institutions performing at least 400 PCI per year with an established 24-hour/7-day service for the treatment of patients with ACS.	
◆ PCI for stable CAD should be performed by trained operators with an annual volume of at least 75 procedures at institutions performing at least 200 PCI per year.	
◆ Institutions with an annual volume < 400 PCI should consider collaboration in networks with high-volume institutions (> 400/ year), with shared written protocols and exchange of operators and support staff.	
Non-emergency high-risk PCI procedures, such as distal LM disease, complex bifurcation stenosis, single remaining patent coronary artery, and complex chronic total occlusions, should be performed by adequately experienced operators at centres that have access to circulatory support and intensive care treatment, and preferentially have cardiovascular surgery on-site.	IIa-C

*: The ESC 2013 GL on stable CAD give a IIb-B recommendation to IVUS and OCT for lesion characterization or stent deployment.
AKI indicates acute kidney injury; CIN: contrast-induced nephropathy; CKD, chronic kidney disease; CTO: chronic total occlusion**;** GFR: glomerular filtration rate; LV: left ventricular; MDCT: multidetector computer tomography; MI, myocardial infarction; and PCI, percutaneous coronary intervention.
ACCF /AHA /SCAI 2011 Guideline for percutaneous coronary intervention: *J Am Coll Cardiol*. 2011;**58**:2550–83, copyright with permission from Elsevier.
ESC /EACTS 2014 Guidelines on myocardial revascularization. *Eur Heart J*. 2014;**35**:2541–619 with permission from Oxford University Press.

Hybrid coronary revascularization

Hybrid coronary revascularization (defined as the planned combination of LIMA-to-LAD artery grafting and DES of ≥1 non-LAD coronary arteries) is reasonable in patients with heavily calcified proximal aorta or poor target vessels for CABG (but amenable to PCI) or unfavourable LAD artery for PCI (i.e. excessive vessel tortuosity or chronic total occlusion). It can also be considered as an alternative to multivessel PCI or CABG in an attempt to improve the overall risk–benefit ratio of the procedures. It is now performed as a staged or concurrent procedure in one-third of US hospitals and appears to be a safe alternative to CABG in high-risk patients,[339] but existing evidence is limited.[340]

The ACCF/AHA recommendations are presented in Table 30.25.

Refractory angina

An increasing number of patients with severe coronary artery disease are not candidates for any form of revascularization and experience angina in spite of optimal medical therapy. Long-term mortality in patients with refractory angina is lower than previously reported.[341] Treatment options are presented in Table 30.26. Recently, implantation of a coronary sinus-reducing device was associated with symptomatic improvement in patients with refractory angina who were not candidates for revascularization.[342]

Table 30.25 ACCF/AHA 2012 GL on stable CAD. Hybrid coronary revascularization*

Hybrid coronary revascularization in patients with one or more of the following: a. Limitations to traditional CABG, such as heavily calcified proximal aorta or poor target vessels for CABG (but amenable to PCI) b. Lack of suitable graft conduits c. Unfavourable LAD artery for PCI (i.e. excessive vessel tortuosity or chronic total occlusion).	IIa-B
Hybrid coronary revascularization as an alternative to multivessel PCI or CABG in an attempt to improve the overall risk-benefit ratio of the procedures.	IIb-C

* Defined as the planned combination of left internal mammary artery-to-LAD artery grafting and PCI of ≥1 non-LAD coronary arteries.
ACCF/AHA/ACP/AATS/PCNA/SCAI/STS 2012 Guideline for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol*. 2012;**60**:e44–e164 with permission from Elsevier.

Table 30.26 Refractory angina

ACCF/AHA 2012 GL on stable CAD. Alternative therapies for relief of symptoms in patients with refractory angina	
Enhanced external counterpulsation for relief of refractory angina.	IIb-B
Spinal cord stimulation for relief of refractory angina.	IIb-C
Transmyocardial revascularization for relief of refractory angina.	IIb-B
Acupuncture for the purpose of improving symptoms or reducing cardiovascular risk.	III-C
ESC 2013 GL on stable CAD. Treatment options in invalidating angina refractory to optimal medical and revascularization strategies	
Enhanced external counterpulsation.	IIa-B
Transcutaneous electrical nerve stimulation.	IIb-C
Spinal cord stimulation.	IIb-B
Transmyocardial revascularization.	III-A

ACCF/AHA/ACP/AATS/PCNA/SCAI/STS 2012 Guideline for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol*. 2012;**60**:e44–e164 with permission from Elsevier.
ESC 2013 Guidelines on the management of stable coronary artery disease. *Eur Heart J*. 2013;**34**:2949–3003, with permission from Oxford University Press.

Long-term management

Measures for secondary prevention are implemented, as described in Tables 30.12 to 30.16. Detailed recommendations on prevention have been released by the ACC/AHA[101] and the ESC.[118] Echocardiography and tests for ischaemia are indicated when new symptoms appear (Tables 30.27, 30.28, and 30.29). Annual treadmill exercise testing in patients who have no change in clinical status may also be performed in moderate- or high-risk patients. However, the value of routine testing or catheterization following stenting is questionable.[343] In patients entering a formal cardiac rehabilitation programme after PCI, treadmill exercise testing is reasonable, but routine periodic stress testing of asymptomatic patients after PCI without specific clinical indications is not recommended (Table 30.27). Sexual activity is allowed in patients who can exercise >3 to 5 METS without angina, excessive dyspnoea, ischaemic ST segment changes, cyanosis, hypotension, or arrhythmia (AHA 2012 on sexual activity and CVD, IIa-C), one or more weeks after uncomplicated MI (IIa-C), several days after PCI if the vascular access site is without complications (IIa-C), and 6–8 weeks after CABG, provided the sternotomy is well healed (IIa-B).

Table 30.27 Follow-up of CAD patients

ACCF/AHA 2012 GL on stable CAD. Follow-up non-invasive testing in patients with known SIHD: new, recurrent, or worsening symptoms not consistent with UA

Test	Exercise status		ECG interpretable			Additional considerations
	Able	Unable	Yes	No		
Patients able to exercise*						
Exercise ECG	X		X		I-B	
Exercise with nuclear MPI or echo	X			X	I-B	
Exercise with nuclear MPI or echo	X		Any		IIa-B	Prior requirement for imaging with exercise Known or at high risk for multivessel disease
Pharmacological stress nuclear MPI/echo/CMR	X		X		III-C (no benefit)	
Patients unable to exercise						
Pharmacological stress nuclear MPI or echo		X	Any		I-B	
Pharmacological stress CMR		X	Any		IIa-B	
Exercise ECG		X		X	III-C (no benefit)	
Irrespective of ability to exercise						
CCTA	Any		Any		IIb-B	Patency of CABG or coronary stent ≥3 mm diameter
CCTA	Any		Any		IIb-B	In the absence of known moderate or severe calcification and intent to assess coronary stent <3 mm in diameter
CCTA	Any		Any		III-C (no benefit)	Known moderate or severe native coronary calcification or assessment of coronary stent <3 mm in diameter in patients who have new or worsening symptoms not consistent with UA

(*Continued*)

Table 30.27 Continued

Non-invasive testing in known SIHD: asymptomatic (or stable symptoms)							
Test	**Exercise status**		**ECG interpretable**		**Pretest probability of ischaemia**		**Additional considerations**
	Able*	**Unable**	**Yes**	**No**			
Exercise or pharmacological stress with nuclear MPI, echo, or CMR at ≥2-year intervals		X		X	Prior evidence of silent ischaemia or high risk for recurrent cardiac event. Meets criteria listed in additional considerations.	IIa-C	a) Unable to exercise to adequate workload, or b) Uninterpretable ECG, or c) History of incomplete coronary revascularization
Exercise ECG at ≥1-year intervals	X		X		Any	IIb-C	a) Prior evidence of silent ischaemia, OR b) At high risk for recurrent cardiac event
Exercise ECG	X		X		No prior evidence of silent ischaemia and not at high risk of recurrent cardiac event.	IIb-C	For annual surveillance
Exercise or pharmacological stress with nuclear MPI, echo, or CMR or CCTA	Any		Any		Any	III-C (no benefit)	a) <5-year intervals after CABG, or b) <2-year intervals after PCI

* Patients are candidates for exercise testing if they are capable of performing at least moderate physical functioning (i.e. moderate household, yard, or recreational work and most activities of daily living) and have no disabling co-morbidity. Patients should be able to achieve 85% of age-predicted maximum heart rate.

CABG indicates coronary artery bypass graft surgery; CCTA, cardiac computed tomography angiography; CMR, coronary magnetic resonance; CMR, cardiac magnetic resonance; ECG, electrocardiogram; echo, echocardiography; MPI, myocardial perfusion imaging; PCI, percutaneous coronary intervention; SIHD, stable ischaemic heart disease; and UA, unstable angina.

ACCF/AHA/ACP/AATS/PCNA/SCAI/STS 2012 Guideline for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol*. 2012;**60**:e44–e164 with permission from Elsevier.

Table 30.28 Follow-up

ESC 2013 GL on stable CAD	
Blood tests for routine re-assessment in patients with chronic stable coronary artery disease	
Annual control of lipids, glucose metabolism, and creatinine is recommended in all patients with known SCAD.	I-C
Re-assessment in patients with stable coronary artery disease	
Follow-up visits every 4–6 months in the first year following therapy which may be extended to 1 year afterwards. Visits (careful history and biochemical testing as appropriate) should be to the general practitioner who may refer to the cardiologist in case of uncertainty.	I-C
Annual resting ECG and additional ECG if a change in anginal status occurred or symptoms suggesting an arrhythmia appeared or medication has been changed which might alter electrical conduction.	I-C
Exercise ECG or stress imaging if appropriate in the presence of recurrent or new symptoms once instability has been ruled out.	I-C
Reassessment of the prognosis using stress testing in asymptomatic patients after the expiration of the period for which the previous test was felt to be valid ('warranty period').	IIb-C
Repetition of an exercise ECG after at least 2 years following the last test (unless there is a change in clinical presentation).	IIb-C
Follow-up of revascularized stable coronary artery disease patients	
General measures	
Secondary prevention and follow-up visit for revascularized patients.	I-A
Instruct patients before discharge about return to work and reuptake of full activities, and to seek immediate medical contact if symptoms (re-)occur.	I-C

(*Continued*)

Table 30.28 Continued

Imaging management	
In symptomatic patients, stress imaging (stress echocardiography, MRI, or MPS) rather than stress ECG.	I-C
In low ischaemic findings (<5% of myocardium) at stress imaging, optimal medical therapy is recommended.	I-C
In high ischaemic findings (>10% of myocardium) at stress imaging, coronary angiography is recommended.	I-C
Late (6 months) stress imaging test after revascularization to detect patients with restenosis after stenting or graft occlusion irrespective of symptoms[a].	IIb-C
After high risk PCIs (e.g. LM disease) late (3–12 months) control angiography, irrespective of symptoms.	IIb-C
Systematic control angiography, early or late after PCI, is not recommended.	III-C
ESC 2014 GL on revascularization	
Long-term medical therapy after myocardial revascularization to improve prognosis and recommendations for lifestyle changes and participation in cardiac rehabilitation programmes	
Coronary artery disease	
Statin therapy with an LDL-C goal <70 mg/dL (<1.8 mmol/L in all patients with CAD after revascularization, unless contraindicated).	I-A
Low-dose ASA (75–100 mg/day) in all patients with CAD	I-A
Clopidogrel in ASA intolerance	I-B
ACE inhibitors (or ARB intolerance) if there is heart failure, hypertension or diabetes	I-A
Lifestyle changes (including smoking cessation, regular physical activity, and a healthy diet).	I-A
Participation in a cardiac rehabilitation programme to modify lifestyle habits	IIa-A
Coronary artery disease and hypertension	
A systolic blood pressure goal <140 mmHg in patients with CAD	IIa-A
A diastolic BP goal of <90 mmHg in all patients.	I-A
In patients with diabetes a DBP goal <85 mmHg is recommended.	
Coronary artery disease and type 2 diabetes	
A target for HbA1c of <7.0% is well established for the prevention of microvascular disease.	I-A
Coronary artery disease and chronic heart failure	
Similar to those provided by the ESC 2012 GL on HF.	
Strategies for follow-up and management in patients after myocardial revascularization	
Asymptomatic patients	
Early imaging testing in:	IIa-C
– patients with safety-critical professions (e.g. pilots, drivers, divers) and competitive athletes;	
– patients engaging in recreational activities for which high oxygen consumption is required;	
– patients resuscitated from sudden death;	
– patients with incomplete or suboptimal revascularization, even if asymptomatic;	
– patients with a complicated course during revascularization (perioperative myocardial infarction, extensive dissection during PCI, endarterectomy during CABG, etc.);	
– patients with diabetes (especially those requiring insulin);	
– patients with multivessel disease and residual intermediate lesions, or with silent ischaemia.	
Routine stress testing >2 years after PCI and >5 years after CABG.	IIb-C
After high-risk PCI (e.g. unprotected LM stenosis) late (3–12 months) control angiography, irrespective of symptoms.	IIb-C
Symptomatic patients	
Reinforce medical therapy and lifestyle changes in patients with low-risk findings at stress testing.	I-C
Coronary angiography with intermediate- to high-risk findings at stress testing (ischaemia at low workload, early onset ischaemia, multiple zones of high-grade wall motion abnormality, or reversible perfusion defect.)	I-C
AHA 2015 Statement on secondary prevention after CABG	
Antiplatelet and antithrombotic therapy	
Aspirin (81-325 mg OD) within 6 h after CABG, continued indefinitely	I-A

(*Continued*)

Table 30.28 Continued

After off-pump CABG, aspirin (81–162 mg OD) and clopidogrel for 1 year	I-A
Clopidogrel in patients who cannot tolerate aspirin	I-C
In patients presenting with an ACS, aspirin and prasugrel or ticagrelor after CABG	IIa-B
As sole antiplatelet, 325 mg od aspirin may be preferable to 81 mg od	IIa-A
Aspirin and clopidogrel for 1 year after on-pump CABG	IIb-A
Warfarin should not be prescribed after CABG, unless other indications exist	III-A
Alternatives to warfarin (dabigatran, apixaban, rivaroxaban) routinely after CABG	III-C
Lipid management	
Statins starting preoperatively and early after surgery	I-A
High intensity (atorvastatin 40–80 mg, rosuvastatin 20–40 mg) for all CABG patients <75 years old	I-A
Moderate intensity if intolerance or age >75 years	I-A
Discontinuation of statins not recommended unless if adverse reactions	III-B
β-blockers	
Perioperatively, to prevent postoperative AF, starting before surgery, unless contraindicated (ie, bradycardia, severe reactive airway disease)	I-A
History of MI	I-A
LV dysfunction (bisoprolol, metoprolol, carvedilol)	I-B
For hypertension (other drugs more effective)	IIb-B
Hypertension management	
β-Blockers, as soon as possible after CABG in the absence of contraindications	I-A
ACE inhibitor in recent MI, LV dysfunction, diabetes mellitus, and chronic kidney disease	I-B
BP goal of <140/85 mmHg after CABG	IIa-B
Additional calcium channel blocker or a diuretic agent if necessary in the perioperative period	IIa-B
For chronic hypertension management if no previous MI or LV dysfunction	IIb-B
Routine ACE inhibitor without recent MI, LV dysfunction, diabetes mellitus, and chronic kidney disease	III-B
Previous MI and LV dysfunction	
β-blockers and ACEI or ARBs if LVEF<40%	I-A/B
Add aldosterone antagonist if LVEF <35% and NYHA II-IV	IIa-B
ICD not recommended in LVEF<35% until 3 months postoperatively	III-A
Diabetes mellitus	
Target HbA1c 7%	IIa-B
Smoking	
Cessation	I-A
Nicotine replacement, bupropion, and varenicline as adjuncts after discharge	IIa-B
Nicotine replacement, bupropion, and varenicline as adjuncts during CABG hospitalization	IIb-B
Cardiac rehabilitation	
Early during the hospital stay	I-A
Mental health and cognitive decline	
Screen for depression after CABG	IIa-B
Cognitive behaviour therapy for depression	IIa-B
Obesity and metabolic syndrome	
Assessment of central distribution of fat by measuring waist and hip circumference and calculating waist-to-hip ratio, even if the BMI is within normal limits	IIa-C
Bariatric surgery in patients with a BMI >35 kg/m^2 if lifestyle interventions have already been attempted without meaningful weight loss	IIb-C
Vitamins and supplements	
In patients with specific vitamin deficiencies	IIb-C
Omega-3 fatty acids and antioxidant vitamins for postoperative AF	IIb-A

(*Continued*)

Table 30.28 Continued

Vaccination	
Annual influenza vaccination	I-B

ACS, acute coronary syndrome; BMS, bare metal stents; CABG, coronary artery bypass graft surgery; DAPT, dual antiplatelet therapy; DES, drug eluting stents; ECG, electrocardiogram; LM, left main; MPS, myocardial perfusion scintigraphy; MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention;
[a] Specific patient subsets indicated for early stress testing:
– patients with safety critical professions (e.g. pilots, drivers, divers) and competitive athletes
– patients who would like to engage in activities, for which high oxygen consumption is required.
ESC /EACTS 2014 Guidelines on myocardial revascularization. *Eur Heart J.* 2014;**35**:2541–619 with permission from Oxford University Press.
ESC 2013 Guidelines on the management of stable coronary artery disease. *Eur Heart J.* 2013;**34**:2949–3003, with permission from Oxford University Press.

Table 30.29 ESC 2014 GL on revascularization. Repeat revascularization

Early post-operative ischaemia and graft failure	
Coronary angiography for: symptoms of ischaemia and/or abnormal biomarkers suggestive of perioperative myocardial infarction ischaemic ECG changes indicating large area of risk new significant wall motion abnormalities haemodynamic instability.	I-C
Make the decision on redo CABG or PCI by *ad hoc* consultation in the Heart Team and based on feasibility of revascularization, area at risk, comorbidities and clinical status.	I-C
PCI over re-operation in patients with early ischaemia after CABG if technically feasible.	IIa-C
If PCI is performed, revascularization of the native vessels or IMA grafts rather than occluded or heavily diseased SVGs	IIa-C
Disease progression and late graft failure	
Repeat revascularization in severe symptoms or extensive ischaemia despite medical therapy if technically feasible.	I-B
PCI as a first choice if technically feasible, rather than re-do CABG.	IIa-C
PCI of the bypassed native artery, if technically feasible.	IIa-C
IMA, if available, is the conduit of choice for re-do CABG.	I-B
Re-do CABG for patients without a patent IMA graft to the LAD.	IIa-B
Re-do CABG in patients with lesions and anatomy not suitable for revascularization by PCI.	IIb-C
PCI in patients with patent IMA graft if technically feasible.	IIb-C
DES for PCI of SVGs.	I-A
Distal protection devices for PCI of SVG lesions if technically feasible.	I-B
Restenosis	
Repeat PCI if technically feasible.	I-C
DES for in-stent re-stenosis (within BMS or DES).	I-A
Drug-coated for in-stent restenosis (within BMS or DES).	I-A
IVUS and/or OCT to detect stent-related mechanical problems.	IIa-C
Stent thrombosis	
Emergency PCI to restore stent and vessel patency and myocardial reperfusion	I-C
DAPT with use of potent P2Y12 inhibitors (prasugrel or ticagrelor) over clopidogrel	I-C
Thrombus aspiration and high-pressure balloon dilation	IIa-C
IVUS and/or OCT to detect stent-related mechanical problems	IIa-C
Hybrid procedures	
Consecutive or combined surgical and percutaneous revascularization in specific patient subsets at experienced centres	IIb-C

BMS: bare-metal stent; CTO: chronic total occlusions; DAPT: dual antiplatelet therapy; DES: drug-eluting stent; IMA: internal mammary artery; IVUS: intravascular ultrasound; OCT: optical coherence tomography; SVG: saphenous vein graft.
ESC /EACTS 2014 Guidelines on myocardial revascularization. *Eur Heart J.* 2014;**35**:2541–619 with permission from Oxford University Press.

Evaluation and risk assessment before non-cardiac surgery

Although current perioperative risk prediction models place greater emphasis on CAD, patients with HF or AF have a significantly higher risk of post-operative mortality than patients with CAD, and even minor procedures carry a risk higher than previously appreciated.[344] The functional capacity of the patient is important for risk prediction. The inability to climb two flights of stairs or run a short distance (<4 METs) indicates poor functional capacity and is associated with an increased incidence of post-operative cardiac events (Figure 30.17). Recommendations on perioperative cardiovascular evaluation are presented in Tables 30.30, 30.31, 30.32, and 30.33, and Figure 30.18.[345,346] Laparoscopic procedures carry a similar risk to the open ones.[346] Regarding vascular interventions, endovascular abdominal aortic aneurysm repair has lower short-term mortality and morbidity than open repair, whereas carotid stenting is associated with a higher rate of stroke or death compared to endarterectomy.[346] The role of pre-operative beta blockers has been questioned, and there has been evidence that when started within 1 day or less before non-cardiac surgery, they may decrease the rate of periprocedural MI but at the expense of increased strokes, hypotension, and overall mortality.[347,348] In addition, preoperative beta-blocker use among patients undergoing non-emergent CABG surgery, who have not had a recent MI, is not associated with improved perioperative outcomes.[349] They are beneficial in patients who undergo non-cardiac surgery in the context of heart failure or a recent MI[350] and in patients with at least three of the following prognostic factors: renal failure, coronary artery disease, diabetes, and surgery in a major body cavity.[351]

The 2014 guidelines on non-cardiac surgery by the ACC/AHA and the ESC have jointly reached a consensus that the initiation of beta blockers in patients who will undergo non-cardiac surgery should not be considered routine (Table 30.31).[345,346]

The earliest optimal time for elective surgery is 30 days after bare metal stent implantation or >90–180 days after drug-eluting stent implantation (Figure 30.19).[352] In a VA study among patients undergoing non-cardiac surgery within 2 years of coronary stent placement, cardiac events were associated with emergency surgery, MI within the prior 6 months, and advanced cardiac disease (Cardiac Risk Index >2).[353] The risk is higher in the first 6 weeks after stenting (2.8%), and becomes 2.0% between 6 weeks and 6 months, and 0.9% after 6 months.[354] In patients needing surgery early after stent implantation, consideration should be given to perioperative continuation of oral antiplatelet therapy (at least aspirin). Preoperative bridging with a glycoprotein IIb/IIIa inhibitor in patients undergoing surgery after coronary stenting does not abolish the risk of perioperative stent thrombosis and may carry increased risk for bleeding.[355] Recommendations on cardiac disease evaluation and management in kidney and liver transplantation candidates have been recently published by AHA/ACCF.[356] Transplantation is generally not recommended 4 weeks after balloon angioplasty, 3 months after BMS, and 12 months after DES. In case of urgent surgery, however, clopidogrel must be stopped for 5 days, or even continued in case of low bleeding risk. In patients without stents, the use of aspirin perioperatively in patients with and without pre-existing vascular disease increases the risk of bleeding without any effect on the rate of a composite of death or non-fatal myocardial infarction (POISE-2 trial).[357]

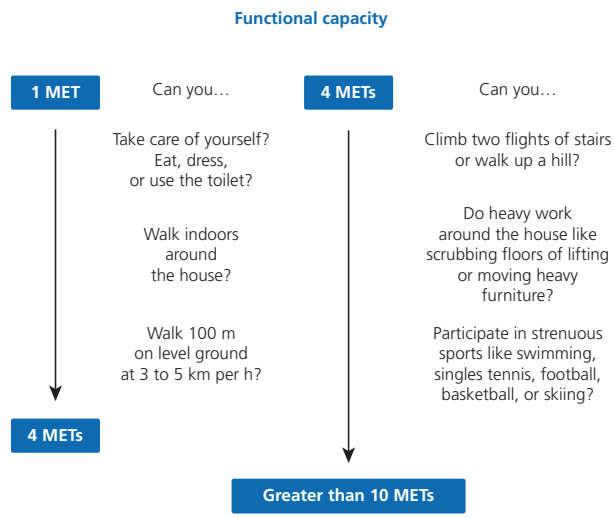

Figure 30.17 ESC 2014 GL on non-cardiac surgery. Estimated energy requirements for various activities.

MET: metabolic equivalent

ESC/ESA 2014 Guidelines on non-cardiac surgery: cardiovascular assessment and management. *Eur Heart J.* 2014;2382–2431, with permission of Oxford University Press.

Table 30.30 Risk assessment before non-cardiac surgery

ESC 2014 GL on non-cardiac surgery. Surgical risk estimate according to type of surgery or intervention		
Low-risk: < 1%	**Intermediate-risk: 1–5%**	**High-risk: >5%**
Superficial surgery Breast Dental Endocrine: thyroid Eye Reconstructive Carotid asymptomatic (CEA or CAS) Gynaecology: minor Orthopaedic: minor (meniscectomy) Urological: minor (transurethral resection of the prostate)	Intraperitoneal: splenectomy, hiatal hernia repair, cholecystectomy Carotid symptomatic (CEA or CAS) Peripheral arterial angioplasty Endovascular aneurysm repair Head and neck surgery Neurological or orthopaedic: major (hip and spine surgery) Urological or gynaecological: major Renal transplant Intra-thoracic: non-major	Aortic and major vascular surgery Open lower limb revascularization or amputation or thromboembolectomy Duodeno-pancreatic surgery Liver resection, bile duct surgery Oesophagectomy Repair of perforated bowel Adrenal resection Total cystectomy Pneumonectomy Pulmonary or liver transplant

ACCF/AHA 2014 GL on preoperative cardiovascular evaluation	
Resting 12-lead ECG	
Patients with known coronary heart disease or other significant structural heart disease, except for low-risk surgery	IIa-B
Asymptomatic patients, except for low-risk surgery	IIb-B
Not useful for asymptomatic patients undergoing low-risk surgical procedures	III-B (No Benefit)
Assessment of LV function	
Patients with dyspnoea of unknown origin	IIa-C
It is reasonable for:	
Patients with HF with worsening dyspnoea or other change in clinical status	IIa-C
Reassessment of LV function in clinically stable patients	IIb-C
Routine preoperative evaluation of LV function is not recommended	III-B (No Benefit)
Exercise stress testing	
Forgo exercise testing in patients with elevated risk and excellent functional capacity (=10 metabolic equivalents [METS])	IIa-B
Perform exercise testing in patients with elevated risk and unknown functional capacity	IIb-B
Cardiopulmonary exercise testing for elevated risk procedures	IIb-B
Forgo exercise testing in patients with elevated risk and moderate to good functional capacity (≥4 METS)	IIb-B
Perform exercise testing in patients with elevated risk and poor (<4 METS) or unknown functional capacity	IIb-C
Routine screening with noninvasive stress testing is not useful	III-B (No Benefit)
Noninvasive pharmacological stress testing	
Dobutamine stress echocardiography or myocardial perfusion imaging for patients at elevated risk for noncardiac surgery with poor functional capacity	IIa-B
Routine screening with noninvasive stress testing is not useful for low-risk noncardiac surgery	III-B (No Benefit)
Preoperative coronary angiography	
Routine preoperative coronary angiography is not recommended	III-C (No Benefit)

ESC GL 2014 GL on non-cardiac surgery	
Cardiac risk stratification	
Clinical risk indices for peri-operative risk stratification.	I-B
The NSQIP model or the Lee risk index are recommended for cardiac peri-operative risk stratification.	I-B
Cardiac troponins in high-risk patients, both before and 48–72 hours after major surgery	IIb-B

(*Continued*)

Table 30.30 Continued

NT-proBNP and BNP for independent prognostic information for perioperative and late cardiac events in high-risk patients.	IIb-B
Universal pre-operative routine biomarker sampling is not recommended.	III-C
Routine pre-operative ECG	
Patients with risk factor(s) and intermediate- or high-risk surgery.	I-C
Patients with risk factor(s) and low-risk surgery.	IIb-C
Patients >65 years, with no risk factors, and intermediate-risk surgery.	IIb-C
Not recommended for patients with no risk factors and low-risk surgery.	III-B
Clinical risk factors according to the revised cardiac risk index (Lee)	
◆ Ischaemic heart disease (angina pectoris and/or previous myocardial infarction[a])	
◆ Heart failure	
◆ Stroke or transient ischaemic attack	
◆ Renal dysfunction (serum creatinine >170 μmol/L or 2 mg/dL or a creatinine clearance of <60 mL/min/1.73 m^2)	
◆ Diabetes mellitus requiring insulin therapy	
Resting echocardiography in asymptomatic patients without signs of cardiac disease or electrocardiographic abnormalities	
In patients undergoing high-risk surgery.	IIb-C
Not recommended in patients undergoing intermediate- or low-risk surgery.	III-C
Imaging stress testing before surgery in asymptomatic patients	
Imaging stress testing is recommended:	
Before high-risk surgery in patients with more than two clinical risk factors and poor functional capacity (<4 METs)	I-C
Before high- or intermediate-risk surgery in patients with one or two clinical risk factors and poor functional capacity (<4 METs).	IIb-C
Not recommended before low-risk surgery, regardless of the patient's clinical risk.	III-C
Pre-operative coronary angiography	
Indications for pre-operative coronary angiography and revascularization are similar to those for the non-surgical setting.	I-C
Urgent angiography in patients with acute ST-segment elevation myocardial infarction requiring non-urgent, non-cardiac surgery.	I-A
Urgent or early invasive strategy in patients with NSTE-ACS requiring non-urgent, noncardiac surgery according to risk assessment.	I-B
Pre-operative angiography in patients with proven myocardial ischaemia and unstabilized chest pain (Canadian Cardiovascular Society Class III–IV) with adequate medical therapy requiring non-urgent, non-cardiac surgery.	I-C
Pre-operative angiography in stable cardiac patients undergoing non-urgent carotid endarterectomy surgery.	IIb-B
Pre-operative angiography is not recommended in cardiac stable patients undergoing low-risk surgery.	III-C

ACC/AHA 2014 Guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *J Am Coll Cardiol*. 2014;**64**:e77–e137, with permission from Elsevier.
BNP. B-type natriuretic peptide; NT-proBNP. N-terminal pro-brain natriuretic peptide.
CAS, carotid artery stenting; CEA, carotid endarterectomy.
ESC/ESA 2014 Guidelines on non-cardiac surgery: cardiovascular assessment and management. *Eur Heart J*. 2014;2382–2431, with permission of Oxford University Press.
NSQIP. National Surgical Quality Improvement Program
Surgical risk estimate is a broad approximation of 30-day risk of cardiovascular death and myocardial infarction that takes into account only the specific surgical intervention, without considering the patient's comorbidities.

Table 30.31 Risk-reduction and perioperative therapy during noncardiac surgery

ACCF/AHA 2014 GL on preoperative cardiovascular evaluation and 2016 update on duration of DAPT	
Coronary revascularization before noncardiac surgery	
Revascularization before noncardiac surgery is recommended when indicated by existing practice guidelines	I-C
Coronary revascularization is not recommended before noncardiac surgery exclusively to reduce perioperative cardiac events	III-B (No Benefit)
Timing of elective noncardiac surgery in patients with previous PCI	
Noncardiac surgery should be delayed 30 days after BMS implantation and 6 months after DES implantation	I-B-NR
When DAPT must be interrupted, aspirin should be continued if possible and the P2Y12 should be restarted as soon as possible after surgery	I-C-EO
Consensus decision as to the relative risks of discontinuation or continuation of antiplatelet therapy	IIa-C-EO
Elective noncardiac surgery 3 months after DES implantation	IIb-C-EO
Elective noncardiac surgery should not be performed within 14 days of balloon angioplasty if aspirin will need to be discontinued perioperatively	III-C (Harm)
Elective noncardiac surgery should not be performed if DAPT will need to be discontinued perioperatively within 30 days after BMS implantation or within 12 months after DES implantation	III-B-NR (Harm)
Perioperative beta-blocker therapy*	
Continue beta blockers in patients who are on beta blockers chronically	I-B
Guide management of beta blockers after surgery by clinical circumstances	IIa-B
In patients with intermediate- or high-risk preoperative tests, begin beta blockers	IIb-C
In patients with ≥3 RCRI factors (e.g., diabetes mellitus, HF, coronary artery disease, renal insufficiency, cerebrovascular accident), begin beta blockers before surgery	IIb-B
Initiating beta blockers in the perioperative setting as an approach to reducing perioperative risk is of uncertain benefit in those with a long-term indication but no other RCRI risk factors	IIb-B
Begin perioperative beta blockers long enough in advance to assess safety and tolerability, preferably >1 d before surgery	IIb-B
Beta-blocker therapy should not be started on the day of surgery	III-B (Harm)
Perioperative statin therapy	
Continue statins in patients currently taking statins	I-B
Perioperative initiation of statin use in patients undergoing vascular surgery	IIa-B
Perioperative initiation of statins in patients with a clinical risk factor who are undergoing elevated-risk procedures	IIb-C
Alpha-2 agonists	
Alpha-2 agonists are not recommended for prevention of cardiac events	III-B (No Benefit)
ACE inhibitors	
Continuation of ACE inhibitors or ARBs perioperatively	IIa-B
If ACE inhibitors or ARBs are held before surgery, restart as soon as clinically feasible postoperatively	IIa-C
Antiplatelet agents	
Continue DAPT in patients undergoing urgent noncardiac surgery during the first 4 to 6 wk after BMS or DES implantation, unless the risk of bleeding outweighs the benefit of stent thrombosis prevention	I-C
In patients with stents undergoing surgery that requires discontinuation of P2Y12 inhibitors, continue aspirin and restart the P2Y12 platelet receptor–inhibitor as soon as possible after surgery	I-C
Management of perioperative antiplatelet therapy should be determined by consensus of treating clinicians and the patient	I-C
In patients undergoing nonemergency/nonurgent noncardiac surgery without prior coronary stenting, continue aspirin when the risk of increased cardiac events outweighs the risk of increased bleeding	IIb-B
Initiation or continuation of aspirin is not beneficial in patients undergoing elective noncardiac noncarotid surgery who have not had previous coronary stenting (III-C, if risk of ischaemic events outweighs risk of surgical bleeding)	III-B (No Benefit)
Perioperative management of patients with CIEDs	
Patients with ICDs should be on a cardiac monitor continuously during the entire period of inactivation, and external defibrillation equipment should be available. Ensure that ICDs are reprogrammed to active therapy	I-C

(*Continued*)

Table 30.31 Continued

ESC GL 2014 GL on non-cardiac surgery	
Recommendations on beta-blockers	
Peri-operative continuation in patients currently receiving beta blockers.	I-B
Pre-operative initiation in patients scheduled for high-risk surgery and who have ≥2 clinical risk factors or ASA status ≥3.	IIb-B
Pre-operative initiation in patients who have known IHD or myocardial ischaemia.*	IIb-b
Atenolol or bisoprolol as a first choice for initiation of beta blockers	IIb-B
Initiation of peri-operative highdose beta-blockers without titration is not recommended.	III-B
Pre-operative initiation of beta blockers is not recommended in low-risk surgery.	III-B
Treatment should ideally be initiated between 30 days and (at least) 2 days before surgery, starting at a low dose, and should be continued post-operatively. The target is a resting heart rate 60–70 bpm, 86 and systolic blood pressure >100 mm Hg.	
Recommendations on statins	
Peri-operative continuation of statins, favouring statins with a long half-life or extended-release formulation.	I-C
Pre-operative initiation of statin therapy in patients undergoing vascular surgery, ideally at least 2 weeks before surgery.	IIa-B
Recommendations on use of ACEIs and ARBs	
Continuation of ACEIs or ARBs, under close monitoring, during non-cardiac surgery in stable patients with heart failure and LV systolic dysfunction.	IIa-C
Initiation of ACEIs or ARBs at least 1 week before surgery in cardiac-stable patients with heart failure and LV systolic dysfunction.	IIa-C
Transient discontinuation of ACEIs or ARBs before non-cardiac surgery in hypertensive patients.	IIa-C
Recommendations on anti-platelet therapy	
Aspirin is continued for 4 weeks after BMS implantation and for 3–12 months after DES implantation, unless the risk of life-threatening surgical bleeding on aspirin is unacceptably high.	I-C
Continuation of aspirin in the perioperative period, based on an individual decision that depends on the perioperative bleeding risk, weighed against the risk of thrombotic complications.	IIb-B
Discontinuation of aspirin therapy, if haemostasis is anticipated to be difficult to control during surgery.	IIa-B
Continuation of P2Y12 inhibitor for 4 weeks after BMS implantation and for 3–12 months after DES implantation, unless the risk of life-threatening surgical bleeding on this agent is unacceptably high.	IIa-C
Postpone surgery for at least 5 days after cessation of ticagrelor and clopidogrel—and for 7 days for prasugrel, unless the patient is at high risk of an ischaemic event.	IIa-C
Recommendations on the timing of non-cardiac surgery in cardiac-stable/asymptomatic patients with previous revascularization	
Except for high-risk patients, asymptomatic patients who have undergone CABG in the past 6 years should be sent for nonurgent, non-cardiac surgery without angiographic evaluation.**	I-B
Non-urgent, non-cardiac surgery after ≥4 weeks and ideally 3 months following BMS implantation.**	IIa-B
Non-urgent, non-cardiac surgery after ≥12 months DES implantation. (6 months for the new generation DES).**	IIa-B
Postpone non-cardiac surgery until at least 2 weeks after balloon angioplasty.	IIa-B
Recommendations for prophylactic revascularization in stable/asymptomatic patients	
Myocardial revascularization according to guidelines for management in stable coronary artery disease.	I-B
Late revascularization after successful non-cardiac surgery in accordance with ESC Guidelines on stable coronary artery disease.	I-C
Prophylactic myocardial revascularization before high-risk surgery, depending on the extent of a stress-induced perfusion defect.	IIb-B
Routine prophylactic myocardial revascularization before low- and intermediate-risk surgery is not recommended.	III-B

*: Supported by the Evidence Review Committee's systematic review.
**: Aspirin to be continued throughout peri-operative period.
ACE indicates angiotensin-converting-enzyme; ARB, angiotensin-receptor blocker; ASA, American Society of Anesthesiologists; BMS, bare-metal stent; CIED, cardiovascular implantable electronic device; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; ICD, implantable cardioverter–defibrillator; RCRI, Revised Cardiac Risk Index
ACC/AHA 2014 Guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *J Am Coll Cardiol*. 2014;**64**:e77–e137, with permission from Elsevier.
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Table 30.32 Anaesthesia and intraoperative management

ACCF/AHA 2014 GL on preoperative cardiovascular evaluation	
Choice of anaesthetic technique and agent	
Either a volatile anaesthetic agent or total IV anaesthesia for patients undergoing noncardiac surgery	IIa-A
Neuraxial anaesthesia for postoperative pain relief to reduce MI in patients undergoing abdominal aortic surgery	IIa-B
Preoperative epidural analgesia to decrease the incidence of preoperative cardiac events in patients with hip fracture	IIb-B
Emergency use of perioperative TOE in patients with haemodynamic instability in patients undergoing noncardiac surgery	IIa-C
Maintenance of normothermia to reduce perioperative cardiac events	IIb-B
Use of haemodynamic assist devices when urgent or emergency noncardiac surgery is required in the setting of acute severe cardiac dysfunction	IIb-C
Pulmonary artery catheterization when underlying medical conditions that significantly affect haemodynamics cannot be corrected before surgery	IIb-C
Routine use of pulmonary artery catheterization	III-A (No Benefit)
Prophylactic intravenous nitroglycerin is not effective in reducing myocardial ischaemia	III-B (No Benefit)
Routine use of intraoperative TOE during noncardiac surgery is not recommended	III-C(No Benefit)
Surveillance and management for perioperative MI: Recommendations	
Measurement of troponin levels in the setting of signs or symptoms suggestive of myocardial ischaemia or MI.	I-A
ECG in the setting of signs or symptoms suggestive of myocardial ischaemia, MI, or arrhythmia.	I-B
Postoperative screening with troponin levels or ECG in patients at high risk for perioperative MI, but without signs or symptoms suggestive of myocardial ischaemia, MI, or arrhythmia in the absence of established risks and benefits of a defined management strategy	IIb-B
Routine postoperative screening with troponin levels in unselected patients without signs or symptoms suggestive of myocardial ischaemia or MI is not useful for guiding perioperative management	III-B
ESC GL 2014 GL on non-cardiac surgery	
ECG monitoring	
Peri-operative ECG monitoring for all patients undergoing surgery.	I-C
Selected lead combinations or twelve-lead ECG for high-risk patients and better detection of ischaemia in the operating room.	IIa-B
12-lead ECG monitoring for high-risk patients	IIa-B
Peri-operative TOE	
In acute sustained severe haemodynamic disturbances during surgery or in the peri-operative period.	I-C
Patients who develop ST-segment changes on intra-operative or peri-operative ECG monitoring.	IIa-C
Patients at high risk of developing myocardial ischaemia, who undergo high-risk non-cardiac surgery.	IIb-C
Increased risk of significant haemodynamic disturbances during and after high-risk non-cardiac surgery.	IIb-C
Patients who present severe valvular lesions during high-risk non-cardiac surgery procedures accompanied by significant haemodynamic stresses.	IIb-C
Anaesthesia	
Patients with high cardiac and surgical risk should be considered for goal-directed therapy.	IIa-B
Natriuretic peptides and high sensitivity troponin after surgery in high-risk patients	IIb-B

(*Continued*)

Table 30.32 Continued

Neuraxial anaesthesia (alone), in the absence of contraindications and after estimation of the risk–benefit ratio, reduces the risk of perioperative mortality and morbidity compared with general anaesthesia	IIb-B
Avoid arterial hypotension (mean arterial pressure <60 mm Hg) for prolonged cumulative periods (>30 minutes)	IIb-B
Neuraxial analgesia, in the absence of contra-indications, to provide post-operative analgesia.	IIb-B
Avoid non-steroidal anti-inflammatory drugs (especially cyclo-oxygenase-2 inhibitors) as the first-line analgesics in patients with IHD or stroke	IIb-B
Arrhythmias and pacemakers	
Continuation of oral antiarrhythmic drugs before surgery	I-C
Anti-arrhythmic drugs for patients with sustained VT, depending on the patient's characteristics.*	I-C
Anti-arrhythmic drugs are not recommended for patients with VPBs.	I-C
Patients with ICDs, whose devices have been pre-operatively deactivated, should be on continuous cardiac monitor throughout the period of deactivation. External defibrillation equipment should be readily available.	I-C
Peri-operative temporary pacing wire in asymptomatic bifascicular or trifascicular block	III-C
Chronic Kidney Disease	
Prophylactic haemofiltration may be considered before complex intervention or high-risk surgery in patients with stage 4 or 5 CKD	IIb-B
In patients with stage 3 CKD, prophylactic haemodialysis is not recommended.	III-B
Established or suspected carotid and peripheral artery disease	
Pre-operative carotid artery and cerebral imaging in patients with a history of TIA or stroke in the preceding 6 months.	I-C
Pre-operative, routine carotid artery imaging in patients with carotid disease undergoing vascular surgery.	IIb-C
Continuation of anti-platelet and statin therapies throughout the perioperative phase	IIa-C
For patients with carotid artery disease undergoing non-cardiac surgery, the same indications for carotid revascularization should apply as for the general population.	IIa-C
Pre-operative routine carotid artery imaging is not recommended in patients undergoing non-vascular surgery.	III-C
Pre-operative stress or imaging testing in patients with peripheral artery disease and >2 clinical risk factors for IHD.	IIa-C
COPD	
In patients with COPD, smoking cessation (>2 months before surgery) is recommended before undertaking surgery.	I-C

* The efficacy of drugs for sustained VT is not established (see Chapter 56).

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Table 30.33 ESC GL 2014 GL on non-cardiac surgery

Summary of pre-operative cardiac risk evaluation and peri-operative management

Step	Urgency	Cardiac condition	Type of surgery[a]	Functional capacity	Number of clinical risk factors[b]	ECG	LV echo[c]	Imaging Stress Testing[d]	BNP and TnT[c]	B-Blockers[e/f]	ACE-inhibitors[e]	Aspirin	Statins[e]	Coronary revascularization
1	Urgent surgery	Stable					III C	III C		I B (continuation)	IIa.C[h] (continuation)	IIb B (continuation)	I C (continuation)	III C
2	Urgent surgery	Unstable[g]												IIa C
	Elective surgery	Unstable[g]				I C[*]	I C[*]	III C	IIb B					I A
3	Elective surgery	Stable	Low risk (< I%)		None	III C	III C	III C	III C	III B	IIa C[h]	I C[m]	III aB[i]	III B
					≥ I	II b C	III C	III C		IIb B[i]	IIa C[h]	I C[m]	IIa B[i]	III B
4	Elective surgery	Stable	Intermediate (I–5%) or high risk (>5%)	Excellent or good			III C	III C	III C	IIb B[i]	IIa C[h]	I C[m]	IIa B[i]	III B
5	Elective surgery	Stable	Intermediate risk (1–5 %)	Poor	None	IIb C	III C[k]		III C[k]	IIb B[i]	IIa C[h]	I C[m]	IIa B[i]	III B
					≥ I	I C	III C[k]	IIb C		IIb B[i]	IIa C[h]	I C[m]	IIa B[i]	III B
6	Elective surgery	Stable	High risk (>5 %)	Poor	I–2	I C	IIb C[k]	IIb C	IIb B[L,K]	IIb B[V]	IIa C[h]	I C[m]	IIa B[i]	IIb B
					≥ 3	I C	IIb C[k]	I C	IIb B[K]	IIb B[V]	IIa C[h]	I C[m]	IIa B[i]	IIb B

ACE, angiotensin converting enzyme; BNP, brain natriuretic peptide; ECG, electrocardiogram; IHD, ischaemic heart disease; LV, left ventricular. Hatched areas: treatment options should be considered by a multidisciplinary Expert Team.

[a] Type of surgery (Table 30.30): risk of myocardial infarction and cardiac death within 30 days of surgery.

[b] Clinical risk factors presented in Table 30.30.

[c] In patients without signs and symptoms of cardiac disease or ECG abnormalities.

[d] Non-invasive testing, not only for revascularization, but also for patient counselling, change of peri-operative management in relation to type of surgery, and anaesthesia technique.

[e] Initiation of medical therapy, but in the case of emergency surgery, continuation of current medical therapy.

[f] Treatment should be initiated ideally less than 30 days and at least 2 days before surgery and should be continued post-operatively, aiming at a target heart rate of 60–70 beats per minute and systolic blood pressure 100 mmHg.

[g] Unstable cardiac conditions: unstable angina, significant arrhythmias, symptomatic valvular disease, and MI <30 days.

[h] In the presence of heart failure and systolic LV dysfunction (treatment should be initiated at least 1 week before surgery).

[i] In patients with known IHD or myocardial ischaemia.

[j] In patients undergoing vascular surgery.

[k] Evaluation of LV function with echocardiography and assessment of BNP are recommended before intermediate- or high-risk surgery in patients with established or suspected HF (I A).

[l] In the presence of American Society of Anesthesiologists class ≥3 or revised cardiac risk index ≥2.

[m] Aspirin should be continued after stent implantation (for 4 weeks after BMS and 3–12 months after DES implantation).

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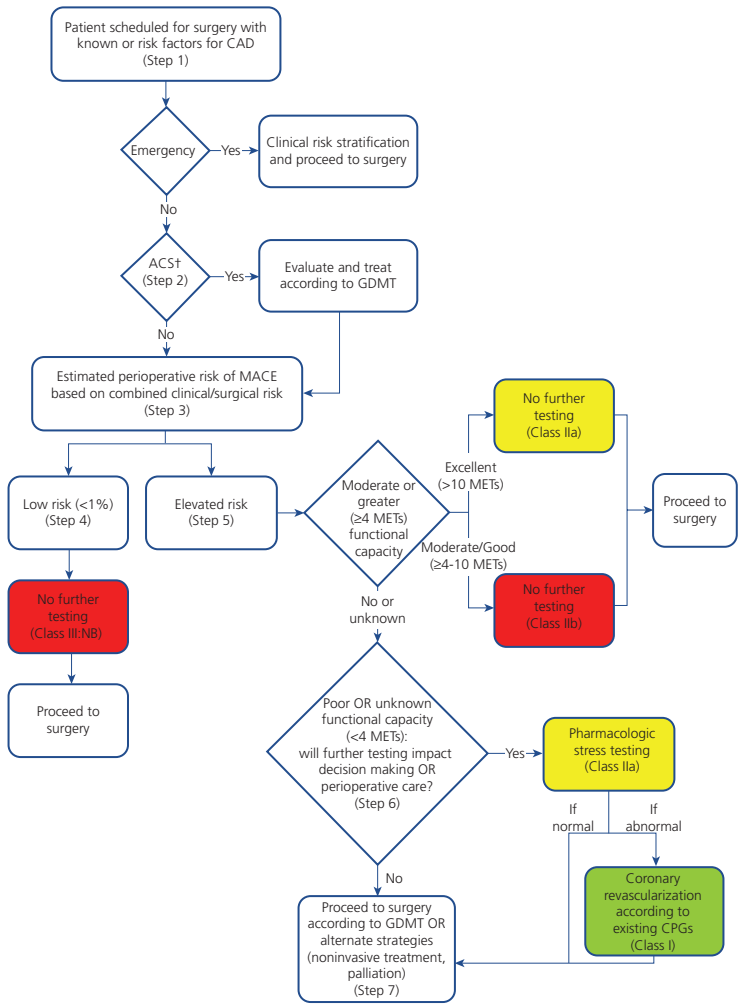

Figure 30.18 ACC/AHA 2014 perioperative guideline. Stepwise approach to perioperative cardiac assessment for CAD.

Step 1: In patients scheduled for surgery with risk factors for, or known, CAD, determine the urgency of surgery. If an emergency, then determine the clinical risk factors that may influence perioperative management and proceed to surgery with appropriate monitoring and management strategies based on the clinical assessment.

Step 2: If the surgery is urgent or elective, determine if the patient has an ACS. If yes, then refer patient for cardiology evaluation and management according to GDMT, according to the UA/NSTEMI and STEMI CPGs.

Step 3: If the patient has risk factors for stable CAD, then estimate the perioperative risk of MACE on the basis of the combined clinical/surgical risk. This estimate can use the American College of Surgeons NSQIP risk calculator (<http://www.surgicalriskcalculator.com>), or incorporate the RCRI with an estimation of surgical risk. For example, a patient undergoing very low-risk surgery (e.g. ophthalmologic surgery), even with multiple risk factors, would have a low risk of MACE, whereas a patient undergoing major vascular surgery with few risk factors would have an elevated risk of MACE.

Step 4: If the patient has a low risk of MACE (< 1%), then no further testing is needed, and the patient may proceed to surgery.

Step 5: If the patient is at elevated risk of MACE, then determine functional capacity with an objective measure or scale such as the DASI. If the patient has moderate, good, or excellent functional capacity (≥ 4 METs), then proceed to surgery without further evaluation.

Step 6: If the patient has poor (< 4 METs) or unknown functional capacity, then the clinician should consult with the patient and perioperative team to determine whether further testing will impact patient decision-making (e.g. decision to perform original surgery or willingness to undergo CABG or PCI, depending on the results of the test), or perioperative care. If yes, then pharmacological stress testing is appropriate. In those patients with unknown functional capacity, exercise stress testing may be reasonable to perform. If the stress test is abnormal, consider coronary angiography and revascularization depending on the extent of the abnormal test. The patient can then proceed to surgery with GDMT or consider alternative strategies, such as non-invasive treatment of the indication for surgery (e.g. radiation therapy for cancer) or palliation. If the test is normal, proceed to surgery according to GDMT.

Step 7: If testing will not impact decision-making or care, then proceed to surgery according to GDMT or consider alternative strategies, such as non-invasive treatment of the indication for surgery (e.g. radiation therapy for cancer) or palliation.

ACS indicates acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; CPG, clinical practice guideline; DASI, Duke Activity Status Index; GDMT, guideline-directed medical therapy; HF, heart failure; MACE, major adverse cardiac event; MET, metabolic equivalent; NB, No Benefit; NSQIP, National Surgical Quality Improvement Program; PCI, percutaneous coronary intervention; RCRI, Revised Cardiac Risk Index; STEMI, ST-elevation myocardial infarction; UA/NSTEMI, unstable angina/non-ST-elevation myocardial infarction; VHD, valvular heart disease.

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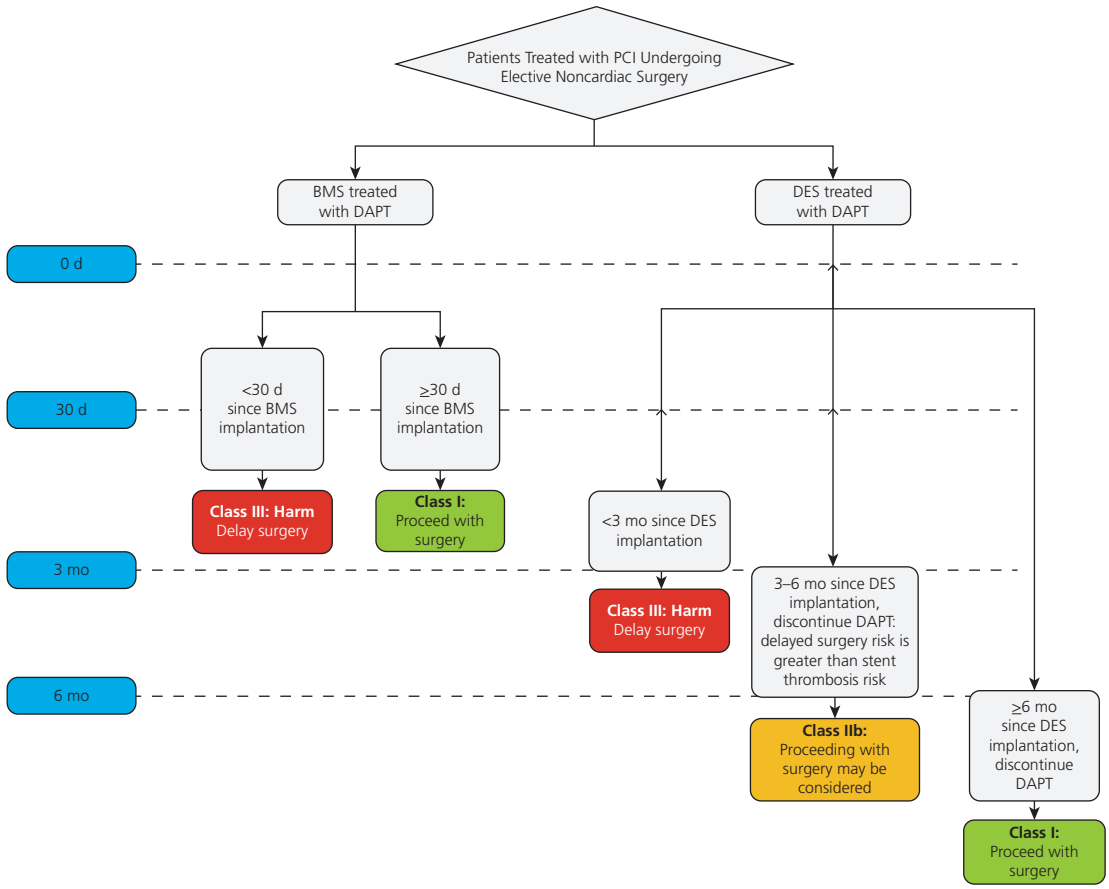

Figure 30.19 ACC/AHA 2016 update on duration of DAPT treatment algorithm for the timing of elective noncardiac surgery in patients with coronary stents.

BMS indicates bare metal stent; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; and PCI, percutaneous coronary intervention.
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Part V

Heart failure

Relevant guidelines

ACCF/AHA 2013 Guideline on heart failure

ACCF/AHA 2013 Guideline for the management of heart failure. *J Am Coll Cardiol.* 2013;**62**:e147–239.

ESC 2012 Guidelines on heart failure

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur Heart J.* 2012;**33**:1787–847.

ACCF/AHA/HRS 2012 Guidelines for device-based therapy of cardiac rhythm abnormalities

2012 ACCF/AHA/HRS Focused update incorporated into the ACCF/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol.* 2013;**61**:e6–75.

ESC 2013 Guidelines on pacing and cardiac resynchronization

2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J.* 2013;**34**:2281–329.

ESC 2015 Guidelines on ventricular arrhythmias and prevention of sudden cardiac death

ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J.* 2015;**36**:2793–2867.

ESC Heart Failure Association/European Society of Emergency Medicine/Society of Academic Emergency Medicine 2015 consensus paper

Recommendations on pre-hospital and early hospital management of acute heart failure. *Eur Heart J.* 2015;**36**:1958–66.

2015 SCAI/ACC/HFSA/STS Statement on the use of percutaneous mechanical circulatory support devices

2015 SCAI/ACC/HFSA/STS Clinical expert consensus statement of the use of percutaneous mechanical circulatory support devices in cardiovascular care. *J Am Coll Cardiol.* 2015;**65**:e7–e26.

ESC 2014 Guidelines on revascularization

2014 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J.* 2014;**35**:2541–619.

ESC/ESA 2014 Guidelines on noncardiac surgery

2014 ESC/ESA Guidelines on noncardiac surgery: cardiovascular assessment and management. *Eur Heart J.* 2014;**67**:980–5.

AHA/ESC 2013 Document on sexual counselling

Sexual counselling for individuals with cardiovascular disease and their partners: a consensus document from the American Heart Association and the ESC Council on Cardiovascular Nursing and Allied Professions (CCNAP). *Eur Heart J.* 2013;**34**:3217–35.

ESC 2011 Guidelines on pregnancy

ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J.* 2011;**32**:3147–97.

Chapter 31

Classification, epidemiology, and pathophysiology of heart failure

Definitions and classification

Heart failure is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. There is a consequent failure to deliver oxygen according to metabolic requirements, despite normal filling pressures (or only at the expense of increased filling pressures).[1,2] Patients have the following features:

- **Typical symptoms** (breathlessness at rest or on exercise, fatigue, tiredness, ankle oedema), and
- **Typical signs** (tachycardia, tachypnoea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral oedema, hepatomegaly, and
- **Objective evidence of a structural or functional abnormality of the heart at rest** (cardiomegaly, third heart sound, cardiac murmurs, abnormality on the echocardiogram, such as reduced LVEF or valve disease or other structural disorder, raised natriuretic peptide concentration).

Heart failure with reduced ejection fraction (<40%) (HFrEF)

Also referred to as **systolic HF**. Randomized clinical trials have mainly enrolled patients with HF*r*EF, and it is only in these patients that efficacious therapies have been demonstrated to date.[1]

Heart failure with preserved ejection fraction (>40%) (HFpEF)

Also referred to as **diastolic HF** (Figure 31.1). To date, efficacious therapies have not been identified. The ACC/AHA[1] have further subdivided this category into:

- **HFpEF, borderline 41–49%**. Borderline or intermediate group with characteristics, treatment patterns, and outcomes similar to those of patients with HF*p*EF.
- **HFpEF, improved >40%**. A subset of patients with HF*p*EF who previously had HF*r*EF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF.

Heart failure with recovered ejection fraction (HF-recovered) refers to recovery of LV function accomplished by optimal medical therapy, devices, or revascularization.[3] These patients have a better event-free survival than HFpEF, but abnormalities in biomarkers and hospitalizations still occur.

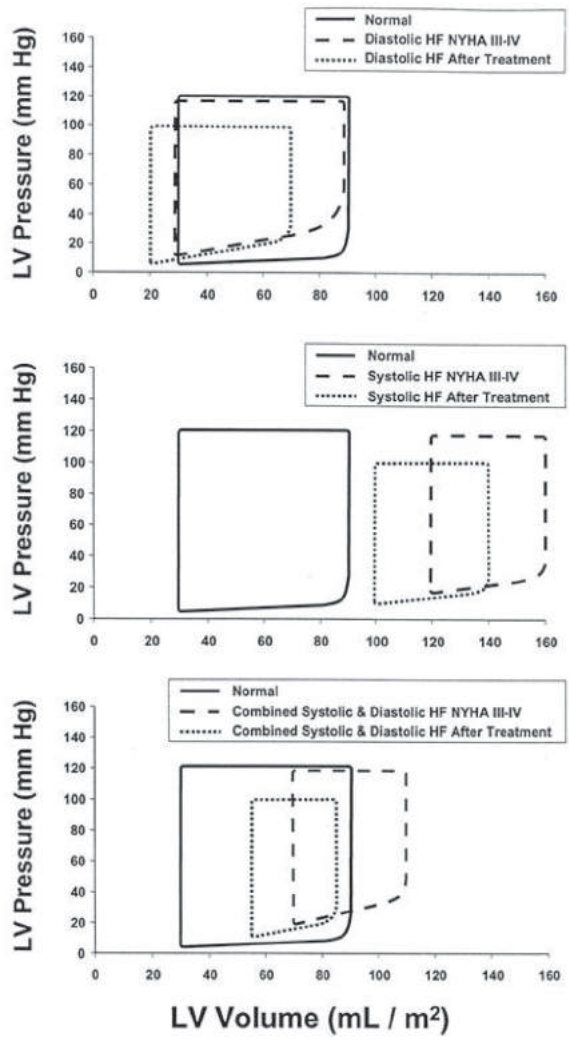

Figure 31.1 Pressure–volume loops contrasting isolated diastolic heart failure (A) with systolic heart failure (B) and combined systolic and diastolic heart failure (C).

Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. *Circulation*. 2002;**105**:1387–93 with permission from Wolters Kluwer.

Left heart failure refers to predominant congestion of the pulmonary veins with fluid retention and pulmonary oedema. **Right heart failure** refers to predominant congestion of the systemic veins with fluid retention and peripheral oedema.[4] These conditions may coexist, and the most common cause of right ventricular failure is raised pulmonary artery pressure due to left ventricular failure.

High-output heart failure refers to the syndrome caused by circulatory high-output conditions, such as anaemia, thyrotoxicosis, septicaemia, arteriovenous shunts, liver failure, Paget's disease, and beriberi.

Preload refers to left and/or right atrial pressures (volume overload) and **afterload** to the work of the myocardium (pressure overload or high impedance).

Epidemiology

The prevalence of heart failure is 1–2% of the adult population in developed countries, and increasing from 0.7% in persons aged 45–54 years to 8.4% for those aged 75 years or older.[5] Heart failure is a global problem with an estimated prevalence of 38 million patients worldwide, a number that is increasing with the ageing of the population. It is the most common diagnosis in patients aged 65 years or older admitted to hospital and in high-income nations.[6] The lifetime risk of developing heart failure is estimated to be 20% for all persons older than 40 years.[7] In the USA, approximately 5.1 million have heart failure that leads to 58 000 deaths per year.[8] With an ageing population, there is a shift towards heart failure with preserved LVEF that predominates in patients over 70 years old. Although there is a trend for reduction of hospitalization for HF both in Europe and the US,[9] it is still the most common cause of hospitalization after normal delivery.[10] The incidence of heart failure has not declined in the past 20 years, and, despite recent advances in its management, the 5-year mortality after hospitalization exceeds 40%.[2]

Aetiology

Hypertension and **coronary artery disease** are the most common causes of heart failure in industrialized countries, whereas, in underdeveloped countries, other causes, such as infectious diseases, are dominant.[11–13] Extensive myocardial necrosis can result in pump failure. Small infarctions may also cause regional contractile dysfunction and adverse remodelling with myocyte hypertrophy, apoptosis, and deposition of extracellular matrix. Long-standing untreated hypertension is associated with both systolic and diastolic heart failure, and 75% of patients presenting with heart failure have hypertension.[12] Even modest decreases in systolic blood pressure reduce mortality and the risk for heart failure.[14] **Valvular heart disease**, **cardiomyopathies**, and **congenital heart disease** are also important causes. Patients with **diabetes mellitus** have a 4-times higher risk for heart failure and higher mortality, compared to non-diabetics.[15] An association of **thiazolidinediones** with heart failure is well established,[16] and the DPP-4 inhibitors **alogliptin** and **saxagliptin** may also increase the rate of hospitalization for heart failure, although this is not confirmed in all studies.[17,18] **Alcohol** is a direct myocardial toxin and a reversible cause of heart failure.[19,20] **Tobacco** and **cocaine** increase the risk for CAD, which can lead to heart failure. Long-term use of **cocaine** results in activation of the sympathetic nervous system, causing left ventricular dysfunction both directly and through the promotion of coronary thrombosis, coronary spasm, and atherosclerosis.[19] Chemotherapeutic agents, such as **anthracyclines (doxorubicin, daunorubicin)** and **trastuzumab**, may also increase the risk of heart failure.[21–24] Anthracyclines impair left ventricular function due to the generation of reactive oxygen species, disruption of mitochondria, and uncoupling of the electron transport chain. Anthracycline cardiotoxicity is dose-dependent, with intermittent high doses and higher cumulative doses increasing the risk of cardiomyopathy and lethal arrhythmias. Antiangiogenic and **anti-vascular endothelial growth factor (VEGF)** chemotherapy agents (such as bevacizumab and sunitinib) may also cause secondary hypertension and LV failure.[22,25] Both **hyperthyroidism** and **hypothyroidism** can be reversible causes of heart failure.[26] Renal and liver failure may result in heart failure. The term **cardiorenal syndrome** now applies to the bidirectional nature of how disease in one organ system affects the function of the other.[27] The term **cirrhotic cardiomyopathy** refers to systolic and diastolic dysfunction with chronotropic incompetence and prolonged QT interval due to liver cirrhosis.[28] **Increased resting heart rate** is associated with cardiovascular morbidity and mortality in the general population and in patients with cardiovascular disease.[29] Changes over time also have predictive value, especially in patients in sinus rhythm.[30] **Persistent tachycardias**, both supraventricular and ventricular, are established causes of heart failure (tachycardiopathies—see Chapter 41), and atrial fibrillation is independently associated with an adverse outcome in patients hospitalized for heart failure.[31] **Pulmonary arterial hypertension** may lead to RV failure. **Male sex, less education, physical inactivity**, and **overweight** have also been identified as independent risk factors for CHF.[11] **Long-chain monosaturated fatty acids** (LCMUFAs), such as erucic acid that is a component of rapeseed oil (also found in low quantities in Canola oil), are cardiotoxic and have been associated with heart failure.[32] LCMUFAs are present in mustard oils and related products, some fish species, and processed meat, and poultry products. Obstructive **sleep apnoea** is associated with hypertension and a higher incidence of heart disease.[33] **Central sleep apnoea** is almost

uniquely associated with heart failure and represents an independent risk factor for reduced survival.[34] Patients with **metabolic syndrome** (abdominal adiposity, hypertriglyceridaemia, low HDL, hypertension, and fasting hyperglycaemia) are at higher risk of cardiovascular disease and heart failure. **HIV infection** is also an important cause of left or biventricular dysfunction. HIV-induced heart failure is mainly a systolic dysfunction, but diastolic dysfunction may also appear.[35]

Pathophysiology

The previously normal heart is subject to either an acute (e.g. myocardial infarction) or a chronic insult (e.g. hypertension) that results in altered loading conditions. These activate compensatory mechanisms, such as increased ventricular preload, or the Frank–Starling mechanism, by ventricular dilatation and volume expansion, peripheral vasoconstriction, renal sodium and water retention to enhance ventricular preload, and initiation of the adrenergic nervous system which raises heart rate and contractile function. Thus, increases in sympathetic outflow directed at the heart, kidneys, and skeletal muscle are the characteristics of heart failure with reduced LVEF.[36] Mechanisms responsible for sympathetic activation are not fully elucidated. The afferent autonomic disturbance considered principally responsible for eliciting increased efferent sympathetic discharge is the loss of its inhibition by cardiopulmonary reflexes arising from stretch-sensitive mechanoreceptors sited in ventricles, atria, and the pulmonary veins. In addition, a paradoxical muscle sympathetic reflex activation in response to increased atrial pressure is a recently described neurogenic disturbance common to heart failure with both reduced and preserved LVEF.[37] These processes are controlled mainly by activation of various neurohormonal vasoconstrictor systems, including RAAS, the adrenergic nervous system, and non-osmotic release of arginine-vasopressin. Initially, these mechanisms are beneficial and adaptive, sustaining heart rate, blood pressure, and cardiac output, and thus maintaining organ perfusion. In the long term, they result in disruptions of β-adrenergic signalling and impaired mobilization of intracellular calcium, with consequent myocyte hypertrophy to preserve wall stress as the heart dilates, apoptosis, fibroblast proliferation, and interstitial collagen accumulation. Changes in size, shape, and pump function of the heart define cardiac remodelling, a determinant of the clinical course of heart failure.[38] The consequences of these structural changes are a reduction in stroke volume, an increase in systemic vascular resistance, and the development of signs and symptoms of congestion and tissue hypoperfusion. Eventually, in untreated cases, cardiac cachexia develops due to activation of proinflammatory cytokines, such as tumour necrosis factor alpha and interleukin 2, with consequent cardiac cell death.[10] Misfolded proteins that are central in the pathophysiology of neurodegenerative disorders such as Parkinson's and Alzheimer disease, have also been found to play a role in pathologic cardiac hypertrophy and dilated and ischaemic cardiomyopathies, thus leading to the suggestion that proteotoxicity is a key contributor to the progression of heart failure.[39] Apart from causing further myocardial injury, activation of neurohormonal vasoconstrictor systems has detrimental effects on other organs such as the kidneys, liver, muscles, intestines, and lungs, and create a 'vicious cycle', that accounts for many of the clinical features of heart failure, including cardiac electrical instability. Heart failure may cause renal failure (cardiorenal syndrome) and the opposite may occur (renocardiac syndrome).[27] Abnormal liver function tests (increased γGT, bilirubin, and alkaline phosphatase) are frequently seen in patients with chronic and, especially, acute heart failure, and are associated with adverse prognosis. Transaminases are moderately increased or even remain normal.[28]

Both systolic and diastolic heart failure may occur, and a decrease in LVEF to <55%, as well as any worsening of diastolic LV function are independently associated with increased mortality.[40] In addition to being a marker of increased risk due to its association with hypertension, diabetes mellitus, ischaemia, and reduced systolic function, diastolic dysfunction may also be a direct contributor to adverse outcomes by limiting cardiac output reserve, accelerating neuroendocrine activation, and promoting physical inactivity. RV hypertrophy predicts an increased risk of heart failure which is usually attributable to LV dysfunction.[41] Lower pulse pressure (especially <53 mmHg) is an independent predictor of mortality in patients with reduced LVEF (<30%) but not necessarily in those with preserved LVEF.[42]

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Chapter 32

Chronic heart failure

Presentation

Presenting symptoms of heart failure, such as **dyspnoea, exercise intolerance**, and **fatigue**, are non-specific and may be mimicked by many other conditions, especially in the elderly. Several classification schemes (the most popular being by the New York Heart Association (NYHA), Canadian Cardiovascular Society (CCS), and Killip) have been presented for a semi-quantitative assessment of symptom severity (Table 32.1).

Orthopnoea, dyspnoea that occurs in the recumbent position, is a later manifestation. It may also be seen in patients with COPD and abdominal obesity or ascites. **Paroxysmal nocturnal dyspnoea** refers to acute episodes of dyspnoea and coughing that occur at night and awaken the patient. It is relatively specific for heart failure, especially in young patients (<60 years) who also present with increased **JVP pressure and hepatomegaly** rather than dyspnoea or peripheral oedema and rales.[1] **Pulmonary oedema** may develop in acute exacerbations of heart failure. Minor episodes of haemoptysis may represent transient, exercise-induced pulmonary oedema. **Cardiac asthma** refers to wheezing due to bronchospasm or increased pressure in the bronchial arteries. **Cheyne–Stokes respiration** is periodic respiration with apnoeic phases during which the arterial PO_2 decreases and the PCO_2 rises. It is due to diminished sensitivity of the respiratory centre to arterial PCO_2 and occurs with advanced failure. Syncope in patients with LVEF <35% (40% arrhythmic) is associated with increased mortality.[2] **Altered mental status** may reflect hypoperfusion. **Anorexia** or **nausea** and **right upper quadrant pain** and **ascites** reflect bowel and liver congestion. **Cardiac cachexia** may be seen with advanced failure. A careful history is mandatory.

Table 32.1 Classifications of heart failure

NYHA functional classification	
Class I Patients with cardiac disease but no resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea, or anginal pain.	
Class II Patients with cardiac disease resulting in slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnoea, or anginal pain. ***By limiting activity, patients still able to lead a normal social life***.	
Class III Patients with cardiac disease resulting in marked limitation of physical activity. Comfortable at rest, but less-than-ordinary physical activity results in fatigue, palpitation, dyspnoea, or anginal pain. ***Patients unable to do any housework***.	
Class IV Patients with cardiac disease resulting in inability to carry out any physical activity without symptoms. Dyspnoea or angina may be present, even at rest. Comfortable at rest, but less-than-ordinary physical activity results in fatigue, palpitation, dyspnoea, or anginal pain. ***Patients incapacitated and virtually confined to bed or a chair***.	
ACC/AHA stages of heart failure	
Stage A At high risk for developing heart failure. No identified structural or functional abnormality; no signs or symptoms.	
Stage B Developed structural heart disease that is strongly associated with the development of heart failure but without signs or symptoms.	
Stage C Symptomatic heart failure associated with underlying structural heart disease.	
Stage D Advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy.	
Killip classification of the severity of heart failure in the context of myocardial infarction	
Stage I	No heart failure. No clinical signs of cardiac decompensation.
Stage II	Heart failure. Diagnostic criteria include rales, S_3 gallop, and pulmonary venous hypertension. Pulmonary congestion with wet rales in the lower half of the lung fields.
Stage III	Severe heart failure. Frank pulmonary oedema with rales throughout the lung fields.
Stage IV	Cardiogenic shock. Signs include hypotension (SBP <90 mmHg) and evidence of peripheral vasoconstriction, such as oliguria, cyanosis, and sweating.

Physical examination

Physical signs are also non-specific:

- Sinus tachycardia or AF in 30% of patients with advanced disease
- Raised jugular venous pressure
- Third heart sound (S_3)
- Basal pulmonary rales
- Peripheral oedema with ankle swelling and hepatomegaly.

Pulmonary rales may be absent despite elevated left-sided filling pressures due to chronic lymphatic hypertrophy, which prevents alveolar oedema despite elevated interstitial pressures.[3] **Pulmonary oedema** may, rarely, be unilateral, involving the right upper lobe (contralateral to the heart) probably due to decreased flow in the left pulmonary artery following compression by the left-sided cardiac enlargement, a severe mitral regurgitation jet that predominantly affects the upper right pulmonary vein, and poorer lymphatic drainage of the right lung. **Ankle oedema** may be caused by heart or renal failure and pericardial constriction (particularly with elevated JVP), chronic venous insufficiency, calcium channel blockers, IVC obstruction, prolonged air travel, idiopathic, liver congestion and hypoalbuminaemia, secondary hyperaldosteronism. Anasarca is rare in cardiac failure, unless untreated, and there is concomitant hypoalbuminaemia. **Unilateral ankle oedema** may be due to venous thrombosis, lymphatic obstruction, and saphenous vein harvesting for CABG. Young patients may be not oedematous despite intravascular volume overload. In obese patients and elderly patients, oedema may reflect peripheral rather than cardiac causes.

The Framingham criteria emphasized the importance of jugular venous pressure elevation, S_3 gallop, and positive hepatojugular reflex in establishing a diagnosis, while minimizing the importance of lower extremity oedema. The **jugular venous pressure** is measured as the vertical distance between the venous pulsation and the sternal angle of Louis (where the manubrium meets the sternum), with the patient semi-recumbent at an angle of about 45°. A distance >3 cm (cm of blood or water) is considered abnormal (1.36 cmH_2O = 1 mmHg). Alternatively, the ability to see venous pulsations above the clavicle in the seated position denotes raised JVP since the clavicle is at least 10 cm above the right atrium.

a wave: atrial contraction, coincident with the P wave of the ECG. Large a wave indicates increased right ventricular end-diastolic pressure (RVEDP) as in pulmonary hypertension and pulmonary valve stenosis, or tricuspid stenosis. Cannon a waves are seen in AV dissociation. Absent in AF.
c wave: not visible (TV closure).
x descent: atrial diastolic suction due to ventricular contraction that pools the tricuspid valve and right atrium floor downward.
v wave: atrial filling. Smaller than the a wave. Accentuated in tricuspid regurgitation (merges with a wave to produce the s wave).
y descent: reflects fall in right atrial pressure after tricuspid valve opening. Blunted in tricuspid stenosis or tamponade, steep in early diastolic filling as in pericardial constriction (pericardial knock).

The normal JVP should fall by at least 3 mmHg with inspiration. A rise or failure to decrease with inspiration is a sign of constrictive pericarditis (**Kussmaul sign**), but it can also be seen in restrictive cardiomyopathy, massive pulmonary embolus, and RV failure. The **abdomino-jugular reflex** refers to sustained rise of >3 cm of JVP for at least 15 s after release of consistent pressure over the upper abdomen for at least 10 s.

Physical examination (Table 32.2) is not helpful in discriminating between systolic and diastolic heart failure.

Table 32.2 ACCF/AHA 2013 GL on HF. History and physical examination in HF

History	
Potential clues suggesting aetiology of HF	A careful family history may identify an underlying familial cardiomyopathy in patients with idiopathic DCM. Other aetiologies should be considered as well.
Duration of illness	A patient with recent-onset systolic HF may recover over time.
Severity and triggers of dyspnoea and fatigue, presence of chest pain, exercise capacity, physical activity, sexual activity	To determine NYHA class; identify potential symptoms of coronary ischaemia.
Anorexia and early satiety, weight loss	Gastrointestinal symptoms are common in patients with HF. Cardiac cachexia is associated with adverse prognosis
Weight gain	Rapid weight gain suggests volume overload.
Palpitations, (pre)syncope, ICD shocks	Palpitations may be indications of paroxysmal AF or ventricular tachycardia. ICD shocks are associated with adverse prognosis.
Symptoms suggesting transient ischaemic attack or thromboembolism	Affects consideration of the need for anticoagulation.

(*continued*)

Table 32.2 Continued

History	
Development of peripheral oedema or ascites	Suggests volume overload.
Disordered breathing at night, sleep problems	Treatment for sleep apnoea may improve cardiac function and decrease pulmonary hypertension
Recent or frequent prior hospitalizations for HF	Associated with adverse prognosis
History of discontinuation of medications for HF	Determine whether lack of GDMT in patients with HFrEF for HF reflects intolerance, an adverse event, or perceived contraindication to use. Withdrawal of these medications has been associated with adverse prognosis
Medications that may exacerbate HF	Removal of such medications may represent a therapeutic opportunity.
Diet	Awareness and restriction of sodium and fluid intake should be assessed.
Adherence to medical regimen	Access to medications; family support; access to follow-up; cultural sensitivity
Physical examination	
BMI and evidence of weight loss	Obesity may be a contributing cause of HF; cachexia may correspond with poor prognosis.
Blood pressure (supine and upright)	Assess for hypertension or hypotension. Width of pulse pressure may reflect adequacy of cardiac output. Response of blood pressure to Valsalva manoeuvre may reflect LV filling pressures.
Pulse	Manual palpation will reveal strength and regularity of pulse rate.
Examination for orthostatic changes in blood pressure and heart rate	Consistent with volume depletion or excess vasodilation from medications
Jugular venous pressure at rest and following abdominal compression	Most useful finding on physical examination to identify congestion
Presence of extra heart sounds and murmurs	S3 is associated with adverse prognosis in HF*r*EF. Murmurs may be suggestive of valvular heart disease.
Size and location of point of maximal impulse	Enlarged and displaced point of maximal impulse suggests ventricular enlargement.
Presence of right ventricular heave	Suggests significant right ventricular dysfunction and/or pulmonary hypertension.
Pulmonary status: respiratory rate, rales, pleural effusion	In advanced chronic HF, rales are often absent despite major pulmonary congestion.
Hepatomegaly and/or ascites	Usually markers of volume overload.
Peripheral oedema	Many patients, particularly those who are young, may not be oedematous despite intravascular volume overload. In obese patients and elderly patients, oedema may reflect peripheral rather than cardiac causes.
Temperature of lower extremities	Cool lower extremities may reflect inadequate cardiac output.

AF indicates atrial fibrillation; BMI, body mass index; DCM, dilated cardiomyopathy; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; LV, left ventricular; and NYHA, New York Heart Association.
ACCF/AHA 2013 Guideline for the management of heart failure. *J Am Coll Cardiol*. 2013;**62**:e147–e239, with permission from Elsevier.

Investigations

Haematocrit and leukocyte count, blood urea nitrogen and creatinine, glucose and HbA_{1c} serum electrolytes, liver function tests, lipid profile, and thyroid function tests are taken routinely (Tables 32.3 to 32.6). Both renal and liver function may be affected by and cause heart failure.[4,5] Typically, elevated transaminases indicate ischaemic hepatitis due to diminished cardiac output, whereas the concomitant presence of cholestasis indicates passive hepatic congestion.

Natriuretic peptide (**BNP**) and its precursor N terminal **pro-BNP** are sensitive and specific indices for discriminating between causes of dyspnoea (Figure 32.1).[6] Low BNP (<100 pg/mL or NT-pro-BNP <400 pg/mL) has a very high negative predictive value, making it a useful rule-out test. This peptide is raised with advanced age, female sex, and renal insufficiency and lowered with obesity. A normal BNP in an untreated patient virtually excludes cardiac disease. High values (BNP >400 pg/mL or NT-pro-BNP >2000 pg/mL) suggest that heart failure is likely, whereas the diagnosis is uncertain with intermediate values. For patients presenting with acute onset or worsening of symptoms, the optimal exclusion cut-off point is 300 pg/mL for NT-pro-BNP and 100 pg/mL for BNP. For patients presenting in a non-acute way, the optimum exclusion cut-off point is 125 pg/mL for NT-pro-BNP and 35 pg/mL for BNP,[2] but the sensitivity and specificity of BNP and

NT-pro-BNP for the diagnosis of HF are lower in this setting. Natriuretic peptide-guided treatment of heart failure reduces hospitalization and mortality in patients aged <75 years.[7] **Cardiac troponins** are detected in most heart failure patients and their values have prognostic significance.[8] In ambulatory chronic heart failure patients, a score derived from **multiple biomarkers** such as high-sensitivity C-reactive protein, myeloperoxidase, B-type natriuretic peptide, soluble fms-like tyrosine kinase receptor-1, troponin I, soluble toll-like receptor-2, creatinine, and uric acid, may also improve prediction of adverse events.[9] Screening for *haemochromatosis, sleep-disturbed breathing, HIV, rheumatological diseases, amyloidosis, or phaeochromocytoma* is also undertaken when there is a clinical suspicion of these diseases.

ECG Left ventricular hypertrophy, atrial enlargement, previous myocardial infarction, active ischaemia, conduction abnormalities, and arrhythmias may be present. An entirely normal ECG makes the diagnosis of systolic dysfunction unlikely (<10%).

Chest radiography may reveal cardiomegaly and/or pulmonary congestion (Kerley B lines and interstitial oedema with upper lobe blood diversion). Pleural effusions may be present, with biventricular failure.

Echocardiography, especially three-dimensional echo,[10] may provide important information about ventricular dimensions, extent of systolic dysfunction, whether dysfunction is global or segmental, the status of valves, and estimates of pulmonary artery pressure (Table 32.4). It is most specific for diagnosis of LV systolic dysfunction. Doppler assessment allows estimation of CVP, atrial, and PV pressures.[11] Assessment of diastolic dysfunction still remains rather elusive, even with tissue Doppler imaging that provides information on patterns of diastolic relaxation and filling and ventricular dyssynchrony (Figure 32.2 and Table 32.7).

Holter monitoring may be considered in patients who are being investigated for ventricular arrhythmias.

MRI provides the most accurate estimate of ventricular structure and function (see Chapter 30 for restrictions regarding its overuse). The use of gadolinium contrast allows detection of inflammation and scarring. It cannot be used in the presence of implanted devices, although now this can be overcome with special techniques. MRI-assessed 4D flow is a novel method for assessment of diastolic dysfunction.[12]

Maximal exercise testing, ideally with respiratory gas exchange analysis is useful to differentiate between cardiac or pulmonary limitation to exercise and to determine functional class in patients who are candidates for cardiac transplantation or in whom the cause of exercise intolerance is unclear. Peak oxygen uptake (peak VO_2), anaerobic threshold, and VE/VCO_2 slope (ventilatory response to exercise) are useful indicators of the functional capacity of the patient with prognostic significance.

Selected ion-flow tube mass-spectrometry (SIFT-MS) of exhaled breath samples (collected within 24 h of hospital admission and following an 8-h fast and before the administration of morning pharmacotherapy) has been recently proposed as a simple test that allows detection of patients with impending decompensation and development of acute HF.[13]

Coronary angiography is indicated when the patient has angina or coronary artery disease is suspected (Table 32.4).

Cardiac catheterization may also be needed when echocardiography is insufficient to define the severity of valve disease and/or pulmonary pressures.

Myocardial ischaemia and viability studies are required in ischaemic patients in whom intervention is planned. Imaging modalities with comparable diagnostic accuracy are dobutamine echocardiography, nuclear imaging by SPECT and/or by PET, MRI with dobutamine and/or with contrast agents, CT with contrast agents (Table 32.4).

Cardiac biopsy on a routine basis is not recommended in CHF. It is only needed when a specific cause is considered, mainly giant cell myocarditis.

Table 32.3 ACCF/AHA 2013 GL on HF

Initial and serial evaluation of the heart failure patient	
Clinical evaluation	
History and physical examination	
Thorough history and physical examination to identify cardiac and non-cardiac disorders or behaviours that might cause or accelerate the development or progression of HF.	I-C
In patients with idiopathic dilated cardiomyopathy (DCM), a 3-generational family history should be obtained for familial DCM.	I-C
Volume status and vital signs should be assessed at each patient encounter. This include serial assessment of weight, jugular venous pressure and peripheral oedema or orthopnoea	I-B

(*continued*)

Table 32.3 Continued

Risk scoring		
Validated multivariable risk scores to estimate subsequent risk of mortality in ambulatory or hospitalized patients with HF.	IIa-B	
Diagnostic tests		
Complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, glucose, fasting lipid profile, liver function tests, and thyroid-stimulating hormone as initial laboratory evaluation.	I-C	
Serial monitoring should include serum electrolytes and renal function.	I-C	
A 12-lead ECG initially on all patients presenting with HF.	I-C	
Screening for haemochromatosis or HIV.	IIa-C	
Diagnostic tests for rheumatologic diseases, amyloidosis, or phaeochromocytoma in clinical suspicion of these diseases.	IIa-C	
Biomarker, application	**Setting**	
Natriuretic peptides		
Diagnosis or exclusion of HF	Ambulatory, Acute	I-A
Prognosis of HF	Ambulatory, Acute	I-A
Achieve GDMT	Ambulatory	IIa-B
Guidance for acute decompensated HF therapy	Acute	IIb-C
Biomarkers of myocardial injury		
Additive risk stratification	Acute, Ambulatory	I-A
Biomarkers of myocardial fibrosis		
Additive risk stratification	Ambulatory	IIb-B
	Acute	IIb-A

Selected causes of elevated natriuretic peptide concentrations

Cardiac	Non-cardiac
• Heart failure, including RV syndromes • Acute coronary syndrome • Heart muscle disease, including LVH • Valvular heart disease • Pericardial disease • Atrial fibrillation • Myocarditis • Cardiac surgery • Cardioversion	• Advancing age • Anaemia • Renal failure • Pulmonary: obstructive sleep apnoea, severe pneumonia, pulmonary hypertension • Critical illness • Bacterial sepsis • Severe burns • Toxic-metabolic insults, including cancer chemotherapy and envenomation

GDMT, guideline-directed medical therapy; HF, heart failure.
LVH: left ventricular hypertrophy; RV: right ventricular
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Table 32.4 ACCF/AHA 2013 GL on HF

Recommendations for non-invasive cardiac imaging	
Patients with suspected, acute, or new-onset HF should undergo a chest X-ray	I-C
A 2-D echocardiogram with Doppler for initial evaluation of HF	I-C
Repeat measurement of EF in patients with a significant change in clinical status or received treatment that might affect cardiac function or for consideration of device therapy	I-C
Non-invasive imaging to detect myocardial ischaemia and viability in HF and CAD	IIa-C
Viability assessment before revascularization in HF patients with CAD	IIa-B
Radionuclide ventriculography or MRI to assess LVEF and volume	IIa-C
MRI when assessing myocardial infiltration or scar	IIa-B
Routine repeat measurement of LV function assessment should not be performed	III-B (no benefit)
Recommendations for invasive evaluation	
Monitoring with a pulmonary artery catheter in patients with respiratory distress or impaired systemic perfusion when clinical assessment is inadequate	I-C
Invasive haemodynamic monitoring for carefully selected patients with acute HF with persistent symptoms and/or when haemodynamics are uncertain	IIa-C
When ischaemia may be contributing to HF, coronary arteriography	IIa-C
Endomyocardial biopsy in patients with HF when a specific diagnosis is suspected that would influence therapy	IIa-C
Routine use of invasive haemodynamic monitoring is not recommended in normotensive patients with acute HF	III-B (no benefit)
Endomyocardial biopsy should not be performed in the routine evaluation of HF	III-C (harm)

CAD indicates coronary artery disease; EF, ejection fraction; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; and MRI, magnetic resonance imaging.
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Table 32.5 ESC 2012 GL on HF

Recommendations for the diagnostic investigations in ambulatory patients suspected of having heart failure[a]	
Investigations to consider in all patients	
Transthoracic echocardiography to evaluate cardiac structure and function, including diastolic function, and to measure LVEF to make the diagnosis of HF, assist in planning and monitoring of treatment, and to obtain prognostic information.	I-C
A 12-lead ECG to determine heart rhythm, heart rate, QRS morphology, and QRS duration, and to detect other relevant abnormalities. This information also assists in planning treatment and is of prognostic importance. A completely normal ECG makes systolic HF unlikely.	I-C
Measurement of blood chemistry (including sodium, potassium, calcium, urea/blood urea nitrogen, creatinine/estimated glomerular filtration rate, liver enzymes and bilirubin, ferritin/TIBC) and thyroid function to: (i) Evaluate patient suitability for diuretic, renin-angiotensin-aldosterone antagonist, and anticoagulant therapy (and monitor treatment). (ii) Detect reversible/treatable causes of HF (e.g. hypocalcaemia, thyroid dysfunction) and co-morbidities (e.g. iron deficiency). (iii) Obtain prognostic information.	I-C
A complete blood count to: (i) Detect anaemia, which may be an alternative cause of the patient's symptoms and signs and may cause worsening of HF. (ii) Obtain prognostic information.	I-C
Measurement of natriuretic peptide (BNP, NT-pro-BNP, or MR-pro-ANP) should be considered to: (i) Exclude alternative causes of dyspnoea (if the level is below the exclusion cut-point, HF is very unlikely). (ii) Obtain prognostic information.	IIa-C
A chest radiograph (X-ray) to detect/exclude certain types of lung disease, e.g. cancer (does not exclude asthma/COPD). It may also identify pulmonary congestion/oedema and is more useful in patients with suspected HF in the acute setting.	IIa-C
Investigations to consider in selected patients	
CMR imaging to evaluate cardiac structure and function, to measure LVEF, and to characterize cardiac tissue, especially in subjects with inadequate echocardiographic images or where the echocardiographic findings are inconclusive or incomplete (but taking account of cautions/contraindications to CMR).	I-C

(*continued*)

Table 32.5 Continued

Coronary angiography in patients with angina pectoris, who are considered suitable for coronary revascularization, to evaluate the coronary anatomy.	I-C
Myocardial perfusion/ischaemia imaging (echocardiography, CMR, SPECT, or PET) in patients thought to have CAD and who are considered suitable for coronary revascularization to determine whether there is reversible myocardial ischaemia and viable myocardium.	IIa-C
Left and right heart catheterization in patients being evaluated for heart transplantation or mechanical circulatory support to evaluate right and left heart function and pulmonary arterial resistance.	I-C
Exercise testing: (i) To detect reversible myocardial ischaemia. (ii) As part of the evaluation of patients for heart transplantation and mechanical circulatory support. (iii) To aid in the prescription of exercise training. (iv) To obtain prognostic information.	IIa-C

BNP, B-type natriuretic peptide: CAD, coronary artery disease; CMR, cardiac magnetic resonance: COPD, chronic obstructive pulmonary disease: ECG, electrocardiogram; HF, heart failure; LV, left vertricular; LVEF, left ventricular ejection fraction: MR-pro-ANP, mid-regional pro-atrial natriuretic peptide; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; PET, positron emission tomography: SPECT, single photon emission computed tomography: TIBC, total iron-binding capacity.

[a] This list is not exclusive, and other investigations are discussed in the text. Additional investigations may be indicated in patients with suspected acute HF in the emergency department/hospital, including troponins and D-dimer measurement and right heart catheterization.

ESC 2012 Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2012;**33**:1787–1847, with permission of Oxford University Press.

Table 32.6 ESC 2012 GL on HF. Common laboratory test abnormalities in heart failure

Abnormality	Causes	Clinical implications
Renal/kidney impairment (creatinine >150 µmol/L/1.7 mg/dL, eGFR <60 mL/min/1.73 m^2)	Renal disease Renal congestion ACE inhibitor/ARB, MRA Dehydration NSAIDs and other nephrotoxic drugs	Calculate eGFR Consider reducing ACE inhibitor/ARB or MRA dose (or postpone dose up-titration) Check potassium and BUN Consider reducing diuretic dose if dehydrated, but, if renal congestion, more diuresis may help Review drug therapy
Anaemia (<13 g/dL or 8.0 mmol/L in men; <12 g/dL or 7.4 mmol/L in women)	Chronic HF, haemodilution, iron loss or poor utilization, renal failure, chronic disease, malignancy	Diagnostic work-up Consider treatment
Hyponatraemia (<135 mmol/L)	Chronic HF, haemodilution, AVP release, diuretics (especially thiazides) and other drugs	Consider water restriction, adjusting diuretic dosage Ultrafiltration, vasopressin antagonist Review drug therapy
Hypernatraemia (>150 mmol/L)	Water loss/inadequate water intake	Assess water intake Diagnostic work-up
Hypokalaemia (<3.5 mmol/L)	Diuretics, secondary hyperaldosteronism	Risk of arrhythmia Consider ACE inhibitor/ARB, MRA, potassium supplements
Hyperkalaemia (>5.5 mmol/L)	Renal failure, potassium supplement, renin-angiotensin-aldosterone system blockers	Stop potassium supplements/potassium-sparing diuretic Reduce dose of/stop ACE inhibitor/ARB, MRA Assess renal function and urine pH Risk of bradycardia and serious arrhythmias
Hyperglycaemia (>6.5 mmol/L/117 mg/dL)	Diabetes, insulin resistance	Evaluate hydration, treat glucose intolerance
Hyperuricaemia (>500 µmol/L/8.4 mg/dL)	Diuretic treatment, gout, malignancy	Allopurinol Reduce diuretic dose
Albumin high (>45 g/L)	Dehydration	Rehydrate
Albumin low (<30 g/L)	Poor nutrition, renal loss	Diagnostic work-up
Transaminase increase	Liver dysfunction Liver congestion Drug toxicity	Diagnostic work-up Liver congestion Review drug therapy

(*continued*)

Table 32.6 Continued

Abnormality	Causes	Clinical implications
Elevated troponins	Myocyte necrosis Prolonged ischaemia, severe HF, myocarditis, sepsis, renal failure	Evaluate pattern of increase (mild increases common in severe HF) Perfusion/viability studies Coronary angiography Evaluation for revascularization
Elevated creatine kinase	Inherited and acquired myopathies (including myositis)	Consider genetic cardiomyopathy (laminopathy, desminopathy, dystrophinopathy), muscular dystrophies Statin use
Abnormal thyroid tests	Hyper-/hypothyroidism Amiodarone	Treat thyroid abnormality Reconsider amiodarone use
Urine analysis	Proteinuria, glycosuria, bacteria	Diagnostic work-up Rule out infection, diabetes
International normalized ratio >3.5	Anticoagulant overdose Liver congestion/disease Drug interactions	Review anticoagulant dose Assess liver function Review drug therapy
CRP >10 mg/L, neutrophilic leukocytosis	Infection, inflammation	Diagnostic work-up

AV, atrioventricular; AVP, arginine vasopressin; MRA, mineralocorticoid receptor antagonist.
ESC 2012 Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2012;**33**:1787–1847, with permission of Oxford University Press.

Table 32.7 ESC 2012 GL on HF. Common echocardiographic measures of LV diastolic dysfunction

Measurement	Abnormality	Clinical implications
e′	Decreased (<8 cm/s septal, <10 cm/s lateral, or <9 cm/s average)	Delayed LV relaxation
E/e′ ratio[a]	High (>15)	High LV filling pressure
	Low (<8)	Normal LV filling pressure
	Intermediate (8–15)	Grey zone (additional parameters necessary)
Mitral inflow E/A ratio[b]	'Restrictive' (>2)	High LV filling pressure
		Volume overload
	'Impaired relaxation' (<1)	Delayed LV relaxation
		Normal LV filling pressure
	Normal (1–2)	Inconclusive (may be 'pseudonormal')
Mitral inflow during Valsalva manoeuvre	Change of the 'pseudonormal' to the 'impaired relaxation' pattern (with a decrease in E/A ratio ≥0.5)	High LV filling pressure (unmasked through Valsalva)
(A pulm–A mitral) duration	>30 ms	High LV filling pressure

A pulm–A mitral, time difference between pulmonary vein flow A-wave duration and mitral flow A-wave duration; E/A, ratio of early to late diastolic mitral inflow waves; e', early diastolic velocity of mitral annulus; E/e', ratio of the mitral inflow E wave to the tissue Doppler e' wave; HF, heart failure; LV, left ventricular.
a: Different cut-off points exist in different consensus documents; for the cut-off points mentioned in this table, both septal and average e' may be used.
b: Highly variable and unsuitable for diagnosis on its own; largely depending on its own; largely depending on loading conditions; age-corrected normal values exist.
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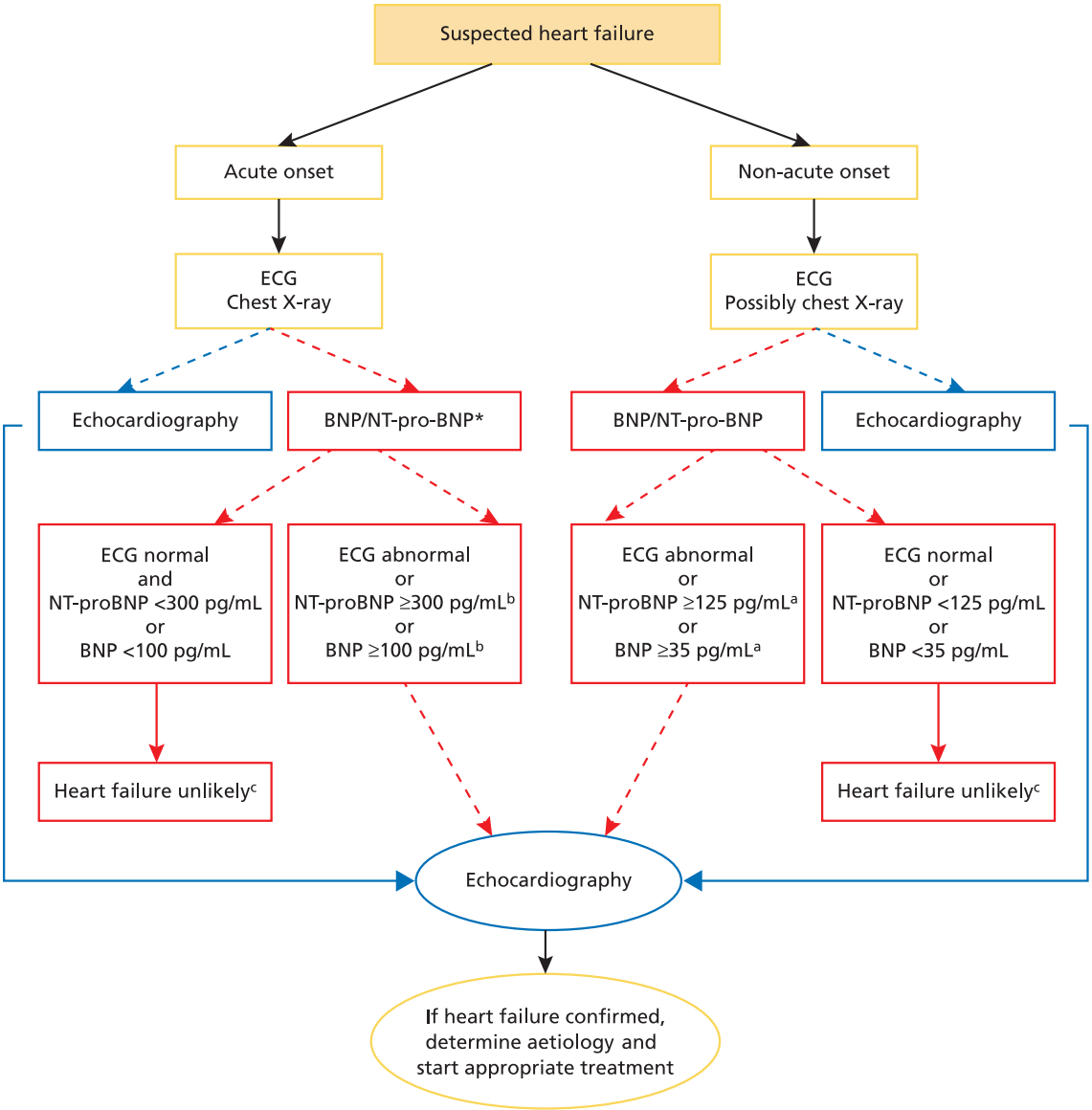

*In the acute setting, MR-proANP may also be used (cut-off point 120 pmol/L. i.e. <120 pmol/L = heart failure unlikely),
BNP = B-type natriuretic peptide; ECG = electrocardiogram; HF = heart failure; MR-proANP= mid-regional pro atrial natriuretic peptide;
NT-proBNP = N-terminal pro B-type natriuretic peptide.
[a] Exclusion cut-off points for natriuretic peptides are chosen to minimize the false-negative rate while reducing unnecessary referrals for echocardiography.
[b] Other causes of elevated natriuretic peptide levels in the acute setting are an acute coronary syndrome, atrial or ventricular arrhythmias, pulmonary embolism and severe chronic obstructive pulmonary disease with elevated right heart pressures, renal failure, and sepsis. Other causes of an elevated natriuetic level in the non-acute setting are: old age (>75 years), atrial arrhythmias, left ventricular hypertrophy, chronic obstrutive pulmonary disease, and chronic kindney disease.
[c] Treatment may reduce natriuretic peptide concentration, and natriuretic peptide concentrations may not be markedly elevated in patients with HF-pEF.

Figure 32.1 ESC 2012 GL on HF. Diagnostic flowchart for patients with suspected heart failure—showing alternative 'echocardiography first' (blue) or 'natriuretic peptide first' (red) approaches.

ESC 2012 Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2012;**33**:1787–1847, with permission of Oxford University Press.

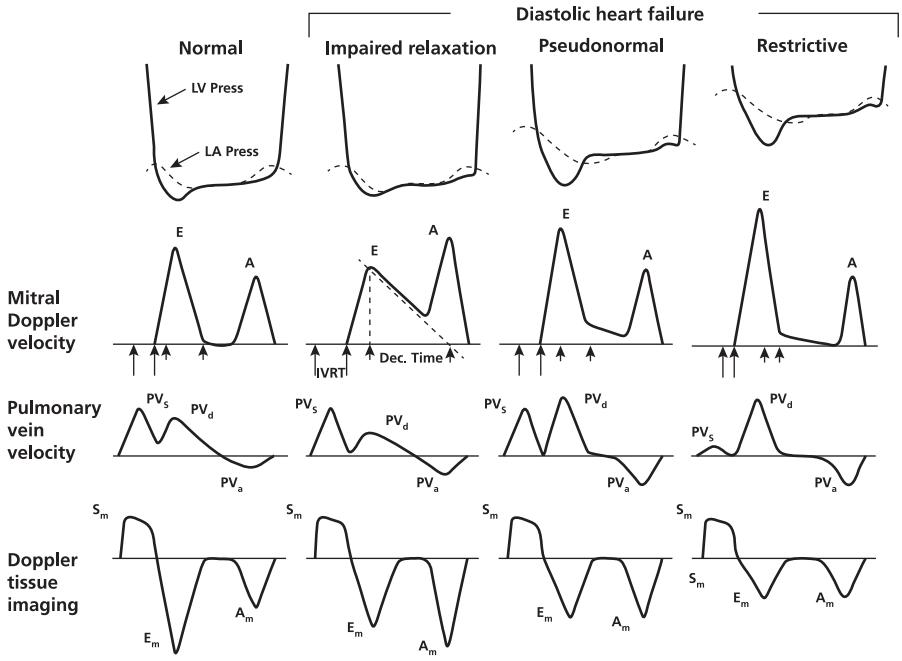

Figure 32.2 LV and left atrial (LA) pressures during diastole, transmitral Doppler LV inflow velocity, pulmonary vein Doppler velocity, and Doppler tissue velocity. IVRT indicates isovolumic relaxation time; Dec. Time, e-wave deceleration time; E, early LV filling velocity; A, velocity of LV filling contributed by atrial contraction; PVs, systolic pulmonary vein velocity; PVd, diastolic pulmonary vein velocity; PVa, pulmonary vein velocity resulting from atrial contraction; Sm, myocardial velocity during systole; Em, myocardial velocity during early filling; and Am, myocardial velocity during filling produced by atrial contraction.

Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. *Circulation*. 2002;**105**:1387–93 with permission from Wolters Kluwer.

Prognosis

Conditions associated with a poor prognosis in heart failure are age, aetiology, NYHA class, LVEF, key co-morbidities (renal dysfunction, diabetes, anaemia, hyperuricaemia), and plasma natriuretic peptide concentration. Poor response to loop diuretics is also associated with a worse prognosis.[14] Recovery of LV function (LVEF > 50%) denotes a better prognosis, but still these patients may experience symptomatology and hospitalizations.[15] Lower pulse pressure (<53 mmHg) is an independent predictor of mortality in patients with LVEF <30% and systolic BP <140 mmHg.[16]

Several risk scores for predicting survival in heart failure have been developed, one of the most useful being that of MAGGIC (www.heartfailure.org).[17]

Therapy

General measures

Patients with heart failure should be enrolled in a multidisciplinary care management programme to reduce the risk of heart failure hospitalization (ESC 2012 GL on HF, I-A).[18] Regular **aerobic exercise** is beneficial for patients with stable, non-decompensated heart failure (ESC 2012 on HF I-A) through various mechanisms.[19] **Salt restriction** is usually advisable, especially in patients with stages C and D, although more data are needed to support a specific sodium intake level.[20] **Fluid restriction** to 1.5–2 L/day may be considered only in patients with severe symptoms and hyponatraemia. **Weight loss** is initially advisable in patients with coronary artery

disease, but, in established heart failure, wasting is an independent risk factor.[21] **Alcohol** has a direct toxicity on myocardium and, at high doses, may cause hypertension and arrhythmias. It should be restricted to 2 units a day and avoided in alcohol-related dilated cardiomyopathy. **Smoking cessation, avoidance of high altitude** (>1500 m), and **vaccination against influenza and pneumococcus** are recommended. **Pregnancy** carries a high risk in patients with heart failure, and any decision should be discussed on an individual basis. **Contraception** with combined hormonal contraceptives is contraindicated due to fluid retention and increased thrombotic risk. Progesterone-only forms are probably safer but still carry a risk of thrombotic risk and osteopenia.[21] Copper intrauterine devices or transcervical tubal occlusion are relatively safer.[22] **Sexual activity** is prohibited only in decompensated or advanced heart failure until stabilization (AHA/ESC 2013 consensus document on sexual counselling, III-C).[23] Patients with **diabetes** should be treated appropriately for blood pressure, lipid and glycaemic control, but avoiding hypoglycaemia potentially associated with drug therapy, targeting a HbA1c <6.5.[24] Thiazolidinediones may increase the risk of heart failure and should not be used in heart failure. Pioglitazone is safer than rosiglitazone in this respect,[25,26] but concerns about association with bladder cancer have emerged (see Chapter 30). Metformin can be used as long as LV dysfunction is not severe and renal function adequate (creatinine <1.5 mg/dL in men and <1.4 mg/dL in women).[27] Recently, saxagliptin and alogliptin, selective inhibitors of dipeptidyl peptidase 4 (DPP-4), were shown not to increase the rates of major adverse cardiovascular events in patients at risk of or after an ACS, respectively, although the rate of hospitalization for heart failure was increased in some but not all trials.[28,29]

Non-steroidal anti-inflammatory drugs (including COX-2 inhibitors) as well as **corticosteroids** and **herbal preparations** (licorice, ginseng, ma huang) cause salt and water retention and should be used with much caution. In gout attacks, **colchicine** is preferred to NSAIDs in symptomatic heart failure patients. **Aspirin** and other indicated antiplatelet agents, when indicated, should be continued in ischaemic patients. Although there has been some evidence that aspirin may interfere with prostaglandin synthesis, leading to a reduced effectiveness of ACE inhibition, the clinical significance of this observation is probably negligible.[30,31] **Tricyclic antidepressants** are contraindicated due to proarrhythmic potential. The value of enhancement of **erythropoiesis** in anaemia is controversial. Erythropoiesis stimulation with darbepoetin alfa corrects haemoglobin deficiency in systolic heart failure but fails to improve mortality or hospitalization rates and may increase thromboembolic risk.[32] A report by the American College of Physicians recommends against the use of erythropoiesis-stimulating agents in patients with mild to moderate anaemia and congestive heart failure or coronary heart disease.[33] However, iron deficiency (ferritin <100 ng/mL or 100–300 ng/mL if transferrin saturation <20%) should be corrected with intravenous iron.[34] Intravenous **ferric carboxymaltose** improves functional capacity and quality of life in iron-deficient patients with heart failure.[34,35] Most cardiotoxicity after **anthracycline** therapy occurs within the first year and is associated with anthracycline dose and LVEF at the end of treatment. Early detection and prompt drug therapy are important for substantial recovery of cardiac function.[36] Chemotherapy-induced cardiomyopathy can also occur acutely soon after treatment, within a few months of treatment, or many years later, and may be prevented by carvedilol (a beta blocker with antioxidant properties) in combination with an ACE inhibitor.[37]

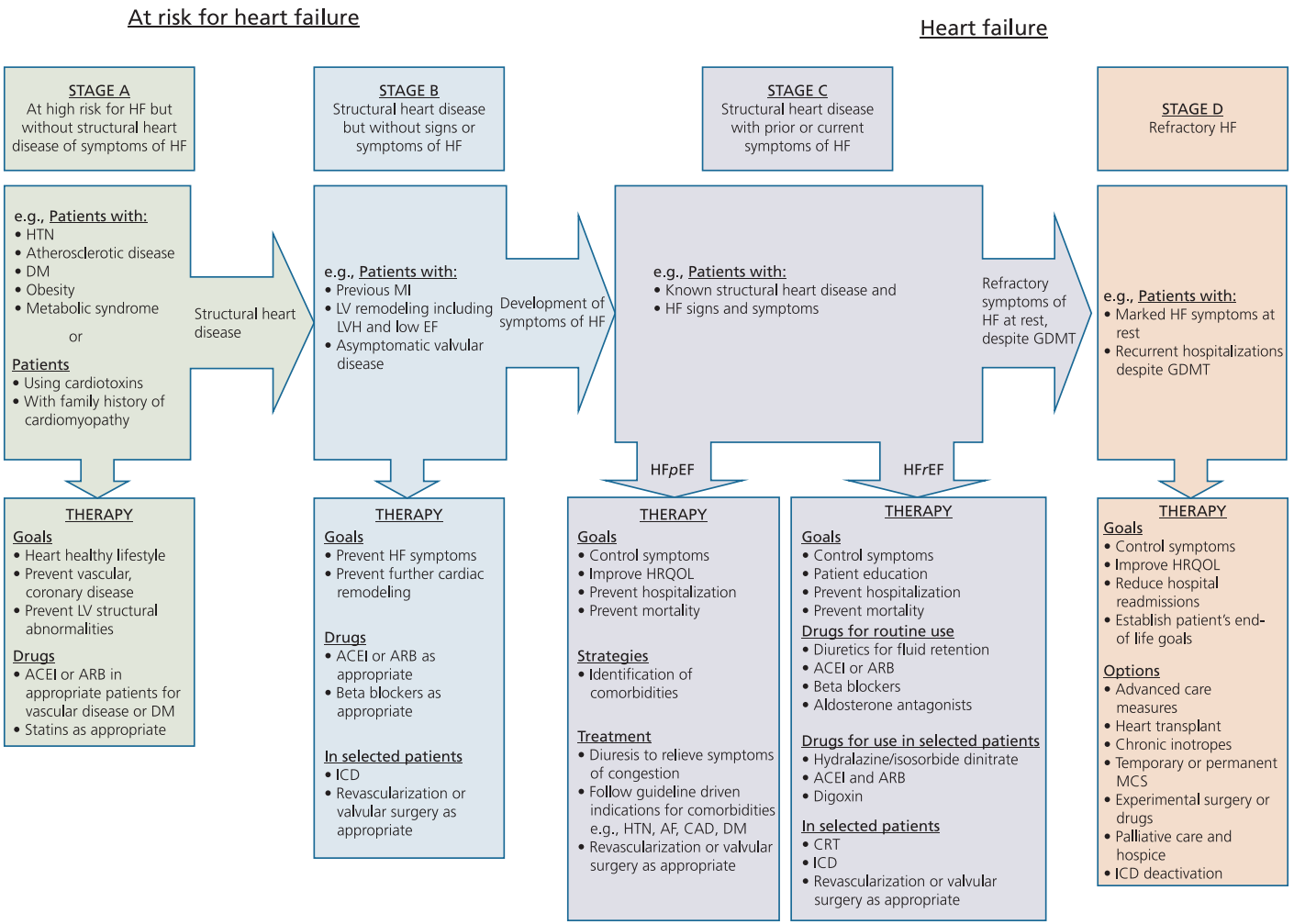

Figure 32.3 ACCF/AHA 2013 GL on HF. Stages in the development of HF and recommended therapy by stage.

ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin-receptor blocker; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; DM, diabetes mellitus; EF, ejection fraction; GDMT, guideline-directed medical therapy; HF, heart failure; HF**p** EF, heart failure with preserved ejection fraction; HF**r** EF, heart failure with reduced ejection fraction; HRQOL, health-related quality of life; HTN, hypertension; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVH, left ventricular hypertrophy; MCS, mechanical circulatory support; and MI, myocardial infarction.

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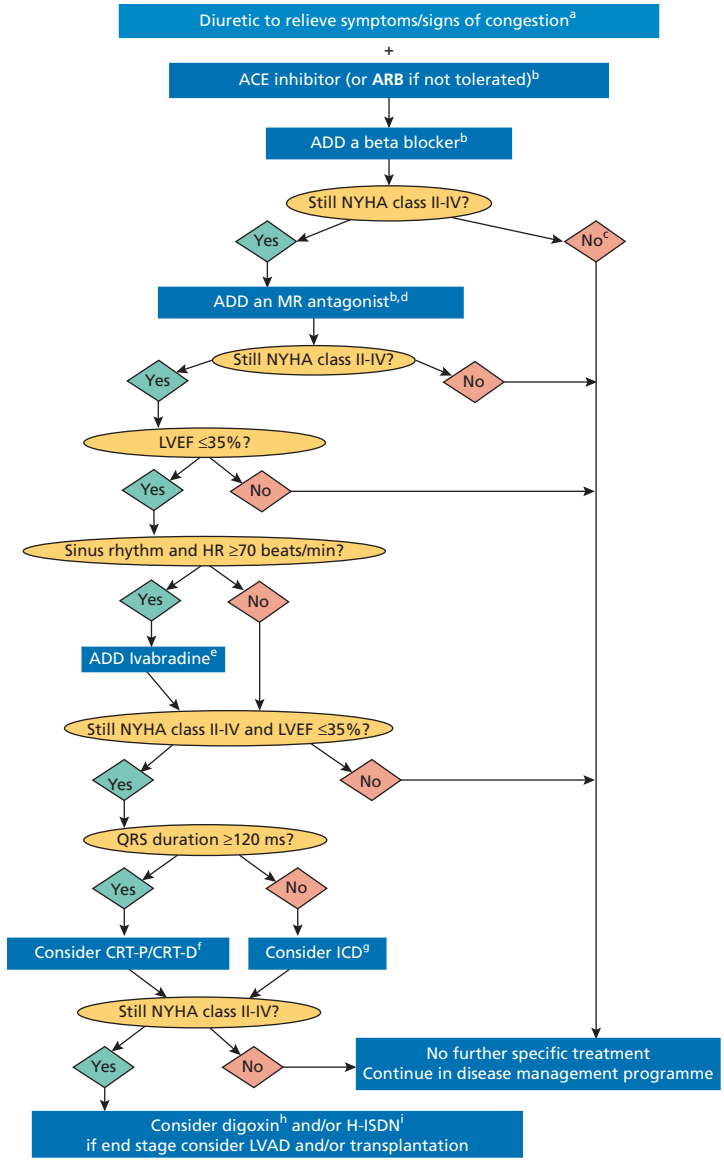

Figure 32.4 ESC 2012 guidelines on HF. Treatment options for patients with chronic symptomatic systolic heart failure (NYHA functional class II–IV).

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; H-ISDN, hydralazine and isosorbide dinitrate; HR, heart rate; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MR antagonist, mineralocorticoid receptor antagonist; NYHA, New York Heart Association. (a) Diuretics may be used, as needed, to relieve the signs and symptoms of congestion, but they have not been shown to reduce hospitalization or death. (b) Should be titrated to evidence-based dose or maximum tolerated dose below the evidence-based dose. (c) Asymptomatic patients with an LVEF ≤35% and a history of myocardial infarction should be considered for an ICD. (d) If mineralocorticoid receptor antagonist is not tolerated, an ARB may be added to an ACE inhibitor as an alternative. (e) European Medicines Agency has approved ivabradine for use in patients with a heart rate ≥75 bpm. May also be considered in patients with a contraindication to a beta blocker or beta blocker intolerance. (f) Indication differs according to heart rhythm, NYHA class, QRS duration, QRS morphology, and LVEF. (g) Not indicated in NYHA class IV. (h) Digoxin may be used earlier to control the ventricular rate in patients with atrial fibrillation—usually in conjunction with a beta blocker. (i) The combination of hydralazine and isosorbide dinitrate may also be considered earlier in patients unable to tolerate an ACEI or an ARB.

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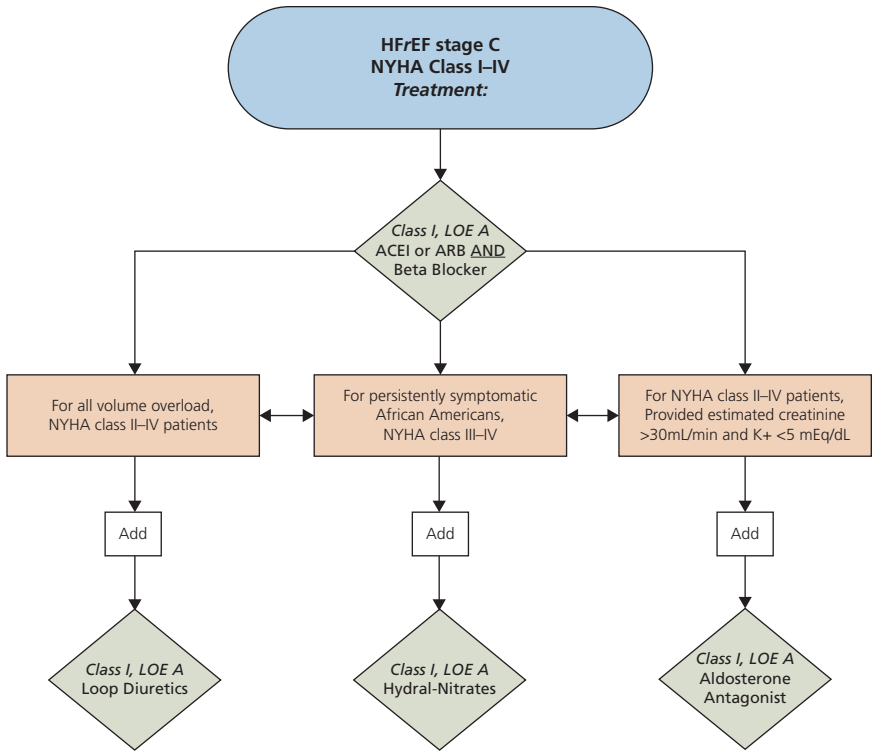

Figure 32.5 ACCF/AHA 2013 GL on HF. Stage C HF with reduced EF: evidence-based, guideline-directed medical therapy.

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; HF**r** EF, heart failure with reduced ejection fraction; Hydral-Nitrates, hydralazine and isosorbide dinitrate; LOE, Level of Evidence; and NYHA, New York Heart Association.

ACCF/AHA 2013 Guideline for the management of heart failure. *J Am Coll Cardiol*. 2013;**62**:e147–e239, with permission from Elsevier.

Drug therapy

Beta blockers and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) are the cornerstones of heart failure therapy (Figures 32.3 to 32.6, Tables 32.8 to 32.13. (For drug doses see also Table 25.14 of Chapter 25).

Angiotensin-converting enzyme inhibitors (ACEI) have multiple pleiotropic actions, including improved endothelial function, antiproliferative effects on smooth muscle cells, and antithrombotic effects. They decrease mortality in established heart failure (up to 23%) as well as in post-MI patients with reduced LVEF.[38] Enalapril, captopril, and lisinopril have been mostly studied in CHF trials and ramipril and trandolapril in post-MI trials, but their benefits appear to be a class effect without differences between tissue or non-tissue ACEI. Patients with heart failure may have increased plasma angiotensin II and, consequently, poor prognosis despite chronic ACE inhibitor therapy.[39]

Angiotensin receptor blockers (ARB) bind competitively to the AT1 receptor. ARBs also reduce mortality in heart failure, are equally effective with ACEI in randomized trials,[40] and are very suitable for patients unable to tolerate ACEI due to cough (occurs in 10% in whites, up to 50% in Chinese). Mainly studied agents in CHF are valsartan and candesartan. Irbesartan has been mainly studied in hypertension and diabetic nephropathy trials. Losartan has produced controversial results on mortality at low doses. In patients with LVEF ≤40% who remain symptomatic on ACEI and beta blockers, addition of eplerenone is preferred to an ARB. The addition of an ARB (or renin inhibitor) to the combination of an ACEI and a mineralocorticoid antagonist is also not recommended (ESC 2012 GL, III-C) because of the risk of renal dysfunction and hyperkalaemia.[41] A combination of ACEI, ARB, beta blockade, and spironolactone has been successfully tried, together with continuous flow LV assist device for reversal of end-stage heart failure.[42] In haemodialysis patients with heart failure and LVEF ≤40%, the addition of telmisartan to ACEI significantly reduced all-cause and cardiac mortality and hospital stays. ARBs are not removed by dialysis and the benefits of the combination may be seen even in normotensive patients.[43]

Contraindications to the use of ACEI/ARB are bilateral renal stenosis, serum potassium >5 mmol/L, and serum creatinine >2.5 mg/dL (relative contraindication). A history of angioedema or the development of severe cough are contraindications for an ACEI. Angioedema is extremely rare with ARB. If creatinine rises above 3 mg/dL or K >5.5 mmol/L, the dose of ACEI should be halved. With values >3.5 mg/dL creatinine or >6 mmol/L K, ACEI should be stopped.[18] However, there is evidence that the use of low-dose (15 to 25% of maximal dose) ACEI or ARB in patients with advanced renal disease (creatinine up to 5 mg/mL) may be beneficial.[44] In this case, once-daily morning dosing is considered (reduced ACE inhibition in the evening permits increased renal excretion of renal potassium), and concomitant use of a loop diuretic and restriction of dietary potassium intake (24-hour urine collection <40 mEq/day) are recommended.[44]

For ACEIs/ARBs, as well other drugs for CHF, see also Chapter 25 on hypertension.

Beta blockers upregulate β-1 receptor density, blunt norepinephrine and renin production, and mitigate the production of deleterious cytokines, including tumour necrosis factor alpha. They reduce mortality (up to 35%) in heart failure, in addition to that offered by ACEI in patients with sinus rhythm. **Carvedilol, bisoprolol**, and **long-acting metoprolol** unequivocally reduce mortality.[45–47] In patients with LVEF ≤30%, QRS ≥130 ms, and LBBB, carvedilol has been found more effective than metoprolol in reducing hospitalization and ventricular arrhythmias.[48] In addition, co-administration of carvedilol with enalapril has been reported to prevent the cardiotoxicity of anthracycline chemotherapy.[37] Nebivolol have also been found efficacious in the elderly.[49] Xamoterol, a beta blocker with intrinsic sympathomimetic activity, and bucindolol, a non-selective beta blocker, have not been found beneficial. Paradoxically, the efficacy of beta blockers has been found reduced in the presence of concomitant AF.[50] Beta blockers are started on low doses (i.e. carvedilol 3.125 mg bd) and titrated upwards every 2 weeks. In patients with newly diagnosed heart failure, it is safe to use either an ACE inhibitor or a beta blocker as first-line therapy.[47]

Contraindications to the use of beta blockers are severe asthma, second- or third-degree AV block, sick sinus syndrome (bradycardia <50 bpm) without permanent pacing, phaeochromocytoma or cocaine use (unopposed alpha receptors causing vasoconstriction). COPD is not a contraindication for their use.[51] In patients with mild to moderate asthma (not in the acute phase) cardioselective beta blockers may be used in minimum doses.[52]

Mineralocorticoid receptor antagonists (MRA) The secondary hyperaldosteronism seen in patients with heart failure promote sodium retention and endothelial dysfunction and may contribute to myocardial fibrosis. Both the selective agent **eplerenone** and the non-selective antagonist **spironolactone** reduce mortality in post-MI patients with LVEF <40% and severe or mild symptoms or in patients with advanced heart failure (Table 32.8).[53,54,55] Spironolactone may cause painful gynaecomastia in men (antagonist of aldosterone and androgen and progesterone receptors). Renal function and serum potassium levels must be closely monitored due to the risk of hyperkalaemia, especially when these agents are used together with an ACE or ARB.

Contraindications to aldosterone antagonists are hyperkalaemia (K >5 mmol/L), creatinine >2.5 mg/dL, and concomitant use of a combination of ACE and ARB.

Aliskiren, a direct renin inhibitor, is not beneficial when added to standard therapy.[56] **Neprilysin** is a neutral endopeptidase responsible for the breakdown of several vasoactive peptides, such as natriuretic peptides, bradykinin, and adrenomedullin, that can attenuate vasoconstriction and sodium retention, and retard cardiac and vascular hypertrophy and remodelling. Recently, the PARADIGM-HF trial reported a 15% reduction in total, and 20% reduction in cardiovascular, mortality over 27 months with LCZ696, a combination of the neprilysin inhibitor sacubitril and valsartan.[57] Angiotensin-neprilysin inhibition also appears to prevent the clinical progression of surviving patients with heart failure more effectively than angiotensin-converting enzyme inhibition.[58] LCZ696 has also been found superior to enalapril in reducing both sudden cardiac deaths and deaths from worsening heart failure.[59]

Loop diuretics, such as **furosemide**, are the only therapy that can acutely produce symptomatic improvement. However, no clinical trial has assessed their effect on mortality in heart failure. They should not be used alone in heart failure since they do not prevent the progression of disease or maintain clinical stability over time. **Torsemide** has better absorption than furosemide, and **bumetanide** is a more powerful diuretic. They should be used in patients not responsive to furosemide. Renal function and electrolytes should be regularly measured with the use of diuretics due to the risk of hyperkalaemia, elevation of BUN, and dilutional hyponatraemia.

In patients resistant to loop diuretics, a thiazide may be added in combination. Several effects, such as the braking phenomenon (acute reduction in diuretic efficacy with repeated loop diuretic dosing), post-diuretic effect (increased sodium retention after the loop diuretic has worn off), rebound sodium retention (increased distal nephron sodium reabsorption due to factors, such as distal tubule hypertrophy), increased angiotensin II levels due to persistent volume reduction, and renal adaptation (hypertrophy and hyperfunction of distal tubule cells, causing increased local sodium uptake and aldosterone secretion) lead to diuretic resistance.[60] By blocking distal tubule sodium reabsorption, thiazides or thiazide-like drugs, such as **metolazone** (up to 10 mg daily for 3–5 days), can

antagonize the renal adaptation to chronic loop diuretic therapy and potentially improve diuretic resistance due to rebound sodium retention, even in patients with renal failure (Figure 32.6).[60] There is increased risk of hypokalaemia, worsening of renal function, fluid depletion that may require fluid resuscitation, and hyponatraemia. Addition of an aldosterone antagonist may reduce hypokalaemia and improve natriuresis. Diuretic combinations may improve symptoms but do not decrease mortality in heart failure.

Digoxin may still have a role in patients with systolic heart failure and concomitant atrial fibrillation. In patients with sinus rhythm, digoxin (concentrations of 0.5–0.8 micrograms/L) has been shown to offer a reduction of hospital admissions, without any impact on mortality.[61] Digoxin blocks the sodium-potassium ATPase, raising intracellular sodium, and reduces calcium efflux by sodium-calcium exchange. Calcium overload of the sarcoplasmic reticulum may trigger arrhythmias. In a recent analysis of the AFFIRM study, digoxin was associated with a significant increase in all-cause mortality in patients with AF, even in the presence of HF,[62] but this finding was not verified in a post-hoc analysis of the same study.[63] If used in patients with HF and AF, serum levels should be <1 ng/mL.

Hydralazine and nitrates are inferior to ACE inhibitors. However, in African-American heart failure patients (who generally have low plasma renin concentrations and, thus, are theoretically less responsive to RAAS blockade), hydralazine and nitrates are helpful.[64] Complications are arthralgia and increased antinuclear antibodies (lupus-like syndrome is rare).

Coenzyme Q10 (CoQ10) is the only antioxidant that humans synthesize in the body and is essential to survival, working as an electron carrier in the mitochondria to produce energy. Symptomatic improvement and a 50% reduction in mortality has been seen in patients with chronic heart failure.[65]

Allopurinol increases ATP conservation and might be beneficial.[66]

Ivabradine High heart rate, that has been identified as a risk factor in chronic heart failure, and ivabradine, a selective inhibitor of hyperpolarization-activated cyclic-nucleotide-gated funny current (I*f*) involved in pacemaking generation and responsiveness of the sinoatrial node have been found to improve outcome (composite of cardiac death or hospital admission) in patients with heart failure.[67] However, an increased incidence of AF has been associated with ivabradine,[68] and the addition of ivabradine in patients with heart failure and CAD did not improve outcomes, despite a reduction in admissions for myocardial infarctions and revascularization.[69]

Verapamil and **diltiazem** are negative inotropes and are contraindicated in patients with heart failure. Dihydropyridine calcium channel blockers, such as **amlodipine** and **felodipine**, may be used safely (e.g. for systemic hypertension and angina), but they have no effect on mortality.

The use of **inotropes** and **phosphodiesterase inhibitors** (see Acute heart failure) in chronic heart failure is not indicated since it is associated with increased mortality.[70] The PROMISE study found that oral milrinone increases mortality,[71] whereas oral enoximone does not offer any improvement.[72] Oral levosimendan may improve symptoms but without any effect on hospitalizations or mortality (PERSIST).[73] New inotropic agents are under development.[74]

Anticoagulation Heart failure is accompanied by a hypercoagulable state, and patients have a 1–3.5% annual risk of stroke that is independent of atrial fibrillation.[75,76] However, there are not sufficient data to support the use of **warfarin** in patients in normal sinus rhythm without a history of thromboembolic events or echocardiographic evidence of LV thrombus. A reduced risk of ischaemic stroke with warfarin used instead of aspirin, or aspirin (WARCEF trial), and clopidogrel (WATCH trial) is offset by an increased risk of major haemorrhage.[30,31] No differences in mortality were seen although a subanalysis of the WARCEF demonstrated lower event rate (ischaemic stroke, intracerebral hemorrhage, or death combined) in patients <60 years old.[77] Ischaemic patients are treated with antiplatelet agents when indicated.

Table 32.8 ACC/AHA 2013 GL on HF. Therapy

Medical therapy for Stage C HFrEF: magnitude of benefit demonstrated in RCTs			
GDMT	**RR reduction in mortality (%)**	**NNT for mortality reduction (standardized to 36 mo)**	**RR reduction in HF hospitalizations**
ACE inhibitor or ARB	17	26	31
Beta blocker	34	9	41
Aldosterone antagonist	30	6	35
Hydralazine/nitrate	43	7	33
Drugs commonly used for Stage C HFrEF			
Drug	**Initial daily dose(s)**	**Maximum dose(s)**	**Mean doses achieved in clinical trials**
ACE inhibitors			
Captopril	6.25 mg 3 times	50 mg 3 times	122.7 mg/d
Enalapril	2.5 mg twice	10–20 mg twice	16.6 mg/d
Fosinopril	5–10 mg once	40 mg once	N/A
Lisinopril	2.5–5 mg once	20–40 mg once	32.5–35.0 mg/d
Perindopril	2 mg once	8–16 mg once	N/A
Quinapril	5 mg twice	20 mg twice	N/A
Ramipril	1.25–2.5 mg once	10 mg once	N/A
Trandolapril	1 mg once	4 mg once	N/A
ARBs			
Candesartan	4–8mg once	32 mg once	24 mg/d
Losartan	25–50 mg once	50–150 mg once	129 mg/d
Valsartan	20–40 mg twice	160 mg twice	254 mg/d
Aldosterone antagonists			
Spironolactone	12.5–25 mg once	25 mg once or twice	26 mg/d
Eplerenone	25 mg once	50 mg once	42.6 mg/d
Beta blockers			
Bisoprolol	1.25 mg once	10 mg once	8.6 mg/d
Carvedilol	3.125 mg twice	50 mg twice	37 mg/d
Carvedilol CR	10 mg once	80 mg once	N/A
Metoprolol succinate extended release (metoprolol CR/XL)	12.5–25 mg once	200 mg once	159 mg/d
Hydralazine and isosorbide dinitrate			
Fixed-dose combination	37.5 mg hydralazine/20 mg isosorbide dinitrate 3 times daily	75 mg hydralazine/40 mg isosorbide dinitrate 3 times daily	~175 mg hydralazine/90 mg isosorbide dinitrate daily
Hydralazine and isosorbide dinitrate	Hydralazine: 25–50 mg, 3 or 4 times daily and isosorbide dinitrate: 20–30 mg 3 or 4 times daily	Hydralazine: 300 mg daily in divided doses and isosorbide dinitrate 120 mg daily in divided doses	N/A

(*continued*)

Table 32.8 Continued

Recommendations for treatment of Stage A HFrEF	
Hypertension and lipid disorders should be controlled in accordance with contemporary guidelines to lower the risk of HF	I-A
Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided	I-C
Recommendations for treatment of Stage B HFrEF	
In patients with a history of MI and reduced EF, ACE inhibitors or ARBs to prevent HF	I-A
In patients with MI and reduced EF, evidence-based beta blockers to prevent HF	I-B
In patients with MI, statins to prevent HF	I-A
Blood pressure control to prevent symptomatic HF	I-A
ACE inhibitors in all patients with a reduced EF to prevent HF	I-A
Beta blockers in all patients with a reduced EF to prevent HF	I-C
ICD in patients with asymptomatic ischaemic cardiomyopathy, at least 40 d post-MI, LVEF ≤30%, and on GDMT	IIa-B
Non-dihydropyridine calcium channel blockers in patients with low LVEF	III-C (harm)
Recommendations for treatment of Stage C HFrEF	
Non-pharmacological interventions	
Patients with HF should receive specific education to facilitate HF self-care	I-B
Exercise training (or regular physical activity) is safe and effective for patients who are able to participate to improve functional status	I-A
Sodium restriction in symptomatic HF to reduce congestive symptoms	IIa-C
Continuous positive airway pressure (CPAP) to increase LVEF and improve functional status in patients with HF and sleep apnoea	IIa-B
Cardiac rehabilitation in clinically stable patients to improve functional capacity, exercise duration, health-related quality of life, and mortality	IIa-B
Pharmacological treatment for stage C HFrEF	
Measures listed as Class I recommendations for patients in stages A and B are recommended where appropriate for patients in stage C.	I-A/B/C
Guideline-directed medical therapy in Figure 32.5	I-A
Diuretics	
Diuretics in patients with HFrEF with fluid retention	I-C
ACE inhibitors	
ACE inhibitors for all patients with HFrEF	I-A
ARBs	
ARBs in patients with HFrEF who are ACE inhibitor intolerant	I-A
ARBS as alternatives to ACE inhibitors as first-line therapy in HFrEF	IIa-A
Addition of an ARB in persistently symptomatic patients with HFrEF on GDMT	IIb-A
Routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist for all stable patients	III-C (harm)
Beta blockers	
Use of 1 of the 3 beta blockers proven to reduce mortality for all stable patients	I-A
Aldosterone receptor antagonists	
Aldosterone receptor antagonists in patients with NYHA class II–IV who have LVEF ≤35%	I-A
Aldosterone receptor antagonists following an acute MI who have LVEF ≤40% with symptoms of HF or DM	I-B
Inappropriate use of aldosterone receptor antagonists may be harmful	III-B (harm)

(*continued*)

Table 32.8 Continued

Hydralazine and isosorbide dinitrate	
The combination of hydralazine and isosorbide dinitrate for African Americans with NYHA class III–IV HFrEF on GDMT	I-A
A combination of hydralazine and isosorbide dinitrate in patients with HFrEF who cannot be given ACE inhibitors or ARBs	IIa-B
Digoxin	
Digoxin in patients with HF*r*EF	IIa-B
Anticoagulation	
Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke should receive chronic anticoagulant therapy*	I-A
The selection of an anticoagulant agent should be individualized	I-C
Chronic anticoagulation for patients with chronic HF who have permanent/persistent/paroxysmal AF but are without an additional risk factor for cardioembolic stroke*	IIa-B
Anticoagulation is not recommended in patients with chronic HFrEF without AF, a prior thromboembolic event, or a cardioembolic source	III-B (no benefit)
Statins	
Statins are not beneficial as adjunctive therapy when prescribed solely for HF	III-A (no benefit)
Omega-3 fatty acids	
Omega-3 PUFA supplementation as adjunctive therapy in HF*r*EF or HFpEF patients	IIa-B
Other drugs	
Nutritional supplements as treatment for HF are not recommended in HFrEF	III-B (no benefit)
Hormonal therapies other than to correct deficiencies are not recommended in HFrEF	III-C (no benefit)
Drugs known to adversely affect the clinical status of patients with HFrEF are potentially harmful and should be avoided or withdrawn	III-B (harm)
Long-term use of an infusion of a positive inotropic drug is not recommended and may be harmful except as palliation	III-C (harm)
Calcium channel blockers	
Calcium channel blocking drugs are not recommended as routine treatment in HFrEF	III-A (no benefit)

Strategies for achieving optimal guideline-directed medical therapy (GDMT)

1. Uptitrate in small increments to the recommended target dose or the highest tolerated dose for those medications listed in the Table with an appreciation that some patients cannot tolerate the full recommended doses of all medications, particularly patients with low baseline heart rate or blood pressure or with a tendency to postural symptoms.
2. Certain patients (e.g., the elderly, patients with chronic kidney disease) may require more frequent visits and laboratory monitoring during dose titration and more gradual dose changes. However, such vulnerable patients may accrue considerable benefits from GDMT. Inability to tolerate optimal doses of GDMT may change after disease modifying interventions such as CRT.
3. Monitor vital signs closely before and during uptitration, including postural changes in blood pressure or heart rate, particularly in patients with orthostatic symptoms, bradycardia, and/or "low" systolic blood pressure (e.g., 80 to 100 mm Hg).
4. Alternate adjustments of different medication classes (especially ACE inhibitors/ARBs and beta blockers) listed in the Table. Patients with elevated or normal blood pressure and heart rate may tolerate faster incremental increases in dosages.
5. Monitor renal function and electrolytes for rising creatinine and hyperkalaemia, recognizing that an initial rise in creatinine may be expected and does not necessarily require discontinuation of therapy; discuss tolerable levels of creatinine above baseline with a nephrologist if necessary.

Table 32.8 Continued

6. Patients may complain of symptoms of fatigue and weakness with dosage increases; in the absence of instability in vital signs, reassure them that these symptoms are often transient and usually resolve within a few days of these changes in therapy.
7. Discourage sudden spontaneous discontinuation of GDMT medications by the patient and/or other clinicians without discussion with managing clinicians.
8. Carefully review doses of other medications for HF symptom control (e.g., diuretics, nitrates) during uptitration.
9. Consider temporary adjustments in dosages of GDMT during acute episodes of noncardiac illnesses (e.g., respiratory infections, risk of dehydration, etc.).
10. Educate patients, family members, and other clinicians about the expected benefits of achieving GDMT, including an understanding of the potential benefits of myocardial reverse remodelling, increased survival, and improved functional status and HRQOL.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; GDMT, guideline directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NNT, number needed to treat; RCTs, randomized controlled trials; and RR, relative risk

* In the absence of contraindications to anticoagulation.

Aldosterone receptor antagonists are given if creatinine ≤2.5 mg/dL in men and ≤2 mg/dL in women (filtration rate >30 mL/min/1.73 m^2), and K <5 mEq/L.

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin-receptor blocker; CR, controlled release; CR/XL, controlled release/extended release; CRT, cardiac resynchronization therapy; DM, diabetes mellitus; EF, ejection fraction; GDMT, guideline directed medical therapy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HRQOL, health-related quality of life; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N/A, not applicable/not available; NNT, number needed to treat; NYHA, New York Heart Association; PUFA, polyunsaturated fatty acids; RCTs, randomized controlled trials; and RR, relative risk.

ACCF/AHA 2013 Guideline for the management of heart failure. *J Am Coll Cardiol*. 2013;**62**:e147–e239, with permission from Elsevier.

Table 32.9 ESC 2012 GL on HF. Recommendations on therapy

Drug therapy of heart failure	
ACEIs in LVEF ≤40%, given with a beta blocker	I-A
Beta blockers in LVEF ≤40%, given with ACEI (or ARB)	I-A
MRA in NYHA II–IV and LVEF ≤35% despite treatment with ACEI (or ARB) and beta blocker	I-A
ARBs in LVEF ≤40% and ACEI intolerance, given with a beta blocker and MRA	I-A
ARBs in NYHA II–IV and LVEF ≤40% despite treatment with ACEI and beta blocker and MRA intolerance	I-A
Ivabradine in SR and LVEF ≤35% and HR ≥70 bpm, NYHA II–IV despite beta blocker (max dose) and ACEI (or ARB) and MRA (or ARB)*	IIa-B
Ivabradine in SR and LVEF ≤35% and HR ≥70 bpm and beta blocker intolerance, given with ACEI (or ARB) and MRA*	IIb-C
Digoxin in SR and LVEF ≤45% and beta blocker intolerance, given with ACE (or ARB) and MRA (or ARB)*	IIb-B
Digoxin in LVEF ≤45% and NYHA II–IV despite beta blocker and ACEI (or ARB) and MRA (or ARB)*	IIb-B
Hydralazine-ISDN as an alternative to an ACE or ARB, if neither is tolerated, in EF ≤45% and dilated LV (or EF ≤35%), given with a beta blocker and an MRA	IIb-B
Hydralazine-ISDN in EF ≤45% and dilated LV (or EF ≤35%) and NYHA II-IV despite beta blocker and ACEI (or ARB) and MRA (or ARB)	IIb-B
n-3 PUFA (with ACEI or ARB and beta blocker and MRA (or ARB))	IIb-B
Harmful treatments in heart failure	
Thiazolidinediones (glitazones)	III-A
Most CCBs (with the exception of amlodipine and felodipine)	III-B
NSAIDs and COX-2 inhibitors (fluid retention and renal dysfunction)	III-B
Addition of an ARB (or renin inhibitor) to the combination of an ACE inhibitor AND a mineralocorticoid antagonist (renal dysfunction and hyperkalaemia)	III-C

* For reduction of hospitalization only.

MRA, mineralocorticoid receptor antagonist; HR, heart rate; SR, sinus rhythm.

ESC 2012 Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2012;**33**:1787–1847, with permission of Oxford University Press.

Table 32.10 ESC 2012 GL on HF. Recommendations for the treatment of hypertension in patients with symptomatic HF (NYHA functional class II–IV) and LV systolic dysfunction

Step 1	
One or more of an ACE inhibitor (or ARB), beta blocker, and MRA as first-, second-, and third-line therapy (reducing the risk of HF hospitalization and reducing the risk of premature death).	I-A
Step 2	
A thiazide diuretic (or if the patient is treated with a thiazide diuretic, switching to a loop diuretic) when hypertension persists despite treatment with a combination of as many as possible of an ACE inhibitor (or ARB), beta blocker, and MRA.	I-C
Step 3	
When hypertension persists despite treatment with a combination of as many as possible of an ACE inhibitor (or ARB), beta blocker, MRA, and diuretic.	
Amlodipine	I-A
Hydralazine	I-A
Felodipine	IIa-B
Moxonidine is not recommended (increased mortality)	III-B
Alpha-adrenoceptor antagonists are not recommended (neurohumoral activation, fluid retention, worsening HF)	III-A

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist.
ESC 2012 Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2012;**33**:1787–1847, with permission of Oxford University Press.

Table 32.11 Doses of diuretics in heart failure

Oral doses	Starting dose (mg)	Maximum dose (mg)
Aldosterone antagonists		
Eplerenone	25 od*	50
Spironolactone	12.5–25 od*	50
Other potassium-sparing diuretics		
Amiloride	2.5 od	20
Triamterene	25 bd	200
Loop diuretics		
Furosemide	20–40 od or bd	600
Bumetanide	0.5–1.0 od or bd	10
Torsemide	10–20 od	200
Thiazide diuretics		
Chlorothiazide	250–500 od or bd	1000
Hydrochlorothiazide	25 mg od or bd	200
Bendrofluazide	2.5 od	10
Thiazide-like		
Metolazone	2.5 mg od	20 mg
Indapamide	2.5 mg od	5 mg
Chlorthalidone	12.5–25 od	100
IV doses		
Furosemide	Max single dose 160–200 mg, or 40 mg load followed by 10–40 mg/h infusion	
Bumetanide	Max single dose 4–8 mg, or 1 mg load followed by 0.5–2 mg/h infusion	
Torsemide	Max single dose of 100–200, or 20 mg load followed by 5–20 mg/h infusion	
Chlorothiazide	500–1000 mg od	

* If eGFR ≥50 mL/min/1.73 m^2. If eGFR=30–49 mL/min/1.73 m^2, eplerenone 25 mg od every other day or spironolactone 12.5 mg od or every other day. After dose initiation for K^+, increase ≤ 6.0 mEq/L or worsening renal function, hold until K^+ <5.0 mEq/L. Consider restarting reduced dose after confirming resolution of hyperkalemia/renal insufficiency for at least 72 h.

Table 32.12 ACC/AHA 2013 GL on HF. Strategies for minimizing the risk of hyperkalaemia in patients treated with aldosterone antagonists

1. Impaired renal function is a risk factor for hyperkalaemia during treatment with aldosterone antagonists. The risk of hyperkalaemia increases progressively when serum creatinine is >1.6 mg/dL.* In elderly patients or others with low muscle mass in whom serum creatinine does not accurately reflect glomerular filtration rate, determination that glomerular filtration rate or creatinine clearance is >30 mL/min/1.73 m^2 is recommended.
2. Aldosterone antagonists would not ordinarily be initiated in patients with baseline serum potassium >5.0 mEq/L.
3. An initial dose of spironolactone of 12.5 mg or eplerenone 25 mg is typical, after which the dose may be increased to spironolactone 25 mg or eplerenone 50 mg if appropriate.
4. The risk of hyperkalaemia is increased with concomitant use of higher doses of ACE inhibitors (captopril ≥75 mg daily; enalapril or lisinopril ≥10 mg daily).
5. In most circumstances, potassium supplements are discontinued or reduced when initiating aldosterone antagonists.
6. Close monitoring of serum potassium is required; potassium levels and renal function are most typically checked in 3 d and at 1 wk after initiating therapy and at least monthly for the first 3 mo.

* Although the entry criteria for the trials of aldosterone antagonists included creatinine <2.5 mg/dL, the majority of patients had much lower creatinine; in 1 trial (425), 95% of patients had creatinine ≤1.7 mg/dL.
ACE indicates angiotensin-converting enzyme.
ACCF/AHA 2013 Guideline for the management of heart failure. *J Am Coll Cardiol*. 2013;**62**:e147–e239, with permission from Elsevier.

Table 32.13 ESC 2012 GL on HF. Recommendations for the pharmacological treatment of stable angina pectoris in patients with symptomatic HF (NYHA functional class II–IV) and LV systolic dysfunction

Step 1: a beta blocker*	
Preferred first-line treatment to relieve angina (reduces the risk of HF hospitalization and premature death).	I-A
Alternatives to a beta blocker	
(i) Ivabradine in patients in SR who cannot tolerate a beta blocker (effective antianginal treatment and safe in HF).	IIa-A
(ii) Oral or transcutaneous nitrate in patients unable to tolerate a beta blocker (effective antianginal treatment and safe in HF).	IIa-A
(iii) Amlodipine in patients unable to tolerate a beta blocker (effective antianginal treatment and safe in HF).	IIa-A
(iv) Nicorandil in patients unable to tolerate a beta blocker (effective antianginal treatment but safety in HF uncertain).	IIb-C
(v) Ranolazine in patients unable to tolerate a beta blocker (effective antianginal treatment but safety in HF uncertain).	IIb-C
Step 2: add a second antianginal drug when angina persists, despite treatment with a beta blocker or alternative (taking account of the combinations not recommended below)	
Ivabradine	I-A
Oral or transcutaneous nitrate	I-A
Amlodipine	I-A
Nicorandil	IIb-C
Ranolazine	IIb-C
Step 3: coronary revascularization	
Coronary revascularization is recommended when angina persists, despite treatment with two antianginal drugs.	I-A
Alternatives to coronary revascularization	
A third antianginal drug from those listed above may be considered when angina persists, despite treatment with two antianginal drugs (excluding the combinations not recommended below).	IIb-C
The following are NOT recommended	
Combination of any of ivabradine, ranolazine, and nicorandil (unknown safety),	III-C
Combination of nicorandil and a nitrate (lack of additional efficacy),	III-C
Diltiazem or verapamil (negative inotropic action and risk of worsening HF).	III-B

* Nitrates and beta blockers are also recommended for angina by ACC/AHA 2009 (I-B).
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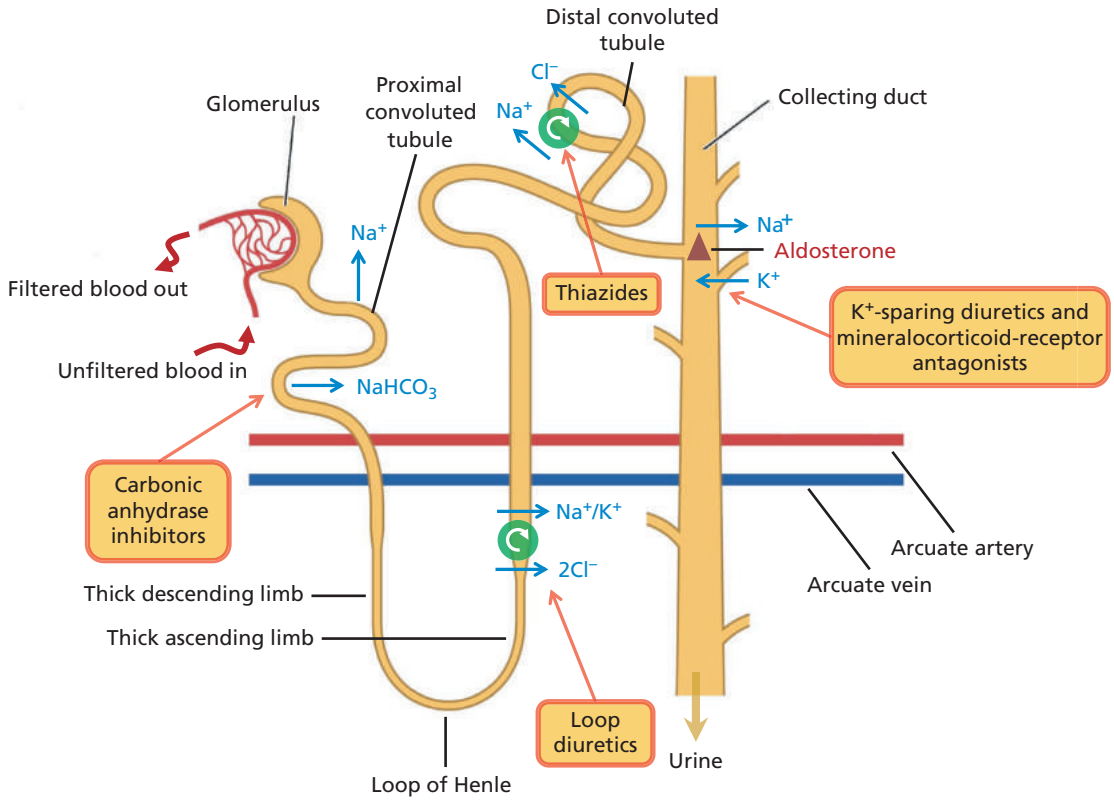

Figure 32.6 Sites of diuretic action in the nephron. The percentage of sodium reabsorbed in a given region is indicated in parentheses. 'K^+-sparing agents' collectively refers to the epithelial sodium channel inhibitors (e.g. amiloride and triamterene) and mineralocorticoid receptor antagonists (e.g. spironolactone and eplerenone). Sodium is reabsorbed in the distal tubule and collecting ducts through an aldosterone-sensitive sodium channel and by activation of an ATP-dependent sodium-potassium pump. Through both mechanisms, potassium is secreted into the lumen to preserve electroneutrality. Sodium channel inhibitors preserve potassium by interfering with the sodium-potassium pump whereas mineralocorticoid receptor antagonists spare potassium through their inhibitory effect on aldosterone. $NaHCO_3$ denotes sodium bicarbonate.

Source data from Ernst ME, Moser M, Use of diuretics in patients with hypertension. *N Engl J Med*. 2009;**361**:2153–64.

Atrial fibrillation

The prevalence of atrial fibrillation in heart failure is 5% (NYHA I) to 25–50% (NYHA III/IV). New-onset AF is most probably associated with increased subsequent risk of mortality and morbidity.[78] It is very important to detect those patients with fast AF who have developed heart failure due to tachycardia-induced cardiomyopathy. Atrial kick contributes up to 30% of stroke volume, and an analysis of the CHF-STAT trial indicated that patients with heart failure who maintained sinus rhythm on amiodarone had improved survival.[79] However, rhythm control has not been found superior to rate control in the randomized AF-CHF trial.[80] In patients with AF and heart failure, **dronedarone** increased mortality,[81] whereas **dofetilide** prevented AF recurrences without any effect on mortality.[82] **Amiodarone** is the only agent that is recommended for prevention of atrial arrhythmia recurrence in patients with heart failure and/or reduced LVEF (Table 32.14). If restoration of SR is required, **electrical cardioversion** in urgent cases (TOE is required if >48 h duration) or IV amiodarone are used.

A combination of beta blocker and digoxin is used for rate control. A non-dihydropyridine calcium channel blocker with digoxin may be considered in patients with heart failure and preserved LVEF. Catheter modification of the AV node and pacing may be considered in drug-refractory cases; however, pulmonary vein isolation with catheter ablation is preferable to AV nodal modification and biventricular pacing.[83] Catheter ablation is also probably preferable to a rate-control strategy with beta blockers and/or digoxin[84] and to amiodarone,[85] and restoration of SR may confer improvement in LV function and quality of life (see Chapter 35).[86]

Table 32.14 Atrial fibrillation in HF

ESC 2012 GL on HF. Symptomatic HF (NYHA functional class II–IV), LV systolic dysfunction, persistent/permanent AF and no evidence of acute decompensation

Pharmacological rate control during atrial fibrillation	
Step 1	
Beta blocker	I-A
Alternative step 1	
Digoxin in beta blocker intolerance.	I-B
Amiodarone in beta blocker and digoxin intolerance.	IIb-C
AV node ablation (possibly CRT) in beta blocker, digoxin, and amiodarone intolerance.	IIb-C
Step 2	
Digoxin, in addition to beta blocker, in beta blocker inadequacy.	I-B
Alternative step 2	
Amiodarone, in addition to either beta blocker or digoxin (but not both). In beta blocker and digoxin inadequacy.	IIb-C
AV node ablation (possibly CRT) in inadequate response to two of beta blocker, digoxin, and amiodarone.	IIb-C
No more than two of beta blocker, digoxin, and amiodarone (or any other drug-suppressing cardiac conduction) should be combined due to risk of bradycardia, AV block, and asystole.	IIa-C
Rhythm control	
Electrical cardioversion or pharmacological cardioversion with amiodarone in persisting symptoms and/or signs of HF, despite optimum pharmacological treatment and adequate rate control.	IIb-C
Amiodarone prior to (and following) successful electrical cardioversion to maintain SR.	IIb-C
Dronedarone is not recommended (increased risk of hospital admissions and premature death).	III-A
Class I antiarrhythmic agents (increased risk of premature death).	III-A
Prevention of thromboembolism	
The CHA2DS2-VASc and HAS-BLED scores are recommended to determine the likely risk-benefit of oral anticoagulation.	I-B
An oral anticoagulant for all patients with paroxysmal or persistent/permanent AF and a CHA2DS2-VASc score ≥1, without contraindications and irrespective of whether a rate or rhythm management strategy is used (including after successful cardioversion).	I-A
In patients with AF of ≥48 h duration or when the duration of AF is unknown, an oral anticoagulant at a therapeutic dose for ≥3 weeks prior to electrical or pharmacological cardioversion.	I-C
Intravenous heparin or LMWH for patients who have not been treated with an anticoagulant and require urgent electrical or pharmacological cardioversion.	I-C

(*continued*)

Table 32.14 Continued

Alternative to i.v. heparin or LMWH	
A TOE-guided strategy may be considered for patients who have not been treated with an anticoagulant and require urgent electrical or pharmacological cardioversion.	IIb-C
Combination of an oral anticoagulant and an antiplatelet agent in patients with chronic (>12 months after an acute event) coronary or other arterial disease (high risk of bleeding).	III-A
AHA/ACC/HRS 2014 GL on AF. Heart failure (HF)	
Control of resting heart rate with either a beta blocker or a nondihydropyridine calcium channel antagonist in persistent or permanent AF and compensated HF with preserved EF (HFpEF)	I-B
In the absence of pre-excitation, IV beta blocker (or a nondihydropyridine calcium channel antagonist in patients with HFpEF) to slow the ventricular response in the acute setting, with caution needed in patients with overt congestion, hypotension, or HF with reduced LVEF	I-B
In the absence of pre-excitation, IV digoxin or amiodarone to control heart rate acutely in patients with HF	I-B
Assessment of heart rate control during exercise and adjustment of pharmacological treatment to keep the rate in the physiological range in symptomatic patients during activity	I-C
Digoxin to control resting heart rate in patients with HF with reduced EF	I-C
A combination of digoxin and a beta blocker (or a nondihydropyridine calcium channel antagonist for patients with HFpEF), to control resting and exercise heart rate	IIa-B
AV node ablation with ventricular pacing to control heart rate when pharmacological therapy is insufficient or not tolerated	IIa-B
IV amiodarone to control the heart rate when other measures are unsuccessful or contraindicated	IIa-C
For AF and rapid ventricular response causing or suspected of causing tachycardia induced cardiomyopathy, achieve rate control by either AV nodal blockade or a rhythm-control strategy	IIa-B
For patients with chronic HF who remain symptomatic from AF despite a rate-control strategy, use a rhythm-control strategy	IIa-C
Oral amiodarone when resting and exercise heart rate cannot be adequately controlled using a beta blocker (or a nondihydropyridine calcium channel antagonist in patients with HFpEF) or digoxin, alone or in combination	IIb-C
AV node ablation when the rate cannot be controlled and tachycardia mediated cardiomyopathy is suspected	IIb-C
AV node ablation should not be performed without a pharmacological trial to achieve rate control	III-C (Harm)
For rate control, IV nondihydropyridine calcium channel antagonists, IV beta blockers, and dronedarone should not be administered in decompensated HF	III-C (Harm)

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ACCF/AHA 2013 Guideline for the management of heart failure. *J Am Coll Cardiol*. 2013;**62**:e147–e239, with permission from Elsevier.

Heart failure guidelines (ACC/AHA 2009 and ESC 2012) recommend routine anticoagulation in all patients with heart failure and AF (by definition CHA2DS2-VASC ≥1). Ischaemic patients are treated with antiplatelet agents when indicated. However, there have been no randomized trials examining the impact of aspirin alone versus placebo in stroke reduction in HF,[75] and routine addition of single-antiplatelet therapy to warfarin in patients with heart failure, AF, and vascular disease is not indicated.[87] No data exist for new oral anticoagulants.

Ventricular arrhythmias

Amiodarone decreased mortality in the GESICA trial (60% non-ischaemic patients)[88] but had no significant effect in the SCD-HeFT (70% ischaemic patients).[89] It may increase non-cardiac mortality in patients with NYHA class III heart failure.[90] It is still recommended in patients with an ICD to reduce shocks, or in patients with VT in whom ICD is not an option (Table 32.15). Other antiarrhythmic drugs are contraindicated in heart failure due to proarrhythmic potential and negative inotropic effects.

Table 32.15 ESC 2012 GL on HF. Ventricular arrhythmias

Correction of potential aggravating/precipitating factors (e.g. electrolyte disorders, use of proarrhythmic drugs, myocardial ischaemia)	I-C
Optimization of therapy with ACEI (or ARB), beta-blocker, and MRA	I-A
Coronary revascularization in patients with coronary artery disease	I-C
ICD in symptomatic or sustained VT or VF	I-A
Amiodarone in patients with an ICD, who continue to have symptomatic ventricular arrhythmias or recurrent shocks despite optimal treatment and device re-programming	I-C
Catheter ablation in patients with an ICD who continue to have ventricular arrhythmias causing recurrent shocks not preventable by optimal treatment device re-programming and amiodarone	I-C
Amiodarone in optimally treated patients in whom an ICD is not appropriate	IIb-C
Routine use of amiodarone in patients with non-sustained ventricular arrhythmias (lack of benefit and potential drug toxicity)	III-A
Other antiarrhythmic drugs (particularly class IC agents and dronedarone) in systolic HF (worsening HF, proarrhythmia, and death)	III-A

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Surgical therapy

Revascularization is thought to improve survival in patients with ischaemic cardiomyopathy and proven myocardial viability by perfusion tests, stress echocardiography, or MRI.[91,92] However, the STICH trial failed to detect any impact of CABG on total mortality in patients with LVEF ≤35% (although cardiac mortality was reduced), even if performed in patients with proven myocardial viability.[93,94] In patients with LVEF ≥35%, indications for CABG are as in IHD (Table 32.16).

In patients with ischaemic cardiomyopathy subjected to CABG, surgical LV reconstruction reduces LV volumes and LV wall stress but offers no benefit in mortality or hospitalizations (STICH Hypothesis 2 trial).[95] Thus, routine LV reconstruction is not recommended. LV volume reduction might play a role when non-viability of the akinetic segment can be established and when the procedure is likely to provide a volume reduction of a magnitude approaching 30%.[21] Ventricular reshaping techniques with new devices are under study.[96]

Table 32.16 Revascularization in HF

ACCF/AHA 2013 GL on HF. Recommendations for surgical/percutaneous/transcather interventional treatments of HF	
CABG or percutaneous intervention for patients (HF*p*EF and HF*r*EF) on GDMT with angina and suitable coronary anatomy, especially for a left main stenosis (>50%) or left main equivalent	I-C
CABG to improve survival in mild to moderate LV systolic dysfunction (EF 35–50%) and significant (≥70% diameter stenosis) multivessel CAD or proximal LAD stenosis when viable myocardium is present in the region of intended revascularization	IIa-B
CABG or medical therapy to improve morbidity and cardiovascular mortality for patients with severe LV dysfunction (EF <35%), HF, and significant CAD	IIa-B
Surgical aortic valve replacement for critical aortic stenosis and a predicted surgical mortality ≤10%	IIa-B
Transcatheter aortic valve replacement after careful candidate consideration for inoperable critical aortic stenosis	IIa-B
CABG with the intent of improving survival in ischaemic heart disease with severe LV systolic dysfunction (EF <35%) and operable coronary anatomy whether or not viable myocardium is present	IIb-B
Transcatheter mitral valve repair or mitral valve surgery for functional mitral insufficiency is of uncertain benefit	IIb-B
Surgical reverse remodelling or LV aneurysmectomy in HF*r*EF for specific indications, including intractable HF and ventricular arrhythmias	IIb-B
ESC 2012 GL on HF. Myocardial revascularization in chronic HF and systolic LV dysfunction	
CABG for patients with angina and significant left main stenosis, who are suitable for surgery and expected to survive >1 year with good functional status.	I-C
CABG for patients with angina and two- or three-vessel coronary disease, including a LAD stenosis, who are suitable for surgery and expected to survive >1 year with good functional status.	I-B
Alternative to CABG:	
PCI as an alternative to CABG in the above categories of patients unsuitable for surgery.	IIb-C
CABG and PCI are NOT recommended in patients without angina AND without viable myocardium.	III-C

(*continued*)

Table 32.16 Continued

ESC 2014 GL on revascularization. Revascularization in patients with chronic heart failure and systolic LV dysfunction (LVEF ≤35%)	
CABG for significant LM stenosis and LM equivalent with proximal stenosis of both LAD and LCx	I-C
CABG for significant LAD stenosis and multivessel disease to reduce death and hospitalization for cardiovascular causes.	I-B
LV aneurysmectomy during CABG in patients with a large LV aneurysm, if there is a risk of rupture, large thrombus formation or the aneurysm is the origin of arrhythmias.	IIa-C
Myocardial revascularization in the presence of viable myocardium.	IIa-B*
CABG with surgical ventricular restoration in patients with scarred LAD territory, especially if a postoperative LVESV index < 70 mL/m^2 can be predictably achieved.	IIb-B*
PCI if anatomy is suitable, in the presence of viable myocardium, and surgery is not indicated.	IIb-C

* These recommendations are rather controversial (see discussion of revascularization in Chapter 29).
CABG indicates coronary artery bypass graft; CAD, coronary artery disease; EF, ejection fraction; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LAD, left anterior descending; LCx, left circumflex; LM, left main stem; and LV, left ventricular.
ACCF/AHA 2013 Guideline for the management of heart failure. *J Am Coll Cardiol*. 2013;**62**:e147–e239, with permission from Elsevier.
ESC 2012 Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2012;**33**:1787–1847, with permission of Oxford University Press

In heart failure due to valve disease, such as AS or MS, surgical or interventional correction may restore an almost normal heart function.

Functional MR is characterized by annular dilatation and leaflet non-coaptation in the setting of anatomically normal papillary muscles and valve leaflets. Ischaemic or infarct-related functional MR is typically associated with leaflet tethering and displacement related to abnormal LV wall motion and geometry or papillary muscle dysfunction. The role of MV surgery (replacement or repair) in this setting remains controversial (see Chapter 17 for a detailed discussion).

Device therapy

Cardiac resynchronization therapy (CRT)

Mechanical dyssynchrony refers to non-synchronous contraction of the wall segments of the left ventricle (intraventricular) or between the left and right ventricles (interventricular). Dyssynchrony impairs systolic function and ventricular filling, increases wall stress, and worsens mitral regurgitation. It is most readily defined by the presence of QRS widening and LBBB configuration on the electrocardiogram and may be visualized on two-dimensional echocardiography. Biventricular pacing by atrial synchronized pacing of the RV and the LV via the coronary sinus to the basal or mid-ventricular LV region[97] accomplishes reverse remodelling of the LV. This remodelling effect, as well as survival benefit, is greater in non-ischaemic patients,[98] although clinical improvement with CRT has been shown in both ischaemic and non-ischaemic heart failure. In patients with NYHA III or IV heart failure and LVEF <35%, and QRS > 120 ms, CRT reduces morbidity and mortality (up to 36%), even without a defibrillator (CARE-HF trial, and others) (Tables 32.17 and 32.18, and Figures 32.7 and 32.8).[99,100,101] Indications for CRT in patients with congenital heart disease are presented in Figure 32.9.

Approximately 30–35% of patients are 'non-responders', in whom CRT fails to result in benefit despite appropriate indications for therapy.[102,103] The presence of RBBB, initial r wave in lead V_1, advanced heart failure (NYHA IV), advanced age, male gender, and ischaemic cardiomyopathy are predictors of poor outcome with CRT, whereas LBBB and QRS >150 s, female gender and non-ischaemic aetiology are predictors of response.[104–106] In patients with LVEF ≤35%, symptoms of heart failure, but a QRS duration <120 ms (LESSER-EARTH trial),[107] or even <130 ms (Echo CRT),[108] CRT may be detrimental. Women are more likely than men to achieve a benefit with QRS 130–149 ms.[109] CRT-D may also be beneficial in non-LBBB patients with PR interval prolongation and LVEF <30%, QRS duration ≥130 ms, and mild heart failure.[110] There has also been evidence that patients with QRS >130 ms may also respond to CRT even if LVEF >30%,[111] while CRT may be beneficial even in mildly symptomatic patients (NYHA I or II) and a QRS >120 msec, especially in the presence of LBBB morphology.[112–114] CRT is also preferable to RV pacing in the presence of LVEF <50% and AV block, but the potential of increased LV lead-related complications should be considered (BLOCK-HF trial).[115]

Echocardiography indices commonly used to detect dyssynchrony are a septal to later LV wall delay in peak systolic velocity of 65 ms by tissue Doppler imaging, and maximal delay in peak systolic velocity of 12 LV segments

of 100 ms. Echocardiography techniques for measurements of intra- and interventricular delay do not reliably identify responders to CRT, and the mortality benefit of CRT may occur in the absence of prospective echocardiographic predictors (PROSPECT and SMART-AV).[116,117] In addition to the ability to accurately detect mechanical delay, successful CRT also is affected by myocardial scar burden and lead position relative to dyssynchronous segments. Thus, decisions to use CRT should not be based on currently available echocardiographic/Doppler variables. However, echo-derived LV dyssynchrony (maximum delay between peak systolic velocities of the septal and the lateral walls >60 ms) may still be clinically important, especially in patients in whom it is detected following CRT.[118] Echocardiography may also be used to identify the AV delay yielding optimal LV filling. Device-based AV and VV optimization algorithms can also be useful.[103] Technological advances, such as electroanatomical mapping and assessment of mechanical discoordination instead of dyssynchrony, are under study.[102] The use of MRI or speckle-tracking echocardiography to target LV lead placement may yield improved clinical outcome (TARGET trial).[119] The presence of scarred infarction does not preclude response to CRT, provided adequate LV lead positioning outside the scar can be achieved.[100] Superesponse, defined as an absolute increase in LVEF ≥10%, or a decrease in ESVI ≥30%, or a decrease in EDVI ≥20% is an indication of favourable outcome after RCT.[120] Recommendations for CRT optimization are presented in Table 32.18.

In summary, biventricular pacing is clearly indicated in SR, QRS >150 ms, LBBB, LVEF ≤35%, and NYHA II–IV.

It is also reasonable in QRS ≥120 ms and LBBB, LVEF ≤35% or non-LBBB but QRS ≥150 ms and LVEF ≤30% (Table 32.17).

Randomized studies on CRT have been almost exclusively restricted to patients with SR. **Permanent AF** is present in 25–30% of CRT candidates, but there is little evidence that CRT is effective in AF (RAFT trial).[121] However, in patients with AF who are treated with CRT, AV junctional ablation is preferred to rate-slowing drugs (Figure 32.8).[122,123] No data exist to guide therapy by means of rate or rhythm control in patients with QRS >130 ms.

Recommendations on lead placement and follow-up of CRT devices have been published.[124]

Technical issues for lead placement are discussed in Chapter 69.

CRT with ICD

The incremental benefits of combined CRT plus implantable cardioverter-defibrillator (ICD) devices vs CRT-alone devices in patients with LV systolic dysfunction remain uncertain.[100,101]

However, in certain patients with heart failure, an ICD is indicated for either **secondary (after VT/VF) or primary prevention** (patients without heart failure, but with LVEF <30% at least 40 days post-MI, or with heart failure NYHA II or III and LVEF <35% at least 40 days post-MI). In these patients, an ICD is indicated; when CRT is also indicated, a combined device with ICD capabilities (CRT-D) should be implanted (Table 32.17).

In trials of **primary prevention** in patients with heart failure, ICD reduced mortality in post-MI patients with LVEF <30% (MADIT II)[125] and ischaemic or non-ischaemic cardiomyopathy with LVEF <35% (SCD-HeFT).[89] There was also a trend for reduced mortality with ICD in non-ischaemic heart failure and LVEF <35% and non-sustained VT (DEFINITE).[126] In patients with LVEF <35%, advanced heart failure (NYHA class III or IV) due to ischaemic or non-ischaemic cardiomyopathies, and a QRS interval >120 ms, the presence of ICD capabilities also reduced mortality (COMPANION).[127] Addition of CRT to patients who already need an ICD also reduces mortality. In the RAFT trial in patients with NYHA II or III heart failure, LEVF ≤30%, and a QRS ≥120 ms or paced QRS ≥200 ms, the addition of CRT to ICD improved survival, albeit at a cost of increased implantation-related complications (RAFT).[128] In the MADIT-CRT, in patients with ischaemic (NYHA I or II) or non-ischaemic (NYHA II) cardiomyopathy, LVEF ≤30%, and QRS ≥130 ms with LBBB morphology, CRT offered an 11% reduction in mortality compared to ICD alone.[113] However, the composite end-point of heart failure or death was lower among patients with a CRT-D system as compared with those with an ICD alone, only when restricted to those with at least 90% biventricular pacing.[129] In a real-world retrospective cohort study using National Cardiovascular Registry data linked with Medicare claims, patients who were eligible for CRT-D, according to established criteria, and who received CRT-D had significantly lower risks for death and readmission than those who received ICD therapy alone.[130]

Patients who meet criteria for both CRT and ICD should receive CRT-D.

In ischaemic patients, ICD should be considered if indications exist at least 40 days after MI.

In patients with end-stage heart failure (NYHA IV), the risks of multiple shocks and quality of life deterioration must be carefully weighed against the survival benefits. ICD may aggravate heart failure either by right ventricular apical pacing that produces dyssynchrony or multiple shocks. When CRT is implanted, however, a non-apical RV lead positioning confers no benefit (see Chapter 69).

Patients with CRT-D who achieve LVEF normalization (>50%) have very low absolute and relative risk of ventricular arrhythmias and a favourable clinical course within 2.2 years of follow-up. Risk of inappropriate ICD therapy is still present, and these patients could be considered for downgrade from CRT-D to CRT-P at time of battery depletion if no ventricular arrhythmias have occurred.[131]

Table 32.17 Device therapy in HF patients receiving optimal, guideline-directed medical therapy

ACCF/AHA 2013 GL on HF. Recommendations for device therapy for management of Stage C HF	
Indications for ICD* (See also Table 56.5)	
Non-ischaemic or ischaemic (at least 40 d post-MI), LVEF ≤35%, NYHA II/III	I-A
Ischaemic, at least 40 d post-MI, LVEF ≤30%, NYHA I	I-B
Patients with a high risk of non-sudden death such as frequent hospitalizations, frailty, or severe co-morbidities**	IIb-B
Indications for CRT	
SR, LVEF ≤35%, LBBB, QRS ≥150 ms, NYHA III/IV	I-A
SR, LVEF ≤35%, LBBB, QRS ≥150 ms, NYHA II	I-B
SR, LVEF ≤35%, LBBB, QRS 120–149 ms, NYHA II/III/IV	IIa-B
SR, LVEF ≤35%, non-LBBB, QRS ≥150 ms, NYHA III/IV	IIa-A
SR, LVEF ≤35%, non-LBBB, QRS 120–149 ms, NYHA III/IV	IIb-B
SR, LVEF ≤30%, non-LBBB, QRS ≥150 ms, NYHA I	IIb-C
SR, LVEF ≤35%, non-LBBB, QRS ≥150 ms, NYHA II	IIb-B
LVEF ≤35%, undergoing new or replacement device with anticipated ventricular pacing >40%	IIa-C
AF, LVEF ≤35%, if the patient requires ventricular pacing or otherwise meets CRT criteria and AV nodal ablation or rate control allows near 100% ventricular pacing	IIa-B
Non-LBBB, QRS <150 ms, NYHA I/II	III-B (no benefit)
Patients whose co-morbidities and/or frailty limit survival to <1 y	III-C (no benefit)
ESC 2013 GL on cardiac pacing and CRT.	
Indications for CRT in patients in sinus rhythm**	
LVEF<35%, QRS > 150 ms, LBBB, NYHA II–IV	I-A
LVEF<35%, QRS 120–150 ms, LBBB, NYHA II–IV	I-B
LVEF<35%, QRS > 150 ms, non-LBBB, NYHA II–IV	IIa-B
LVEF<35%, QRS 120–150 ms, non-LBBB, NYHA II–IV	IIb-B
QRS < 120 ms	III-B
Indications for CRT in patients in permanent AF**	
LVEF≤35%, QRS ≥120, NYHA III/IV, provided that a BiV pacing as close to 100% as possible can be achieved	IIa-B
AV junction ablation should be added in case of incomplete BiV pacing	IIa-B
Uncontrolled heart rate and reduced LVEF who are candidates for AV junction ablation for rate control	IIa-B
Indication for upgraded or de novo CRT in patients with conventional pacemaker indications and heart failure**	
Upgrade from conventional PM or ICD	
LVEF <35%, NYHA III/IV and high percentage of ventricular pacing	I-B

(*continued*)

Table 32.17 Continued

De novo CRT	
Reduced EF and expected high percentage of ventricular pacing in order to decrease the risk of worsening HF	IIa-B
Choice of pacing mode (and cardiac resynchronization therapy optimization)	
Achieve BiV pacing as close to 100% as possible (survival benefit and reduction in hospitalization are strongly associated with an increasing percentage of BiV pacing)	IIa-B
Apical position of the LV lead should be avoided	IIa-B
LV lead placement targeted at the latest activated LV segment	IIb-B
ESC 2015 GL on VA and SCD.	
CRT in patients in sinus rhythm and NYHA functional class III/ambulatory class IV****	
LVEF ≤ 35%, LBBB, QRS>150 ms	I-A
LVEF ≤ 35%, LBBB, QRS 120–150 ms	I-B
LVEF ≤ 35%, no LBBB, QRS >150 ms	IIa-B
LVEF ≤ 35%, no LBBB, QRS 120–150 ms	IIb-B
CRT in patients in permanent AF and NYHA functional class III/ambulatory class IV***	
LVEF ≤ 35%, QRS >120–150 ms and 100% biventricular pacing achievable	I-B
AV nodal ablation in incomplete biventricular pacing	IIa-B
CRT-D in patients in sinus rhythm with mild (NYHA functional class II) heart failure	
LVEF ≤ 30%, LBBB, QRS >130 ms	I-A
LVEF ≤ 35%, QRS ≥150 ms	IIb-A

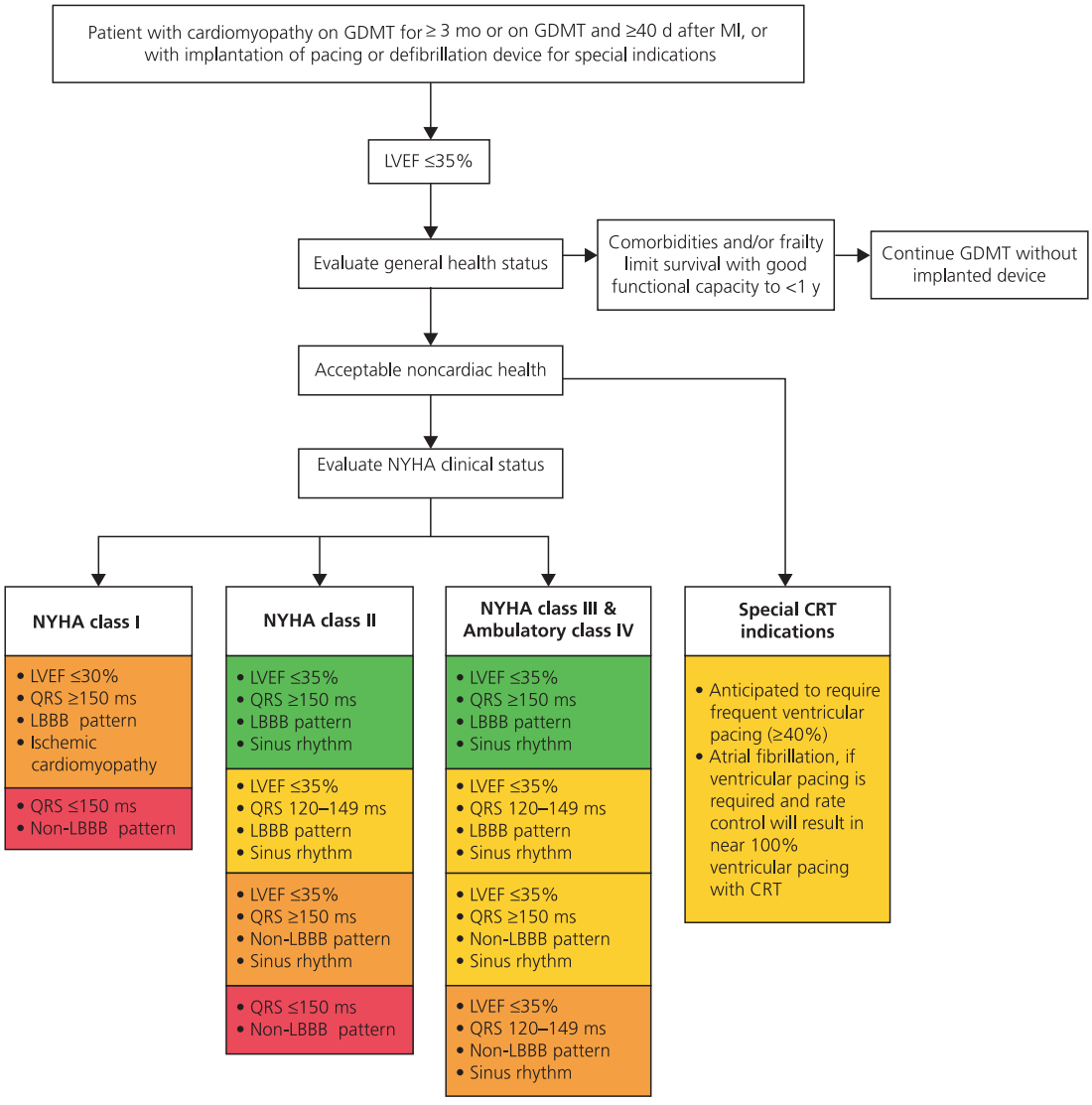
* In patients expected to live >1 y.
** Patients should generally not be implanted during admission for acute decompensated HF. In such patients, guideline-indicated medical treatment should be optimized and the patient reviewed as an out-patient after stabilization. It is recognized that this may not always be possible.
*** Despite at least 3 months optimal pharmacological therapy and with a life expectancy > one year with good functional status.
ACCF/AHA 2013 Guideline for the management of heart failure. *J Am Coll Cardiol*. 2013;**62**:e147–e239, with permission from Elsevier.
ESC 2013 Guidelines on cardiac pacing and cardiac resynchronization therapy. *Europace*. 2013;**15**:1070–118 with permission from Oxford University Press.
ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015;**36**: 2793–2867 with permission from Oxford University Press.

Table 32.18 ESC 2013 GL on cardiac pacing and CRT

Summary of current evidence for CRT optimization

Parameter	Standard (current practice)	CRT optimization	Additional clinical benefit (compared to standard)
LV lead position	Posterolateral	• Avoid apical • Target latest activated area	Benefit likely (less hospitalization for HF) Benefit likely (one RCT showed more responders, less hospitalization for HF)
AV delay	Fixed empirical AV interval 120 ms (range 100–120 ms)	• Echo-Doppler: shortest AV delay without truncation of the A-wave (Ritter's method) or change in LV systolic function	• Uncertain or mild (one small RCT and several observational positive)
		• Device-based algorithms (SmartDelay, QuickOpt)	• Uncertain (two RCTs negative)
VV delay	Simultaneous BiV	• Echo: residual LV dyssynchrony	• Uncertain or mild (one RCT showed mild benefit)
		• Echo-Doppler: largest stroke volume	• Uncertain (one RCT negative, one controlled positive)
		• ECG: narrowest LV-paced QRS; difference between BiV and preimplantation QRS	• Unknown (no comparative study)
		• Device-based algorithms (Expert-Ease, Quick-Opt, Peak endocardial acceleration)	• Uncertain (three RCTs negative)
LV pacing alone	Simultaneous BiV	n.a.	Non-inferior

AV, atrioventricular; BiV, biventricular; CRT, cardiac resynchronization therapy; DTI, tissue Doppler imaging; HF, heart failure; LV, left ventricular; n.a., not available; RCT, randomized controlled trial; VV, interventricular delay.
ESC 2013 Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J*. 2013;**34**:2281–329, with permission from Oxford University Press.



Colors correspond to class of recommendations; green: I, yellow: IIa, orange: IIb, red: III.
Benefit for NYHA class I and II patients has only been shown in CRT-D trials, and while patients may not experience immediate symptomatic benefit, late remodeling may be avoided along with long-term HF consequences. There are no trials that support CRT-pacing (without ICD) in NYHA class I and II patients. Thus, it is anticipated these patients would receive CRT-D unless clinical reasons or personal wishes make CRT-pacing more appropriate. In patients who are NYHA class III and ambulatory class IV, CRT-D may be chosen but clinical reasons and personal wishes may make CRT-pacing appropriate to improve symptoms and quality of life when an ICD is not expected to produce meaningful benefits in survival.

Figure 32.7 ACCF/AHA 2013 on HF. Indications for CRT therapy algorithm.

CRT indicates cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy-defibrillator; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LBBB, left bundle-branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and NYHA, New York Heart Association.
ACCF/AHA 2013 Guideline for the management of heart failure. *J Am Coll Cardiol*. 2013;**62**:e147–e239, with permission from Elsevier.

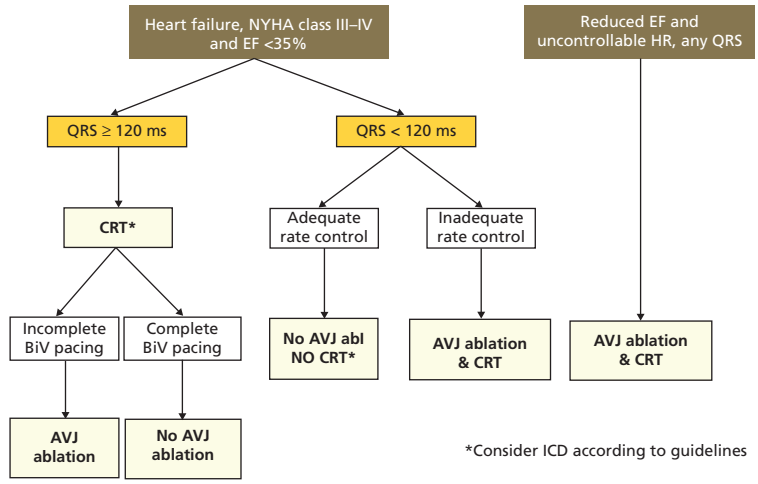


Figure 32.8 ESC 2013 GL on cardiac pacing and CRT.

Indication for atrioventricular junction (AVJ) ablation in patients with symptomatic permanent atrial fibrillation (AF) and optimal pharmacological therapy. BiV, biventricular; CRT, cardiac resynchronization therapy; EF, ejection fraction; HR, heart rate; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association. ESC 2013 Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J.* 2013;**34**:2281–329, with permission from Oxford University Press.

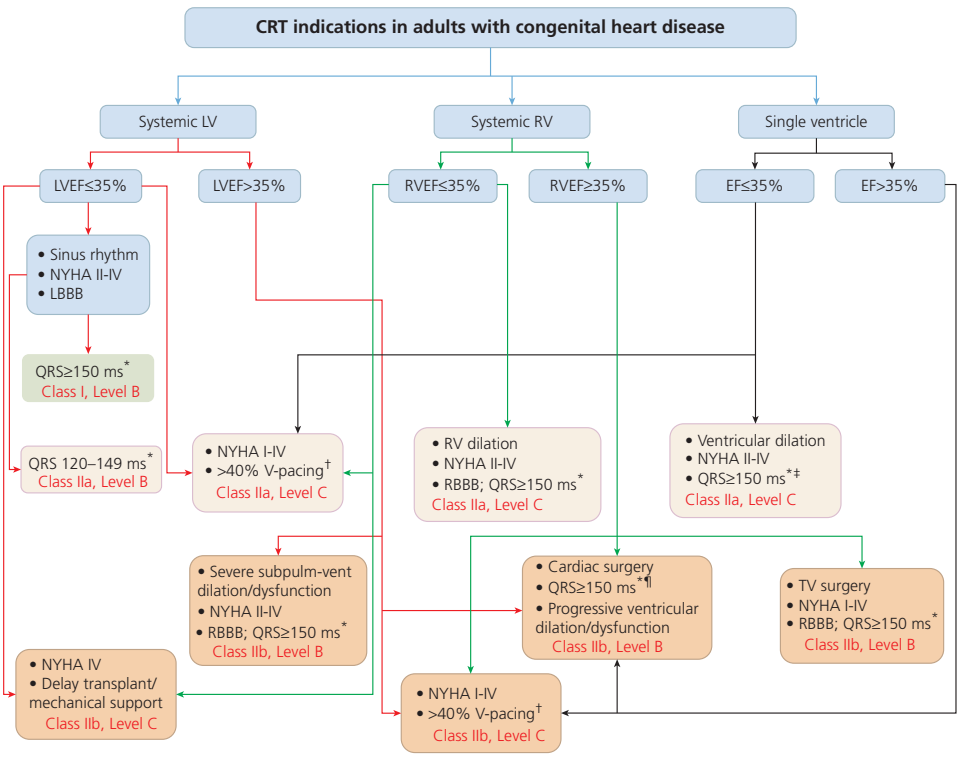


Figure 32.9 PACES/HRS 2014 Consensus statement of arrhythmias in ACHD. Overview of recommendations for cardiac resynchronization therapy (CRT) in adults with congenital heart disease (CHD).

PACES /HRS Expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease. *Heart Rhythm*. 2014;**11**:e102–165 with permission from Elsevier.

Advanced heart failure

Definition and identification of patients with advanced HF are presented in Table 32.19. The INTERMACS classification is presented in Table 32.20. Principles of therapy are indicated in Table 32.21. Acute heart failure and cardiogenic shock are discussed in Chapter 34.

Table 32.19 Advanced HF

Definition of advanced HF proposed by the Heart Failure Association of the ESC and adopted by the ACCF/AHA 2013 GL on HF
1. Severe symptoms of HF with dyspnoea and/or fatigue at rest or with minimal exertion (NYHA class III or IV)
2. Episodes of fluid retention (pulmonary and/or systemic congestion, peripheral oedema) and/or reduced cardiac output at rest (peripheral hypoperfusion)
3. Objective evidence of severe cardiac dysfunction shown by at least 1 of the following: a. LVEF <30% b. Pseudonormal or restrictive mitral inflow pattern c. Mean PCWP >16 mm Hg and/or RAP >12 mm Hg by PA catheterization d. High BNP or NT-proBNP plasma levels in the absence of non-cardiac causes
4. Severe impairment of functional capacity shown by 1 of the following: a. Inability to exercise b. 6-minute walk distance ≤ 300 m c. Peak VO_2 <12 to 14 mL/kg/min
5. History of ≥1 HF hospitalization in past 6 mo
6. Presence of all the previous features despite 'attempts to optimize' therapy, including diuretics and GDMT, unless these are poorly tolerated or contraindicated, and CRT when indicated
ACCF/AHA 2013 GL on HF. Clinical events and findings useful for identifying patients with advanced HF
Repeated (≥2) hospitalizations or ED visits for HF in the past year
Progressive deterioration in renal function (e.g., rise in BUN and creatinine)
Weight loss without other cause (e.g. cardiac cachexia)
Intolerance to ACE inhibitors due to hypotension and/or worsening renal function
Intolerance to beta blockers due to worsening HF or hypotension
Frequent systolic blood pressure <90 mm Hg
Persistent dyspnoea with dressing or bathing requiring rest
Inability to walk 1 block on the level ground due to dyspnoea or fatigue
Recent need to escalate diuretics to maintain volume status, often reaching daily furosemide equivalent dose >160 mg/d and/or use of supplemental metolazone therapy
Progressive decline in serum sodium, usually to <133 mEq/L
Frequent ICD shocks

ACE indicates angiotensin-converting enzyme; BNP indicates B-type natriuretic peptide; BUN, blood urea nitrogen; CRT, cardiac resynchronization therapy; ED, emergency department; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NT-proBNP, N3 terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery; PWCP, pulmonary capillary wedge pressure; and RAP, right atrial pressure.
ESC 2012 Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2012;**33**:1787–1847, with permission of Oxford University Press.

Table 32.20 Interagency Registry for Mechanical assist Devices (INTERMACS)

INTERMACS Levels of limitation and time frame of need for consideration of mechanical circulatory support		
INTERMACS profile level	**Status**	**Time frame**
1	Critical cardiogenic shock	Hours
2	Progressive decline	Days to week
3	Stable but inotrope-dependent	Weeks
4	Recurrent advanced heart failure	Weeks to few months if baseline restored
5	Exertion intolerant	Weeks to months
6	Exertion limited	Months if nutrition and activity maintained
7	Advanced NYHA class III	

(*continued*)

Table 32.20 Continued

ACCF/AHA 2013 FL on HF. INTERMACS profiles

Profile*	Profile description	Features
1	Critical cardiogenic shock ('Crash and burn')	Life-threatening hypotension and rapidly escalating inotropic/pressor support, with critical organ hypoperfusion often confirmed by worsening acidosis and lactate levels
2	Progressive decline ('Sliding fast' on inotropes)	"Dependent" on inotropic support but nonetheless shows signs of continuing deterioration in nutrition, renal function, fluid retention, or other major stress indicator. Can also apply to a patient with refractory volume overload, perhaps with evidence of impaired perfusion, in whom inotropic infusions cannot be maintained due to tachyarrhythmias, clinical ischaemia, or other intolerance
3	Stable but inotrope-dependent	Clinically stable on mild-moderate doses of intravenous inotropes (or has a temporary circulatory support device) after repeated documentation of failure to wean without symptomatic hypotension, worsening symptoms, or progressive organ dysfunction (usually renal)
4	Resting symptoms on oral therapy at home	Patient who is at home on oral therapy but frequently has symptoms of congestion at rest or with activities of daily living (dressing or bathing). He or she may have orthopnoea, shortness of breath during dressing or bathing, gastrointestinal symptoms (abdominal disconfort, nausea, poor appetite), disabling ascites, or severe lower-extremity oedema
5	Exertion intolerant ('housebound')	Patient who is comfortable at rest but unable to engage in any activity, living predominantly within the house or housebound
6	Exertion limited ('walking wounded')	Patient who is comfortable at rest without evidence of fluid overload but who is able to do some mild activity. Activities of daily living are comfortable and minor activities outside the home such as visiting friends or going to a restaurant can be performed, but fatigue results within a few minutes or with any meaningful physical exertion
7	Advanced NYHA class III	Patient who is clinically stable with a reasonable level of comfortable activity, despite a history of previous decompensation that is not recent. This patient is usually able to walk more than a block. Any decompensation requiring intravenous diuretics or hospitalization within the previous month should make this person a Patient Profile 6 or lower.

* Modifier options: Profiles 3–6 can be modified with the designation FF (frequent flyer) for 1 patients with recurrent decompensations leading to frequent (generally at least 2 in last 3 mo or 3 in last 6 mo) emergency department visits or hospitalizations for intravenous diuretics, ultrafiltration, or brief inotropic therapy. Profile 3 can be modified in this fashion if the patient is usually at home. If a Profile 7 patient meets the definition of FF, the patient should be moved to Profile 6 or worse. Other modifier options include A (arrhythmia), which should be used in the presence of recurrent ventricular tachyarrhythmias contributing to the overall clinical course (e.g. frequent ICD shocks or requirement of external defibrillation, usually more than twice weekly); or TCS (temporary circulatory support) for hospitalized patients profiles 1–3.
ICD indicates implantable cardioverter-defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; and NYHA, New York Heart Association.
Alba AC, *et al.* Usefulness of the INTERMACS scale to predict outcomes after mechanical assist device implantation. *J Heart and Lung Trans.* 2008;**28**:827–33, with permission from Elsevier.

Table 32.21 ACCF/AHA 2013. Therapy of advanced heart failure

Fluid restriction	
Fluid restriction (1.5 to 2 L/d) in stage D, especially in patients with hyponatraemia, to reduce congestive symptoms	IIa-C
Recommendation for therapies in the hospitalized patient	
HF patients hospitalized with fluid overload should be treated with intravenous diuretics	I-B
HF patients receiving loop diuretic therapy should receive an initial parenteral dose greater than or equal to their chronic oral daily dose; then should be serially adjusted	I-B
HFrEF patients requiring HF hospitalization on GDMT should continue GDMT unless haemodynamic instability or contraindicated	I-B
Initiation of beta-blocker therapy at a low dose is recommended after optimization of volume status and discontinuation of intravenous agents	I-B
Thrombosis/thromboembolism prophylaxis is recommended for patients hospitalized with HF	I-B
Serum electrolytes, urea nitrogen, and creatinine should be measured during titration of HF medication, including diuretics	I-C
When diuresis is inadequate, it is reasonable to: (a) give higher doses of intravenous loop diuretics; or (b) add a second diuretic (e.g., thiazide)	IIa-B
Low-dose dopamine infusion may be considered with loop diuretics to improve diuresis	IIb-B

(*continued*)

Table 32.21 Continued

Ultrafiltration may be considered for patients with obvious volume overload	IIb-B
Ultrafiltration may be considered for patients with refractory congestion	IIb-C
Intravenous nitroglycerin, nitroprusside, or nesiritide may be considered an adjuvant to diuretic therapy for stable patients with HF	IIb-A
In patients hospitalized with volume overload and severe hyponatraemia, vasopressin antagonists may be considered	IIb-B
Recommendations for inotropic support, mechanical support and cardiac transplantation	
Inotropic support	
Cardiogenic shock pending definitive therapy or resolution	I-C
BTT or MCS in stage D refractory to GDMT	IIa-B
Short-term support for threatened end-organ dysfunction in hospitalized patients with stage D and severe HFrEF	IIb-B
Long-term support with continuous infusion palliative therapy in selected stage D HF	IIb-B
Routine intravenous use, either continuous or intermittent, is potentially harmful in stage D HF	III-B (harm)
Short-term intravenous use in hospitalized patients without evidence of shock or threatened end-organ performance is potentially harmful	III-B (harm)
MCS	
MCS is beneficial in carefully selected* patients with stage D HF in whom definitive management (e.g., cardiac transplantation) is anticipated or planned	IIa-B
Nondurable MCS is reasonable as a "bridge to recovery" or "bridge to decision" for carefully selected* patients with HF and acute profound disease	IIa-B
Durable MCS is reasonable to prolong survival for carefully selected* patients with stage D HFrEF	IIa-B
Cardiac transplantation	
Evaluation for cardiac transplantation is indicated for carefully selected patients with stage D HF despite GDMT, device, and surgical management	I-C

Intravenous inotropic agents used in management of HF

Inotropic agent	Dose (mcg/kg)		Drug kinetics and metabolism	Effects				Adverse effects	Special considerations
	Bolus	Infusion (/min)		CO	HR	SVR	PVR		
Adrenergic agonists									
Dopamine	N/A	5 to 10	$T_{1/2}$: 2 to 20 min R,H,P	↑	↑	↔	↔	T, HA, N, tissue necrosis	Caution: MAO-I
	N/A	10 to 15		↑	↑	↑	↔		
Dobutamine	N/A	2.5 to 5.0	$T_{1/2}$ 2 to 3 min H	↑	↑	↓	↔	↑/↓BP, HA, T, N, F, hypersensitivity	Caution: MAO-I; CI: suffle allergy
	N/A	5 to 20		↑	↑	↔	↔		
PDE inhibitor									
Milrinone	N/R	0.125 to 0.75	$T_{1/2}$: 2.5 h H	↑	↑	↓	↓	T, ↓BP	Renal dosing, monitor LFTs

* Although optimal patient selection for MCS remains an active area of investigation, general indications for referral for MCS therapy include patients with LVEF <25% and NYHA class III -IV functional status despite GDMT, including, when indicated, CRT , with either high predicted 1- to 2-y mortality (as suggested by markedly reduced peak oxygen consumption, clinical prognostic scores, etc.) or dependence on continuous parenteral inotropic support. Patient selection requires a multidisciplinary team of experienced advanced HF and transplantation cardiologists, cardiothoracic surgeons, nurses, and, ideally, social workers and palliative care clinicians.

BTT indicates bridge to transplant; BP, blood pressure; CI, contraindication; CO, cardiac output; CRT, cardiac resynchronization therapy; EF, ejection fraction; F, fever; GDMT, guideline-directed medical therapy; H, hepatic; HA, headache; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; LFT, liver function test; MAO-I, monoamine oxidase inhibitor; MCS, mechanical circulatory support; N, nausea; N/A, not applicable; N/R, not recommended; NYHA, New York Heart Association; P, plasma; PDE, phosphodiesterase; PVR, pulmonary vascular resistance; R, renal; SVR, systemic vascular resistance; and T, tachyarrhythmias; and t½ indicates elimination half-life.

ACCF/AHA 2013 Guideline for the management of heart failure. *J Am Coll Cardiol*. 2013;**62**:e147–e239, with permission from Elsevier.

Mechanical circulatory support

Inotrope-dependent patients (i.e. levels 1 to 3 according to the Interagency Registry for Mechanical Assist Devices—INTERMACS classification, Table 32.20) who can be maintained on a single inotropic agent can be discharged home either on long-term IV inotropic support or on oral levosimendan but with detrimental or no effect on mortality. Left ventricular assist devices (LVAD) are portable blood pumps that can be used in patients with end-stage heart failure (Tables 32.22 and 32.23):[132,133]

Table 32.22 ESC 2012 GL on HF. Ventricular assist devices

Ventricular assist device indications	
LVAD or BiVAD in selected patients with end-stage HF, despite optimal pharmacological and device treatment and who are otherwise suitable for heart transplantation.	I-B
LVAD in highly selected patients who have end-stage HF, despite optimal pharmacological and device therapy, and who are not suitable for heart transplantation but are expected to survive >1 year with good functional status.	IIa-B
Patients potentially eligible for implantation of a ventricular assist device	
Patients with >2 months of severe symptoms, despite optimal medical and device therapy, and more than one of the following:	
LVEF <25% and, if measured, peak VO_2 <12 mL/kg/min	
≥3 HF hospitalizations in previous 12 months without an obvious precipitating cause	
Dependence on IV inotropic therapy	
Progressive end-organ dysfunction (worsening renal and/or hepatic function) due to reduced perfusion and not to inadequate ventricular filling pressure (PCWP ≥20 mmHg and SBP ≤80–90 mmHg or CI ≤2 L/min/m^2)	
Deteriorating right ventricular function	

ESC 2012 Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2012;**33**:1787–1847, with permission of Oxford University Press.

Table 32.23 Short-term and long-term mechanical support devices

Device	Location and implantation	Flow type and maximal cardiac output	Configuration	Duration	Uses
Impella (Abiomed Inc, Danvers, MA)	Intracorporeal, percutaneous, or surgical placement	Axial flow LVAD 3- to 5-d BTR, 2.5 or 5 L/min	LVAD	Short	BTR/BTD/BIT
TandemHeart (Cardiac Assist, Inc, Pittsburgh, PA)	Extracorporeal, percutaneous, or surgical placement	Centrifugal flow LVAD, 3- to 5-d BTR, 4 L/min	LVAD	Short	BTR/BTD/BIT
Centrimag (Levitronix LLC, Waltham, MA)	Extracorporeal, surgical placement	Centrifugal flow, 10 L/min	LVAD ± RVAD	Short	BTR/BTD/BIT
Thoratec PVAD (Thoratec Corp, Pleasanton, CA)	Extracorporeal, surgical placement	Pulsatile flow, 6–7 L/min	LVAD ± RVAD	Intermediate to long	BTT
Abiomed BVS 5000 (Abiomed Inc, Danvers, MA)	Extracorporeal, surgical placement	Pulsatile flow, 6–7 L/min	LVAD ± RVAD	Intermediate to long	BTT
Heartmate II (Thoratec Corp, Pleasanton, CA)	Intracorporeal, surgical placement	Axial flow, 10 L/min	LVAD	Long	BTT, DT
Heartmate XVE (Thoratec Corp, Pleasanton, CA)	Intracorporeal, surgical placement	Pulsatile 10 L/min	LVAD	Long	BTT, DT
Heartware HVAD (Heartware Inc, Miami Lakes, PL)	Intracorporeal, surgical placement	Centrifugal flow, 10 L/min	LVAD	Long	BTT (D)
Jarvik 2000 Flowmaker (Jarvik Heart Inc, New York, NY)	Intracorporeal, surgical placement	Axial flow, 7 L/min	LVAD	Long	BTT (D)
Duraheart LVAS (Terumo Heart Inc, Ann Arbor, MI)	Intracorporeal, surgical placement	Centrifugal flow, 10 L/min	LVAD	Long	BTT (D)
CardioWest (Syncardia Systems, Tucson, AZ)	Intracorporeal, surgical placement	Pulsatile, >9 L/min	TAH	Long	BTT

LVAD indicates left ventricular assist device; BTR, bridge to recovery; BTD, bridge to decision; BTT, bridge to transplantation; RVAD, right ventricular assist device; DT, destination therapy; ID, investigational device; and TAH, total artificial heart.
Ahmad T, *et al.* When the heart runs out of heartbeats: treatment options for refractory end-stage heart failure. *Circulation*. 2012;**125**:2948–55 with permission from Wolters Kluwer.

- As bridge to recovery in people with potentially reversible forms of heart failure, such as myocarditis or post-partum cardiomyopathy
- As bridge to transplantation within the next weeks
- As destination therapy for patients unsuitable for transplantation.

The randomized REMATCH trial in patients with end-stage heart failure unsuitable for transplantation detected a significantly better survival at 1 and 2 years in the device group than in the medical therapy group (52% vs 25% at 1 year and 23% vs 8% at 2 years, respectively). [134] New intrapericardial systems or non-pulsatile devices may yield better clinical outcomes.[135–139] Bleeding complications due to aggressive anticoagulation are the most common post-operative adverse events.[140] Haemorrhage may also occur later due to acquired von Willebrand's disease, platelet damage, and development of mucosal AV malformations.[141,142] Device infection occurs in 22% of patients per year despite the use of newer, smaller devices, and affects mortality.[143] Thrombosis, device failure, and RV failure may also occur. Recently, an unexpected increase of HeartMate II thrombosis, 8.5% at 3 months post-implantation, was reported,[144] and according to a recent FDA report (August 2015), the HeartMate II is linked to increased pump thrombosis, whereas the HeartWare is linked to increased stroke rates; both devices are associated with bleeding complications. Balloon pumps, coagulopathy, and cardiopulmonary resuscitation before short-term mechanical support are among the most significant predictors of mortality.[145] Although the long-term efficacy and safety of LVADs as an alternative to heart transplantation or medical therapy remains uncertain, the limited availability of organs for transplantation, as well as the use of LVADs as a bridge to recovery, especially before terminal stages of the disease, suggest expansion of their use.[146,147] However, their cost-effectiveness is still not established.[148] The development of an artificial heart by bioprosthetic material appears to provide thromboembolic protection (CARMAT-TAH) is a new exciting development if this device demonstrate durability.[149]

Heart transplantation

Approximately 5% and 10% of all patients with heart failure have advanced disease, which is associated with a very high mortality and very poor quality of life. Heart transplantation has been the only means of improving the quality of life and survival in these patients. With the advances in immunosuppression therapy, 1-year survival after cardiac transplantation approaches 90%, with 50% of patients surviving >11 years.[150] The listing criteria and evaluation and management of patients undergoing cardiac transplantation have been described in detail by the International Society for Heart and Lung Transplantation.[151] Indications and contraindications for transplantation by the ESC are also presented in Table 32.24. Heart transplantation is indicated in hospitalized patients with status I classification (United Network of Organ Sharing), who need intravenous inotropes or a circulatory support device. In ambulatory (status II) patients, transplantation does not improve survival; these patients might benefit from long-term LVAD unloading that may allow recovery of myocardial contractility in patients with dilated cardiomyopathy. Indication for permanent pacing are presented in Chapter 66.

Table 32.24 Cardiac transplantation

ESC 2012 GL on HF. Heart transplantation: indications and contraindications

Patients to consider
End-stage heart failure with severe symptoms, a poor prognosis, and no remaining alternative treatment options
Motivated, well informed, and emotionally stable
Capable of complying with the intensive treatment required post-operatively
Contraindications
Active infection
Severe peripheral arterial or cerebrovascular disease
Current alcohol or drug abuse
Treated cancer in previous 5 years
Unhealed peptic ulcer
Recent thromboembolism
Significant renal failure (e.g. creatinine clearance <50 mL/min)
Significant liver disease
Systemic disease with multiorgan involvement
Other serious co-morbidity with poor prognosis
Emotional instability or untreated mental illness
High, fixed pulmonary vascular resistance (>4–5 Wood Units and mean transpulmonary gradient >15 mmHg)

ESC 2012 Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2012;**33**:1787–1847, with permission of Oxford University Press.

Non-cardiac surgery

Recommendations by the ESC are provided in Table 32.25.[152]

Table 32.25 ESC 2014 GL on non-cardiac surgery

Recommendations on heart failure	
Evaluation of LV function and/or assessment of natriuretic peptides in patients with established or suspected heart failure, who are scheduled for noncardiac intermediate or high-risk surgery	I-A
Patients with established heart failure, who are scheduled for intermediate or high-risk non-cardiac surgery, should be therapeutically optimized as necessary, using beta-blockers, ACEIs or ARBs, and mineralocorticoid antagonists and diuretics	I-A
In patients with newly diagnosed heart failure, intermediate- or high-risk surgery should be deferred, preferably for at least 3 months after initiation of heart failure therapy, to allow time for therapy uptitration and possible improvement of LV function.	I-C
Beta blockade should be continued throughout the peri-operative period, whereas ACEIs/ARBs may be omitted on the morning of surgery, depending on patient's blood pressure. If ACEIs/ARBs are given, it is important to carefully monitor the patient's haemodynamic status and give appropriate volume replacement when necessary.	I-C
Unless there is adequate time for dose-titration, initiation of high-dose beta-blockade before non-cardiac surgery in patients with heart failure is not recommended.	III-B

ESC/ESA 2014 Guidelines on noncardiac surgery: cardiovascular assessment and management. *Eur Heart J.* 2014;**35**:2383–431 with permission from Oxford University Press.

New therapeutic approaches

Efforts are underway to treat heart failure by enhancing myofilament sensitivity to Ca^{2+}, transfer of the gene for SERCA2a, the protein that pumps calcium into the sarcoplasmic reticulum of the cardiomyocyte, and short, non-coding microRNAs.[153] Autologous stem cell intracoronary transplantation may also improve LVEF in ischaemic heart failure, but any impact on mortality is not established.[154] A novel approach for creating a left-to-right atrial shunt for left atrial decompression in patients with high pulmonary capillary wedge pressure with use of specific devices, is under study.[155]

Hospital discharge

Recommendations are provided in Table 32.26.

Table 32.26 ACCF/AHA 2013 GL on HF.

Recommendation for hospital discharge	
Performance improvement systems in the hospital and early postdischarge outpatient setting to identify HF for GDMT	I-B
Before hospital discharge, at the first postdischarge visit, and in subsequent follow-up visits, the following should be addressed: a. initiation of GDMT if not done or contraindicated; b. causes of HF, barriers to care, and limitations in support; c. assessment of volume status and blood pressure with adjustment of HF therapy; d. optimization of chronic oral HF therapy; e. renal function and electrolytes; f. management of comorbid conditions; g. HF education, self-care, emergency plans, and adherence; and h. palliative or hospice care	I-B
Multidisciplinary HF disease-management programs for patients at high risk for hospital readmission are recommended	I-B
A follow-up visit within 7 to 14 d and/or a telephone follow-up within 3 d of hospital discharge is reasonable	IIa-B
Use of clinical risk-prediction tools and/or biomarkers to identify higher-risk patients is reasonable	IIa-B

GDMT indicates guideline-directed medical therapy; HF, heart failure.
ACCF/AHA 2013 Guideline for the management of heart failure. *J Am Coll Cardiol*. 2013;**62**:e147–e239, with permission from Elsevier.

Table 32.27 ESC 2011 GL on pregnancy

Recommendations for the management of cardiomyopathies and heart failure	
Anticoagulation in patients with intracardiac thrombus detected by imaging or with evidence of systemic embolism.	I-A
Women with HF during pregnancy should be treated according to current guidelines for non-pregnant patients, respecting contraindications for some drugs in pregnancy.	I-B
Women with DCM should be informed about the risk of deterioration of the condition during gestation and peripartum.	I-C
In patients with a past history or family history of sudden death, close surveillance with prompt investigation is recommended if symptoms of palpitations or presyncope are reported.	I-C
LMWH or vitamin K antagonists, according to stage of pregnancy, for patients with AF.	I-C
Delivery with β-blocker protection in women with HCM.	IIa-C
β-blockers in all patients with HCM and more than mild LVOTO or maximal wall thickness >15 mm to prevent sudden pulmonary congestion.	IIa-C
In HCM, cardioversion should be considered for persistent atrial fibrillation.	IIa-C
Due to high metabolic demands of lactation and breastfeeding, preventing lactation may be considered in post-partum cardiomyopathy (PPCM).	IIb-C
Subsequent pregnancy is not recommended if LVEF does not normalize in women with PPCM.	III-C

DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; HF: heart failure; LMWH: low molecular weight heparin; LVEF: left ventricular ejection fraction; LVOTO: left ventricular outflow tract obstruction; PPCM: peripartum cardiomyopathy.
ESC 2011 Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J.* 2011;**32**:3147–97 with permission from Oxford University Press.

Pregnancy

Recommendations for pregnant women with heart failure are presented in Table 32.27.[156]

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Chapter 33

Heart failure with preserved left ventricular ejection fraction

Definition

Heart failure with preserved ejection fraction (>50% although definitions vary), (HFpEF), or diastolic HF is seen in approximately 50% of patients with HF.[1] The condition should be distinguished from heart failure with recovered ejection fraction (HFrEF; see Chapter 31) that bears a better prognosis.[2] The diagnosis of HFpEF is challenging because it is established by excluding other potential non-cardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified. The ACC/AHA have further subdivided this category into HFpEF, borderline 41–49%, and HFpEF, improved >40% (see Chapter 31 on classification of HF).

Aetiology and pathophysiology

Heart failure with preserved LVEF may be seen in various conditions, such as diastolic dysfunction, pressure overload hypertrophy from valvular disease (especially AS), pericardial disease, and RV dysfunction. **Diastolic dysfunction** is caused by a decrease in ventricular relaxation and/or an increase in ventricular stiffness probably due to fibrosis and myocardial hypertrophy. Common causes are long-standing arterial hypertension, ischaemic heart disease, diabetes, severe sepsis, and increased age (Table 33.1). **Diastolic heart failure** occurs when the ventricular chamber is unable to accept an adequate volume of blood during diastole at normal diastolic pressures and at volumes sufficient to maintain an appropriate stroke volume (see Figure 31.1 in Chapter 31).[3–5] Systolic dysfunction may coexist: LVEF is an imperfect measure of systolic function, and stroke volume and cardiac output may be reduced despite a normal LVEF. RV dysfunction is common in HFpEF patients and associated with clinical and echocardiographic evidence of more advanced HF and predictive of poorer outcomes.[6,7]

Table 33.1 Differential diagnosis in a patient with heart failure and normal left ventricular ejection fraction

Incorrect diagnosis of HF
Diastolic dysfunction
Severe hypertension, myocardial ischaemia
Episodic or reversible LV systolic dysfunction
Primary valvular disease
HF associated with high metabolic demand (high output states) Anaemia, thyrotoxicosis, arteriovenous fistulae
Restrictive (infiltrative) cardiomyopathies Amyloidosis, sarcoidosis, haemochromatosis
Pericardial constriction
Pulmonary hypertension (usually with right HF)
Atrial myxoma
Obesity

Epidemiology

The prevalence of heart failure with preserved LVEF is estimated to be 50% among heart failure populations, and its pathophysiology is incompletely understood.[8] It

is dominant in the elderly who have multiple non-cardiac co-morbidities that mainly affect their prognosis.[9] The mortality rate for patients with diastolic heart failure is slightly better than those with systolic heart failure (approaching 30% in 1 year, compared with 1% for age-matched controls).[10,11] However, progression from normal to abnormal diastolic function is an independent predictor of mortality in patients with normal LVEF.[12]

Clinical presentation

May be identical to that of systolic heart failure. Diabetes usually has a more severely impaired exercise tolerance and worse disease phenotype.[13]

Diagnosis

The ESC has proposed the following criteria:[14]

- Symptoms and signs of heart failure, LVEF >45%, and the presence of abnormal LV relaxation or diastolic stiffness
- Others, including ACC/AHA, have adopted an LVEF >50%.[4]

Proposed criteria vary and are mostly empiric.

Echocardiographic indices indicative of diastolic dysfunction include transmitral and pulmonary venous Doppler filling profiles and tissue Doppler imaging that provides information on patterns of diastolic relaxation and filling and ventricular dyssynchrony (see Figure 32.1, and Table 32.7). However, assessment of diastolic dysfunction remains still rather elusive. RV dysfunction may be seen.

Plasma BNP amounts are raised in patients with heart failure with preserved LVEF but, in general, to a lesser extent than in systolic heart failure.

Invasive exercise testing may also be useful. An excessive rise of pulmonary capillary wedge pressure during exercise, despite normal values at rest, is associated with increased mortality and may be considered as early HFpEF.[15]

Therapy

Therapy of heart failure with preserved systolic function is not satisfactory (Table 33.2). Therapies addressing specific patient phenotypes may prove to be a more effective approach than the traditional model of applying a uniform treatment.[16] Blood pressure control, rate/rhythm control in underlying AF, control of pulmonary congestion with diuretic agents, and revascularization, when indicated, are recommended.[1,14] Blood pressure control improves diastolic function, irrespective of the type of antihypertensive agent used.[17] ARBs, beta-blockers to control tachycardia and increase the duration of diastole, diuretics in smaller doses than in systolic heart failure (aldosterone antagonists are promising), and calcium channel blockers (diltiazem or verapamil) are used for symptomatic relief. Despite a lower rate of hospitalizations, no reduction in mortality has been shown with ACEI or ARBs or beta-blockers.[18–20] In addition, an unexpected worsening of renal function with ARB therapy was recently reported by the I-PRESERVE trial.[21] Spironolactone has also not been beneficial in patients already taking ACEI/ARBs and diuretics (TOPCAT trial).[22] Recently, phosphodiesterase 9A (PDE9A) inhibition that is not dependent on nitric oxide levels, as occurs with conventional PDE5A inhibitors used in pulmonary hypertension, has been found promising in animals with induced cardiac hypertrophy and heart failure.[23]

Table 33.2 ACC/AHA 2013 GL on HF

Recommendations for treatment of HFpEF	
Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines	I-B
Diuretics for relief of symptoms due to volume overload	I-C
Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischaemia is present despite GDMT	IIa-C
Management of AF according to published clinical practice guidelines for HFpEF to improve symptomatic HF	IIa-C
Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF	IIa-C
ARBs to decrease hospitalizations in HFpEF	IIb-B
Nutritional supplementation is not recommended in HFpEF	III-C (no benefit)

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARBs, angiotensin-receptor blockers; CAD, coronary artery disease; GDMT, guideline-directed medical therapy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction.
ACCF/AHA 2013 Guideline for the management of heart failure. *J Am Coll Cardiol*. 2013;**62**:e147–e239, with permission from Elsevier.

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Chapter 34

Acute heart failure and cardiogenic shock

Acute heart failure

Definition

Acute heart failure, or acute decompensated HF, refers to rapid onset or acute worsening of symptoms and signs of heart failure.[1,2]

Aetiology

In most cases acute HF arises as a result of deterioration in patients with a previous diagnosis of HF (either HFrEF or HFpEF), but may also be the first presentation of HF ('de novo' acute HF) (Table 34.1). The most common co-morbid conditions are hypertension (73%), coronary artery disease (57%), and diabetes (44%).

Presentation and prognosis

Clinical presentation depends on cardiac output and alterations in vascular compliance (Figure 34.1). Most of the patients with acute HF present with normal or high blood pressure and with symptoms and/or signs of congestion rather than low cardiac output.[2] Chest X-ray is variably sensitive for the presence of interstitial or alveolar oedema, but natriuretic peptides, both BNP and NT-proBNP, are invariably elevated.

Table 34.1 ESC 2012 GL on HF

Precipitants and causes of acute heart failure
Events usually leading to rapid deterioration
• Rapid arrhythmia or severe bradycardia/conduction disturbance
• Acute coronary syndrome
• Mechanical complication of acute coronary syndrome (e.g. rupture of interventricular septum, mitral valve chordal rupture, right ventricular infarction)
• Acute pulmonary embolism
• Hypertensive crisis
• Cardiac tamponade
• Aortic dissection
• Surgery and perioperative problems
• Peripartum cardiomyopathy
Events usually leading to less rapid deterioration
• Infection (including infective endocarditis)
• Exacerbation of COPD/asthma
• Anaemia
• Kidney dysfunction
• Non-adherence to diet/drug therapy
• Iatrogenic causes (e.g. prescription of an NSAID or corticosteroid; drug interactions)
• Arrhythmias, bradycardia, and conduction disturbances not leading to sudden, severe change in heart rate
• Uncontrolled hypertension
• Hypothyroidism or hyperthyroidism
• Alcohol and drug abuse

AHF, acute heart failure; COPD, chronic obstructive pulmonary disease; NSAID, non-steroidal anti-inflammatory drug.
ESC 2012 Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2012;**33**:1787–1847, with permission of Oxford University Press.

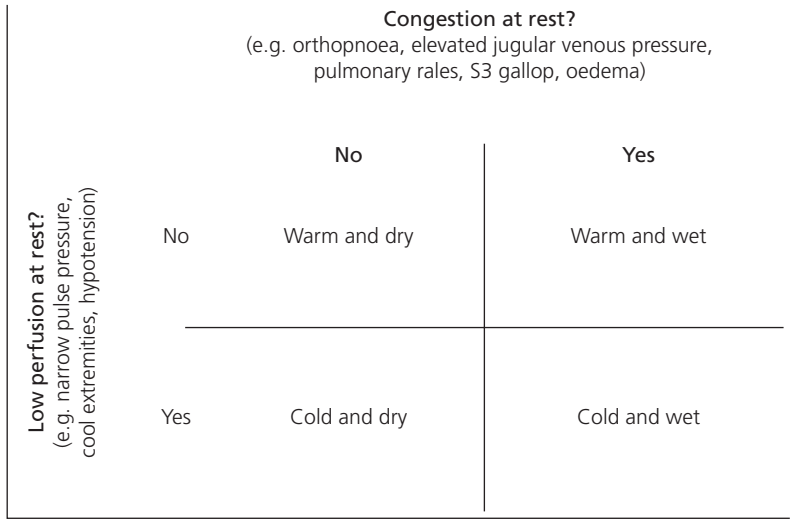

Figure 34.1 ACCF/AHA 2013 GL on HF. Classification of patients presenting with acutely decompensated HF.
ACCF/AHA 2013 Guideline for the Management of Heart Failure. *J Am Coll Cardiol*. 2013;**62**:e147–e239, with permission from Elsevier..

The **cardiorenal syndrome** is a recognized complication of acute heart failure.[3] It is exacerbated by continuing use of diuretics that reduce glomerular filtration rate. Renal dysfunction, systolic blood pressure <115 mmHg, and an elevated troponin level are associated with worse outcome (Table 34.2).[4,5] In-hospital mortality is 4% and one-year mortality approaches 50%.[4] Preserved systolic function is found in up to 50% of patients and carries a better prognosis.[5]

Table 34.2 ACCF/AHA 2013 GL on HF

Initial and serial evaluation of the hospitalized/acute heart failure patient	
BNP or NT-proBNP for diagnosis or exclusion of HF	I-A
BNP or NT-proBNP and/or cardiac troponin for prognosis	I-A
BNP or NT-proBNP-guided therapy	IIb-C
Biomarkers of myocardial injury or fibrosis for additive risk stratification	IIb-A

ACCF/AHA 2013 Guideline for the management of heart failure. *J Am Coll Cardiol*. 2013;**62**:e147–e239, with permission from Elsevier.

Therapy

General principles are presented in Table 34.3 and 34.4, and Figures 34.2 and 34.3. See also advanced HF in Chapter 32. For post-MI cardiogenic shock see also chapter on MI. Routine use of pulmonary artery catheter is not recommended and should be restricted to cases that do not respond to IV diuretics.[6] Pulmonary capillary wedge pressure is not an accurate measure of LV end-diastolic pressure in patients with mitral stenosis, aortic regurgitation, pulmonary venous occlusive disease, ventricular interdependence, high airway pressure, respiratory treatment, or a poorly compliant LV.

Oxygen is administered via a nasal cannula (4 L/min). Care should be taken in serious obstructive airways disease to avoid hypercapnia.

Non-invasive ventilation (NIV) refers to all modalities that assist ventilation without the use of an endotracheal tube, but rather with a sealed face mask. NIV is more effective in improving symptoms, but has no effect on outcome (a PEEP of 5–10 cmH_2O; FiO_2 delivery ≥0.40, usually for 30 min/h). With PEEP, it improves LV function by reducing LV afterload. NIV with positive end-expiratory pressure (PEEP) should be considered as early as possible in every patient with acute cardiogenic pulmonary oedema and hypertensive acute HF, as it improves clinical parameters, including respiratory distress. Potential complications are worsening of right ventricular failure and pneumothorax, and it should be used with caution in cardiogenic shock and right ventricular failure.

Morphine may be required for alleviation of acute symptoms but has been associated with worse outcome.[7]

Intravenous loop diuretics are essential. When large doses are required, a continuous infusion has greater efficacy and less ototoxicity than IV boluses. High doses of IV loop diuretics do not substantially worsen renal failure.[8] Additional use of a thiazide, such as **metolazone**, provides a synergistic effect, even in patients with renal failure.[9] Diuresis is continued until physical findings (JVP) and biomarker trends suggest euvolaemia. Weight loss is desirable but cannot be used as a surrogate marker for clinical outcomes. A urinary catheter is helpful.

Vasodilators, such as **nitroglycerin**, starting with 10–20 mcg/min IV and targeting a systolic BP not lower than 95 mmHg. Tolerance is being developed on continuous use after 24–48 h, and the efficacy and safety of IV nitrates is uncertain.[10] Alternatively, **nitroprusside** (starting dose 0.1–0.3 micrograms/kg/min with BP monitoring through an arterial line) can be given. It is light-sensitive, and the administration line should be covered.

Ultrafiltration is an invasive fluid removal technique implemented through two large-bore, peripherally inserted venous lines. It may supplement or obviate the need for diuretic therapy, particularly in non-responders,[11] but its efficacyis not established.[10]

Beta-blockers are discontinued only in the haemodynamically unstable patient. Withdrawal of beta-blocker in patients with decompensated heart failure is associated with increased mortality.[12]

Inotropes are **synthetic cathecholamines, phosphodiesterase inhibitors**, and **calcium sensitizers**. They are indicated in the development of cardiogenic shock, e.g. low cardiac output with hypotension and/or pulmonary congestion, despite appropriate afterload reduction, and development of cardiorenal syndrome. They should be used with caution, even in the short term, since they increase both in-hospital and post-discharge mortality, particularly with long-term therapy.[13,14] Beta-blockers should not be used concomitantly with inotropes to avoid competitive binding of beta receptors.[15]

Catecholamines mediate their cardiovascular actions through alpha 1-, beta 1-, and beta 2-adrenergic, and dopaminergic receptors (see Chapter 32).[16] Beta 1-adrenergic receptor stimulation results in enhanced myocardial contractility through Ca-mediated facilitation of the actin-myosin complex binding with troponin C and enhanced chronotropy, through Ca channel activation. Beta 2-adrenergic receptor stimulation on vascular smooth muscle cells results in increased Ca uptake by the sarcoplasmic reticulum and vasodilation. Activation of alpha1-adrenergic receptors on arterial vascular smooth muscle cells results in smooth muscle contraction and

Table 34.3 ESC 2012 GL on HF. Acute heart failure

Patients with pulmonary congestion/oedema without shock	
IV loop diuretic. Symptoms, urine output, renal function, and electrolytes should be monitored regularly.	I-B
High-flow oxygen in oxygen saturation <90% or PaO_2 <60 mmHg (8.0 kPa).	I-C
Thromboembolism prophylaxis (e.g. LMWH) in patients not already anticoagulated and with no contraindication to anticoagulation.	I-A
Non-invasive ventilation (e.g. CPAP) in dyspnoeic patients with pulmonary oedema and a respiratory rate >20 breaths/min. Should not be used in systolic BP <85 mmHg (and BP should be monitored regularly).	IIa-B
IV opiate (with an antiemetic) in particularly anxious, restless, or distressed patients. Alertness and ventilatory effort should be monitored frequently.	IIa-C
IV infusion of a nitrate in pulmonary congestion/oedema and systolic BP >110 mmHg, in the absence of severe mitral or aortic stenosis. Symptoms and BP should be monitored frequently.	IIa-B
IV infusion of sodium nitroprusside in pulmonary congestion/oedema and systolic BP >110 mmHg, in the absence of severe mitral or aortic stenosis. Caution in acute MI. Symptoms and BP should be monitored frequently.	IIa-B
Inotropic agents not recommended, unless the patient is hypotensive (systolic BP <85 mmHg), hypoperfused, or shocked (risk of atrial and ventricular arrhythmias, myocardial ischaemia, and death).	III-C
Patients with hypotension, hypoperfusion or shock	
Electrical cardioversion if an atrial or ventricular arrhythmia is contributing to haemodynamic compromise.	I-C
IV infusion of an inotrope (e.g. dobutamine) in hypotension (systolic BP <85 mmHg) and/or hypoperfusion. The ECG should be monitored continuously (risk of arrhythmias and myocardial ischaemia).	IIa–C
Short-term mechanical circulatory support (as a 'bridge to recovery') in patients severely hypoperfused despite inotropic therapy and with a potentially reversible cause (e.g. viral myocarditis) or a potentially surgically correctable cause.	IIa-C
IV infusion of levosimendan (or a phosphodiesterase inhibitor) to reverse the effect of beta-blockade if beta-blockade is contributing to hypoperfusion. ECG (risk of arrhythmias and myocardial ischaemia) and BP (vasodilation and hypotension) should be monitored continuously.	IIb-C
A vasopressor (e.g. dopamine or norepinephrine) in cardiogenic shock despite treatment with an inotrope. ECG should be monitored (risk of arrhythmias and myocardial ischaemia), and intra-arterial blood pressure measurement should be considered.	IIb-C
Short-term mechanical circulatory support (as a 'bridge to decision') in patients deteriorating rapidly before a full diagnostic and clinical evaluation can be made.	IIb-C
Patients with an ACS	
Immediate primary PCI (or CABG in selected cases) is recommended if there is an ST elevation or a new LBBB.	I-A
Alternative to PCI or CABG: Intravenous thrombolytic therapy (if PCI/CABG cannot be performed), if there is ST segment elevation or new LBBB.	I-A
Early PCI (or CABG in selected patients) if there is non-ST elevation ACS. Urgent revascularization if the patient is haemodynamically unstable.	I-A
Eplerenone in EF ≤40%.	I-B
ACE inhibitor (or ARB) in EF ≤40%, after stabilization.	I-A
Beta-blocker in EF ≤40%, after stabilization.	I–B
IV opiate (along with an antiemetic) in patients with ischaemic chest pain. Alertness and ventilatory effort should be monitored frequently.	IIa-C
Patients with AF and a rapid ventricular rate	
Full anticoagulation (e.g. with IV heparin), if not already anticoagulated and with no contraindication to anticoagulation.	I-A
Electrical cardioversion in patients haemodynamically compromised by AF.	I-C
Electrical cardioversion or pharmacological cardioversion with amiodarone to restore sinus rhythm non-urgently ('rhythm control' strategy). Only with a first episode of AF of <48 h duration (or no evidence of left atrial appendage thrombus on TOE).	I-C
IV administration of a cardiac glycoside for rapid control of the ventricular rate.	I-C
Dronedarone is not recommended (increased risk of hospital admission and premature death), particularly in patients with an EF ≤40%.	III-A
Class I antiarrhythmic agents are not recommended (increased risk of premature death), particularly in patients with LV systolic dysfunction.	III-A
Patients with severe bradycardia or heart block	
Pacing if haemodynamically compromised by severe bradycardia or heart block.	I-C

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Table 34.4 Management of oral therapy in AHF in the first 48 h

	Normotension/ hypertension	Hypotension		Low heart rate		Potassium		Renal impairment	
		<100 >85 mmHg	<85 mmHg	<60 >50 bpm	<50 bpm	<3.5 mg/dL	>5.5 mg/dL	Cr < 2.5, eGFR > 30	Cr > 2.5, eGFR < 30
ACE-I/ARB	Review/increase	Reduce/stop	Stop	No change	No change	Review/ increase	Stop	Review	Stop
Beta-blocker	No change	Reduce/stop	Stop	Reduce	Stop	No change	No change	No change	No change
MRA	No change	No change	Stop	No change	No change	Review/ increase	Stop	Reduce	Stop
Diuretics	Increase	Reduce	Stop	No change	No change	Review/No change	Review/ increase	No change	Review
Other vasodilators (nitrates)	Increase	Reduce/stop	Stop	No change	No change	No change	No change	No change	No change
Other heart-rate slowing drugs (amiodarone, CCB, ivabradine)	Review	Reduce/stop	Stop	Reduce/ stop	Stop	Review/ stop (*)	No change	No change	No change

an increase in systemic vascular resistance. Stimulation of D1 and D2 dopaminergic receptors in the kidney and splanchnic vasculature probably results in renal and mesenteric vasodilation through activation of complex second messenger systems, although the mode of action of dopamine is debated. cAMP stimulation by these agents, and consequent Ca overload of the sarcoplasmic reticulum and release of Ca into the cytoplasm, may trigger arrhythmias and increase mortality.

Dobutamine binds beta 1 and beta 2 receptors at a 3:1 ratio. It has minor effect on alpha1 receptors, and, at doses <5 micrograms/kg/min, the net effect is mild vasodilation. At doses <15 micrograms/kg/min, it increases cardiac contractility without affecting peripheral resistance. It can be given by a peripheral IV line. Tolerance may develop after a few days, and arrhythmias may occur at any dose as with any other inotrope.[14]

Dopamine binds beta 1, beta 2, alpha 1, and dopaminergic receptors. It is indicated in severe hypotension and worsening of renal function (cardiorenal syndrome). In 'renal' doses (0.5–3 micrograms/kg/min), dopamine promotes vasodilation and increases blood flow to renal tissue and has natriuretic effects on renal tubules. However, it does not increase glomerular filtration rate, and a renal protective effect has not been demonstrated.[17] In patients with acute heart failure and renal dysfunction (estimated glomerular filtration rate of 15–60 mL/min/1.73 m^2), neither low-dose dopamine nor low-dose nesiritide enhanced decongestion or improved renal function when added to diuretic therapy, and there was a trend of worse outcomes in patients with preserved left ventricular systolic function (ROSE trial).[18] At doses of 3–10 micrograms/kg/min, there is increased cardiac contractility and systemic vascular resistance. Dopamine should be given through a central line to avoid tissue extravasation. Combination of dobutamine (7.5 micrograms/kg/min) and dopamine (7.5 micrograms/kg/min) is better than one only agent at higher doses in cardiogenic shock. If, despite this, the blood pressure remains <70 mmHg, **norepinephrine** (0.01–3 micrograms/kg/min) is preferred to epinephrine that may promote coronary thrombosis.[19]

Milrinone inhibits phosphodiesterase 3, an enzyme in the sarcoplasmic reticulum that breaks down cAMP into AMP. It has inotropic, vasodilator (especially pulmonary), and lusitropic (improvement of diastolic relaxation) effects. It causes more significant RV afterload reduction and less myocardial oxygen consumption than the catecholamines, and no tolerance is developed with prolonged use. However, outcomes are similar to those with dobutamine in acute decompensated failure.[20] Milrinone may be deleterious in ischaemic cardiomyopathy.[21]

Levosimendan is a calcium sensitizer that improves contractility by enhancing binding of calcium to troponin C. Its superiority over dobutamine is controversial,[22,23] and its efficacy and safety by means of proarrhythmia and hypotension uncertain.[10] New inotropic agents are under development.[24]

Other drugs *Vasopressin* (antidiuretic hormone) causes vascular smooth muscle constriction (V1 receptors) and water reabsorption (V2 receptors). It causes less coronary and cerebral vasoconstriction than catecholamines. It is mainly used in cardiopulmonary arrest (40 U bolus).

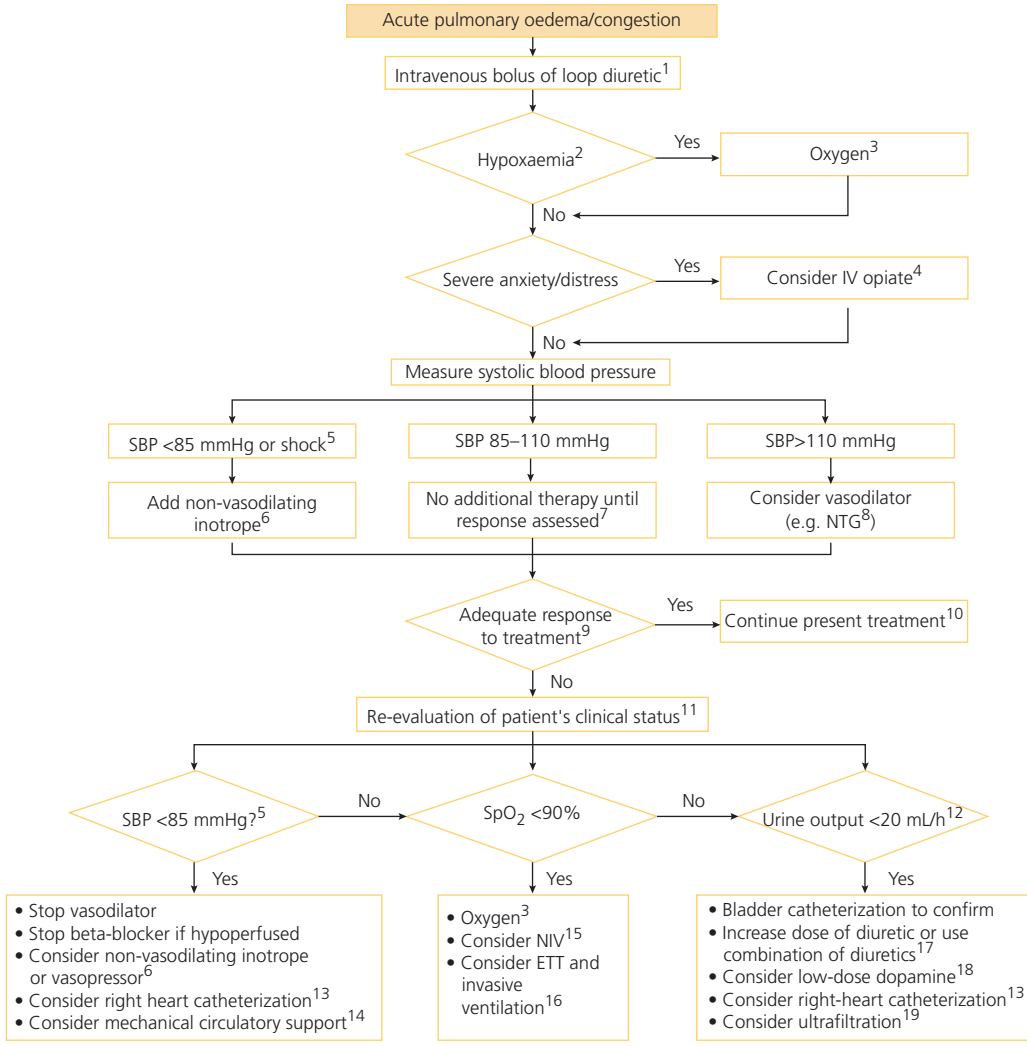

Figure 34.2 ESC 2012 guidelines on HF. Algorithm for management of acute pulmonary oedema/congestion.

(1) In patients already taking diuretic, 2.5 times existing oral dose recommended. Repeat as needed. (2) Pulse oximeter oxygen saturation <90% or PaO_2 <60 mmHg (<8.0 kPa). (3) Usually start with 40–60% oxygen, titrating to SpO_2 >90%; caution required in patients at risk of CO_2 retention. (4) For example, 4–8 mg of morphine plus 10 mg of metoclopramide; observe for respiratory depression. Repeat as needed. (5) Cold skin, low pulse volume, poor urine output, confusion, myocardial ischaemia. (6) For example, start an IV infusion of dobutamine 2.5 micrograms/kg/min, doubling dose every 15 min according to response or tolerability (dose titration usually limited by excessive tachycardia, arrhythmias, or ischaemia). A dose >20 micrograms/kg/min is rarely needed. Even dobutamine may have mild vasodilator activity as a result of beta-2 adrenoceptor stimulation. (7) Patient should be kept under regular observation (symptoms, heart rate/rhythm, SpO_2, SBP, urine output) until stabilized and recovered. (8) For example, start IV infusion at 10 micrograms/min and doubled every 10 min according to response and tolerability (usually dose uptitration is limited by hypotension). A dose of >100 micrograms/min is rarely needed. (9) An adequate response includes reduction in dyspnoea and adequate diuresis (>100 mL/h urine production in first 2 h), accompanied by an increase in oxygen saturation (if hypoxaemic) and usually a reduction in heart and respiratory rate (which should occur in 1–2 h). Peripheral blood flow may also increase, as indicated by a reduction in skin vasoconstriction, an increase in skin temperature, and improvement in skin colour. There may also be a decrease in lung crackles. (10) Once the patient is comfortable and a stable diuresis has been established, withdrawal of IV therapy can be considered (with substitution of oral diuretic treatment). (11) Assess for symptoms relevant to HF (dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea), associated co-morbidity (e.g. chest pain due to myocardial ischaemia), and treatment-related adverse effects (e.g. symptomatic hypotension). Assess for signs of peripheral and pulmonary congestion/oedema, heart rate and rhythm, blood pressure, peripheral perfusion, respiratory rate, and respiratory effort. An ECG (rhythm/ischaemia and infarction) and blood chemistry/haematology (anaemia, electrolyte disturbances, kidney failure) should also be examined. Pulse oximetry (or arterial blood gas measurements) should be checked and echocardiography performed (if not already carried out). (12) Less than 100 mL/h over 1–2 h is an inadequate initial response to IV diuretic (confirm if inadequate by catheterizing bladder). (13) In patients with persistently low blood pressure/shock, consider alternative diagnoses (e.g. pulmonary embolism), acute mechanical problems, and severe valve disease (particularly aortic stenosis). Pulmonary artery catheterization may identify patients with an inadequate left ventricular filling pressure (and characterize the patient's haemodynamic pattern, enabling more precise tailoring of vasoactive therapy). (14) An intra-aortic balloon pump or other mechanical circulatory support should be considered in patients without contraindications. (15) CPAP or NIPPV should be considered in patients without contraindications. (16) Consider endotracheal intubation and invasive ventilation if worsening hypoxaemia, failing respiratory

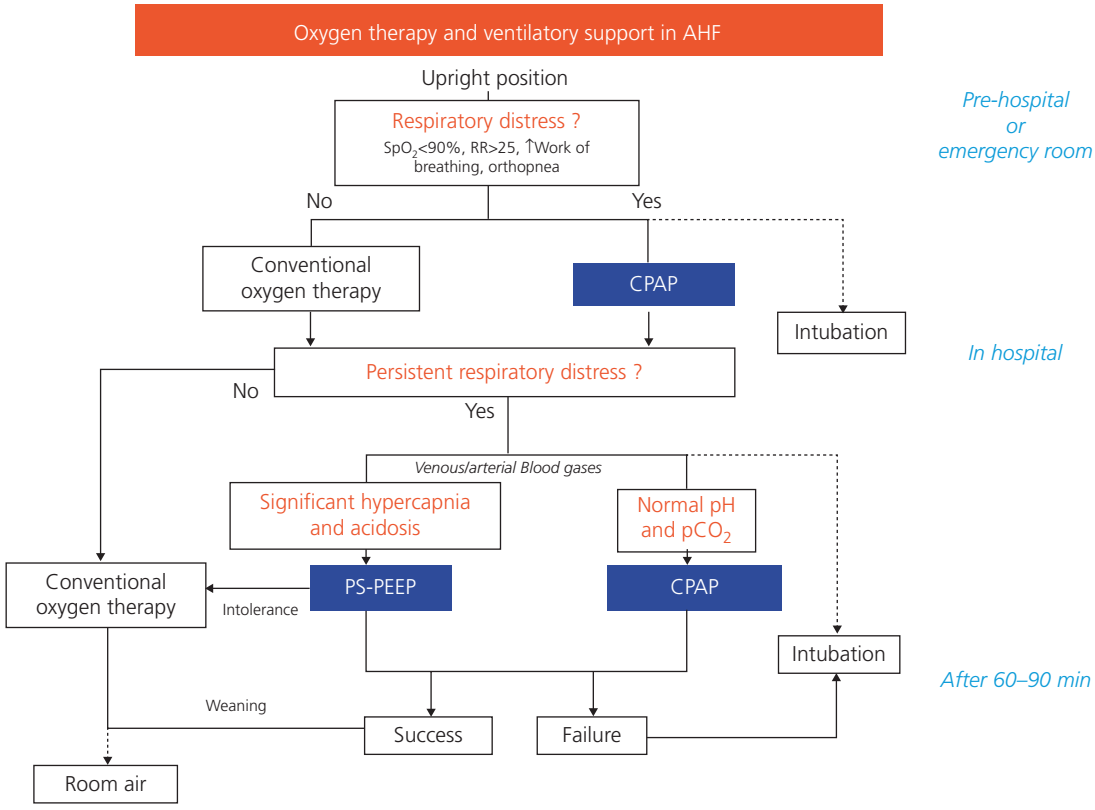

Figure 34.3 Oxygen and ventilator support in acute heart failure.

PS-PEEP, pressure support - positive end - expiratory pressure; CPAP, continuous positive airway pressure; RR, respiration rate; SPO_2, oxygen saturation.
ESC/ESEM/SAEM 2015 Recommendations on pre-hospital and early hospital management of acute heart failure. *Eur Heart J.* 2015;**36**:1958–66 with permission from Oxford University Press.

Serelaxin, a recombinant human relaxin–2 and vasoactive peptide hormone, was recently associated with a reduction of 180 day mortality in patients admitted with acute heart failure (RELAX-AHF trial),[25] although the effects on mortality were primarily driven by reduction in mortality from other cardiovascular causes and sudden death, without apparent impact on HF deaths.[26] The beneficial effects have also been seen in acute heart failure in the context of preserved LVEF.[27]

Nesiritide is a recombinant BNP that was approved for normotensive patients who do not respond to adequate doses of diuretics, but no benefit was seen in the ASCEND-HF[28] or the ROSE[18] trial. It may cause arrhythmias and hypotension.

Ularitide, the chemically synthesized form of urodilatin, a human natriuretic peptide, has also been promising.[29]

Intra-aortic balloon counterpulsation may be required in non-responsive cases. It can be used up to 3–4 weeks. Contraindicated in AR or aortic dissection.

Left ventricular assist device (LVAD) support may also be used as a bridge to recovery in potentially reversible forms of acute heart failure (see Chapter 32).

effort, increasing confusion, etc. (17) Double dose of loop diuretic up to equivalent of furosemide 500 mg (doses of 250 mg and above should be given by infusion over 4 h). (18) If no response to doubling of dose of diuretic despite adequate left ventricular filling pressure (either inferred or measured directly), start IV infusion of dopamine 2.5 micrograms/kg/min. Higher doses are not recommended to enhance diuresis. (19) If steps 17 and 18 do not result in an adequate diuresis and the patient remains in pulmonary oedema, venovenous isolated ultrafiltration should be considered.
CPAP, continuous positive airway pressure; ETT, endotracheal tube; IV, intravenous; NIPPV, non-invasive positive pressure ventilation; NIV, non-invasive ventilation; NTG, nitroglycerin; PaO_2, partial pressure of oxygen; SBP, systolic blood pressure; SpO_2, saturation of peripheral oxygen.
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Cardiogenic shock

Definition

Cardiogenic shock is a state of systemic hypoperfusion due to cardiac causes such as end-stage or acute heart failure, myocardial infarction, advanced valvular disease, and arrhythmias.

Aetiology and pathophysiology

Cardiogenic shock due to heart failure accounts for 16% of all types of shock, the remainder being due to sepsis or anaphylaxis (62%), hypovolaemia (16%), and other causes such as tamponade, pulmonary embolism and pneumothorax.[30] Cardiogenic shock occurs in 5–8% of patients with ST elevation myocardial infarction and 2.5% of non-STEMI. Predominant RV shock represents 5% of all cardiogenic shock cases.[31] Risk factors for development of shock in the context of MI include delayed reperfusion, old age, anterior MI, hypertension, diabetes mellitus, multivessel coronary artery disease, history of prior MI or heart failure, and left bundle branch block. Mechanical complications of MI, including rupture of the ventricular septum (mortality >80%), free wall, or papillary muscles and chordae cause 12% of cardiogenic shock cases. Abnormalities of ventricular relaxation and compliance, neurohormonal changes, excessive nitric oxide production, and inappropriate vasodilation as part of the systemic inflammatory response syndrome caused by MI, and excessive use of medications, such as beta-blockers, ACE inhibitors, morphine, and diuretics, have been postulated as additional responsible factors. Although LVEF may be moderately depressed (in the SHOCK trial, mean LVEF was 30%), it is still a prognostic indicator.[32]

Presentation

The patient typically presents with cool and clammy extremities, decreased urine output (<0.5 mL/kg/h), and altered mental status status (obtundation, disorientation, and confusion). Haemodynamic status:

- Systolic blood pressure <80 mmHg or mean arterial pressure 30 mmHg lower than baseline
- Cardiac index <1.8 L/min/m^2 without support or <2.0 to 2.2 L/min/m^2 with support)
- Adequate or elevated filling pressure (e.g. LVEDP >18 mmHg or right ventricular end-diastolic pressure >10 to 15 mmHg).

Clinical examination and chest radiograph are not reliable predictors of pulmonary capillary wedge pressure, and pulse oximetry may be unreliable due to peripheral vasoconstriction. Pulmonary artery and pulmonary wedge pressures can be measured with a pulmonary catheter or with Doppler echocardiography. A short mitral deceleration time (≤140 ms) is highly predictive of pulmonary capillary wedge pressure ≥20 mmHg in cardiogenic shock.

Therapy

Mortality even with optimum therapy is approximately 50%.[33]

The VIP rule, ie ventilate (oxygen administration), infuse (fluid resuscitation), and pump (vasoactive agents), is useful.

Arterial oxygenation and near-normal pH should be maintained if necessary with **mechanical ventilation via mask or intubation in case of hypoxaemia and pH <7.30)**. Positive end-expiratory pressure decreases preload and afterload. An abrupt decrease in arterial pressure after the initiation of invasive mechanical ventilation strongly suggests hypovolaemia and a decrease in venous return. The use of sedative agents should be kept to a minimum to avoid further decreases in arterial pressure and cardiac output.

Fluid administration, in order to ensure adequate right-sided filling pressure and LV preload, may be necessary. Fluids (usually crystalloid solutions) should be infused rapidly but without exceeding 300–500 mL over 20–30 minutes. When the RVEDP is >20 mmHg, ventricular septum shift towards the LV may impair systolic function, and to avoid pulmonary oedema, the central venous pressure should be monitored.

Inotropic, and especially **vasopressor**, agents should be used in the lowest possible doses. Preferred agents are dopamine, with or without dobutamine, and norepinephrine for more severe hypotension.

In post–MI shock, **early revascularization** with PCI or CABG (even in suitable patients >75 years of age) remains the cornerstone of therapy, offering >10% increases in survival.[30] The survival benefit may be seen as long as 48 hours after MI and 18 hours after shock onset. See Table 28.11 in Chapter 28.

Percutaneous post-MI VSD closure is also an evolving therapeutic modality.

Intensive insulin therapy improves survival in hyperglycaemic critically ill patients and is recommended for use in complicated MI.

Use of **intra-aortic balloon** pumping theoretically improves coronary and peripheral perfusion via diastolic balloon inflation, and augments LV performance via systolic balloon deflation with an acute decrease in afterload. Its use is recommended by both the ACC/AHA and ESC guidelines; however, in the IABP-SHOCK II randomized trial, intra-aortic balloon counterpulsation did not significantly reduce 30 day mortality in patients with cardiogenic shock complicating acute myocardial infarction for whom an early revascularization strategy was planned.[34]

Venoarterial extracorporeal membrane oxygenation (**ECMO**) or **percutaneous ventricular assist** devices (Impella pump, and the Tandem-Heart) may also be used, but they have not been shown to improve outcome.[35–37]

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Part VI

Cardiomyopathies

Relevant guidelines

ACCF/AHA 2011 Guidelines on HCM

2011 ACCF/AHA Guideline for the diagnosis and treatment of hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2011;**58**:e212–60.

ESC 2014 Guidelines on HCM

2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy. *Eur Heart J*. 2014;**35**:2733–79.

ACCF/AHA 2013 Guideline on heart failure

2013 ACCF/AHA Guideline for the management of heart failure. *J Am Coll Cardiol*. 2013;**62**:e147–239.

ESC 2012 Guidelines on heart failure

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur Heart J*. 2012;**33**:1787–847.

ACC/AHA/HRS 2012 Update for device-based therapy of cardiac rhythm abnormalities

2012 ACCF/AHA/HRS Focused update incorporated into the ACCF/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2013;**61**:e6–75.

ESC 2015 Guidelines on ventricular arrhythmias and prevention of sudden cardiac death

2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015;**36**:2793–2867.

ESC 2013 Guidelines on pacing and cardiac resynchronization

2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J*. 2013;**34**:2281–329.

HRS 2014 Expert consensus statement on arrhythmias in cardiac sarcoidosis

HRS Expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm*. 2014;**11**:1305–23.

HRS/EHRA 2011 Expert consensus statement on the state of genetic testing for channelopathies and cardiomyopathies

HRS/EHRA Expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Heart Rhythm*. 2011;**8**:1308–39.

ESC 2011 Guidelines on the management of cardiovascular diseases during pregnancy

ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**:3147–97.

Chapter 35

Classification of cardiomyopathies

Introduction

Classification schemes have been proposed by the WHO (1995), the AHA (2006), and the ESC (2008). Recently, the MOGE(S) scheme attempted a comprehensive classification.

American Heart Association classification

Definition

A heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure-related disability.[1]

Classification

- **Primary cardiomyopathies** are those solely, or predominantly, confined to heart muscle.
- **Secondary cardiomyopathies** show pathological myocardial involvement as part of a large number and variety of generalized systemic (multiorgan) disorders. Ion channelopathies are considered forms of primary genetic cardiomyopathy.[2]

European Society of Cardiology classification

Definition

Myocardial disorders, in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease, and congenital heart disease sufficient to cause the observed myocardial abnormality.[3]

Classification

Cardiomyopathies are classified into the conventional phenotypes of **hypertrophic cardiomyopathy**, **dilated cardiomyopathy**, **arrhythmogenic right ventricular dysplasia**, and **unclassified forms** (such as non-compaction). Each phenotype is then subclassified into familial and non-familial forms.

Familial refers to the occurrence, in more than one family member, of either the same disorder or a phenotype that is (or could be) caused by the same genetic mutation and not to acquired cardiac or systemic diseases in which the clinical phenotype is influenced by genetic polymorphism. Traditionally, most familial cardiomyopathies are considered monogenic disorders (the gene defect is sufficient by itself to cause the trait). A monogenic cardiomyopathy can be sporadic when the causative mutation is *de novo*, i.e. has occurred in an individual for the first time within the family (or at the germinal level in one of the parents). Patients with identified *de novo* mutations are assigned to the familial category, as their disorder can be subsequently transmitted to their offspring. There has been evidence, however, that inherited cardiomyopathies are genetically heterogeneous; within each category, there are multiple disease genes and many different mutations, each of which is uncommon. The degree of genetic heterogeneity varies among the cardiomyopathies and determines the extent to which a final common pathway of pathogenesis can be identified for each condition (Figure 35.1).[4] A glossary of genetic terms used is provided in Chapter 56 on genetic channelopathies.

Non-familial cardiomyopathies are clinically defined by the presence of cardiomyopathy and absence of disease in other family members (based on pedigree analysis and clinical evaluation). They are subdivided into **idiopathic** (no identifiable cause) and **acquired** cardiomyopathies in which ventricular dysfunction is a complication, rather than an intrinsic feature, of the disease.

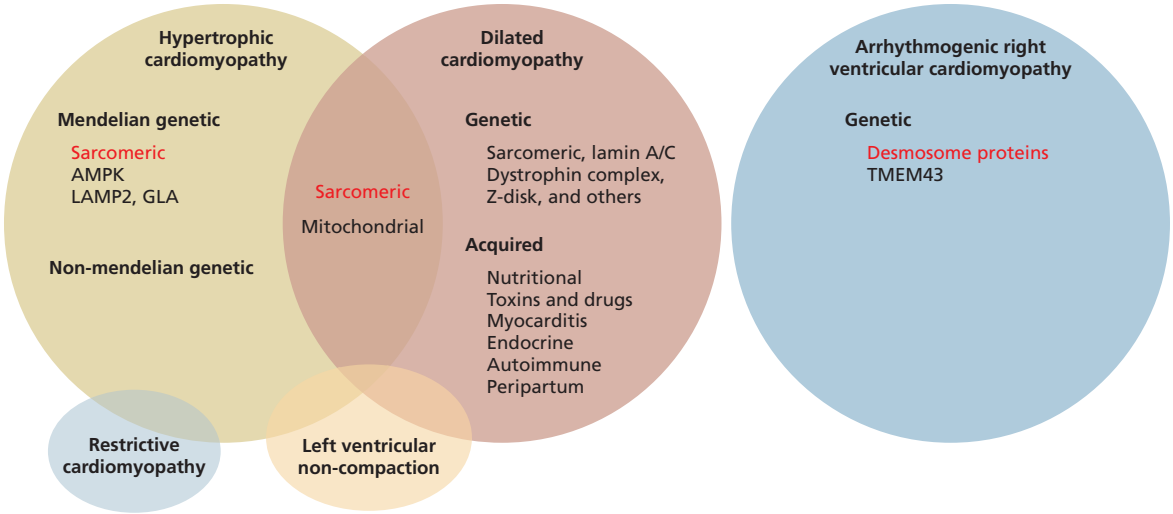

Figure 35.1 The clinical categories of inherited cardiomyopathies and their genetic basis.

The clinical entities hypertrophic cardiomyopathy and dilated cardiomyopathy share some disease genes with each other, as well as with restrictive cardiomyopathy and left ventricular noncompaction, which are less common. Arrhythmogenic right ventricular cardiomyopathy appears to be a genetically distinct category, although its clinical phenotype cannot always be easily distinguished from that of dilated cardiomyopathy.
AMPK denotes AMP-activated protein kinase; GLA, α-galactosidase A; LAMP2, lysosomal-associated membrane protein 2; and TMEM43, transmembrane protein 43.
Classes of genes shown in red are the overwhelmingly predominant cause of disease within the respective categories.
Watkins H, *et al*. Inherited cardiomyopathies. *N Engl J Med*. 2011;**364**:1643–56 with permission from Massachusetts Medical Society.

MOGE(S) classification

The recently proposed MOGE(S) nosology system embodies all of these characteristics, and describes the morphofunctional phenotype (**M**), organ(s) involvement (**O**), genetic inheritance (**G**), etiological annotation including genetic defect or underlying disease/substrate (**E**), and the functional status (**S**) of the disease using both the American College of Cardiology/American Heart Association stage and New York Heart Association functional class (Figure 35.2).[5] The proposed nomenclature is supported by a web-assisted application and assists in the description of cardiomyopathy in symptomatic or asymptomatic patients and family members in the context of genetic testing.

Presentation and laboratory tests that raise the suspicion of specific cardiomyopathies are presented in Tables 35.1 and 35.2.[6]

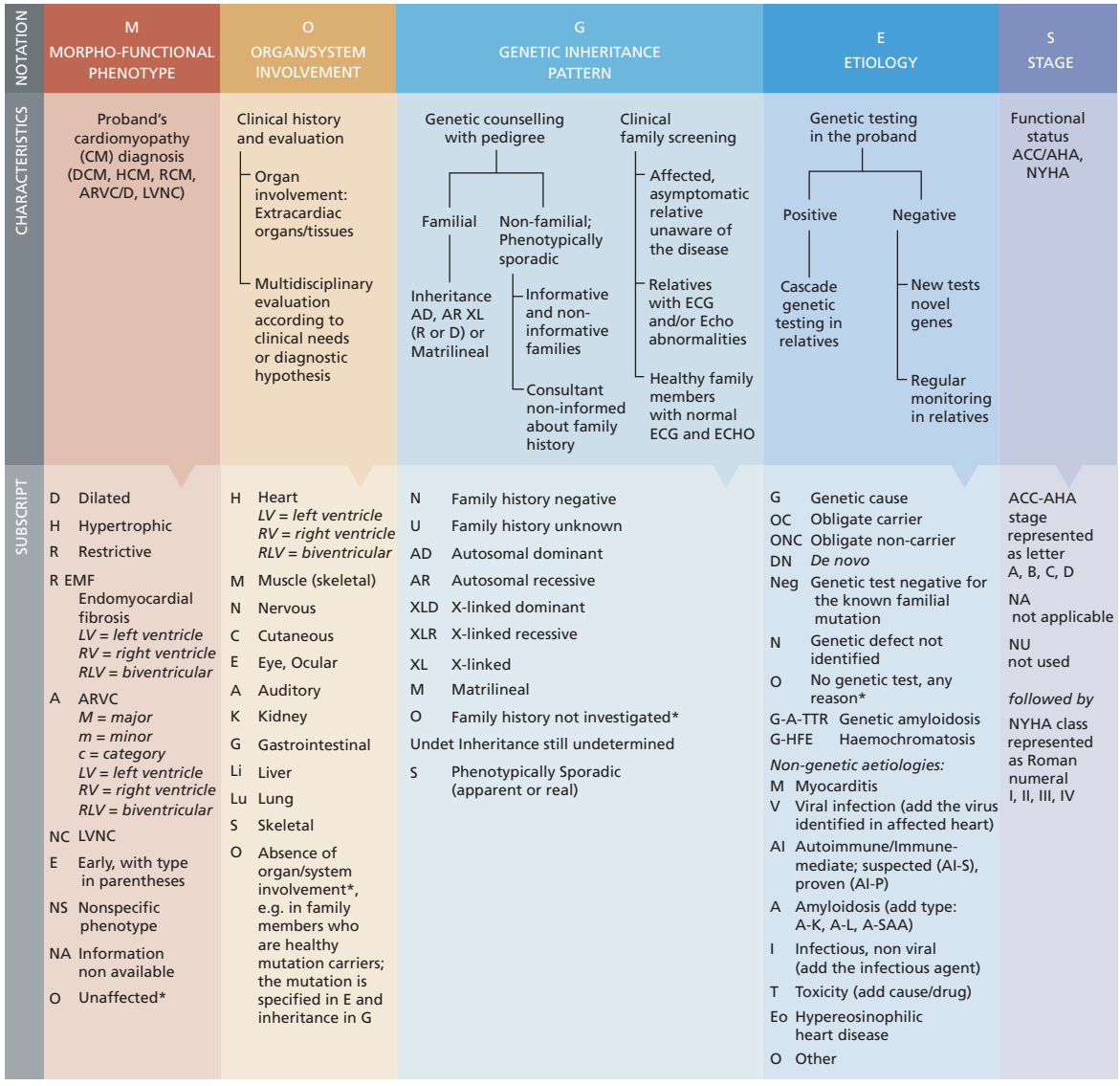

Figure 35.2 The MOGE(S) nosology system for classifying CM patients.

Evaluation of cardiomyopathy patients and development of MOGE(S) nosology. (**M**) The morphofunctional phenotype description may contain more information using standard abbreviations: AVB = atrioventricular block; LQT = prolongation of the QT interval; •PR = short PR interval; •R = low electrocardiographic voltages; WPW = Wolff Parkinson White syndrome; and other clinical red flags. These red flags are to be placed in parentheses after the notation of morphofunctional phenotype. Overlapping (H+R), (D+A), (NC+H), (H+D), (D+NC), or more complex combinations such as (H+R+NC). *Notation is zero (0) not the letter 'O.' (**E**) The aetiologic annotation provides the description of the specific disease gene and mutation, as well as a description of nongenetic aetiology. Even when genetic analysis is not available, the (**G**) may inform about a genetic disease, supporting family monitoring strategies. According to the Human Genome Variation Society, genetic variants should be classified based on their effects on gene function as: affecting function, probably affecting function, unknown (variants of unknown significance [VUS]), probably not affecting function, and not affecting function. A colour code assigned to each variant can provide information about the potential role of the identified variant: affects function or probably affects function (**red**); Variant of Unknown Significance (VUS) (**yellow**); and probably does not affect function (or probably no functional effect) or does not affect function (no functional effect) (**green**). The compilation is guided by the MOGES app. ACC, American College of Cardiology; AHA, American Heart Association; ARVC/D, arrhythmogenic right ventricular cardiomyopathy/dysplasia; DCM, dilated cardiomyopathy; ECG, electrocardiogram; ECHO, echocardiogram; HCM, hypertrophic cardiomyopathy; LVNC, left ventricular noncompaction; NYHA, New York Heart Association; RCM, restrictive cardiomyopathy
Arbustini E, *et al*. The MOGE(S) classification of cardiomyopathy for clinicians. *J Am Coll Cardiol*. 2014;**64**:304–18 with permission from Elsevier.

Table 35.1 Examples of signs and symptoms that should raise the suspicion of specific diagnoses grouped according to the main echocardiographic phenotype

Finding	Main echocardiographic phenotype			
	HCM	**DCM**	**ARVC**	**RCM**
Learning difficulties, mental retardation	Mitochondrial diseases Noonan syndrome Danon disease	Dystrophinopathies Mitochondrial diseases Myotonic dystrophy *PKTN* mutations		Noonan syndrome
Sensorineural deafness	Mitochondrial diseases Anderson–Fabry disease LEOPARD syndrome	Epicardin mutation Mitochondrial diseases		
Visual impairment	Mitochondrial diseases (retinal disease, optic nerve) TTR-related amyloidosis (vitreous opacities, cotton wool type) Danon disease (retinitis pigmentosa) Anderson–Fabry disease (cataracts, corneal opacities)	*CRYAB* (polar cataract) *Type 2 myotonic dystrophy* (subcapsular cataract)		
Gait disturbance	Friedreich's ataxia	Dystrophinopathies Sarcoglycanopathies Myofibrillar myopathies		
Myotonia (involuntary muscle contraction with delayed relaxation)		Myotonic dystrophy (type 1 and type 2)		
Paraesthesiae/sensory abnormalities/neuropathic pain	Amyloidosis Anderson–Fabry disease			Amyloidosis
Carpal tunnel syndrome (bilateral)	TTR-related amyloidosis			Amyloidosis
Muscle weakness	Mitochondrial diseases Glycogenosis *FHL*1 mutation	Dystrophinopathies Sarcoglycanopathies Laminopathies Myotonic dystrophy Desminopathy		Desminopathies (generally distal progressing to proximal)
Palpebral ptosis	Mitochondrial diseases Myotonic dystrophy			
Lentigines/café au lait spots Angiokeratomas Hypohydrosis	LEOPARD syndrome Anderson–Fabry disease			
Pigmentation of skin and scars Palmoplantar keratoderma and woolly hair		Haemochromatosis Carvajal syndrome	Naxos and Carvajal syndromes	

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy; TTR, transthyretin.

Rapezzi C, *et al*. Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2013;**34**:1448–58 with permission from Oxford University Press.

Table 35.2 Abnormalities in routine laboratory tests that should raise suspicion of specific cardiomyopathies, grouped according to the main cardiac phenotype

Finding	Main cardiac phenotype		
	HCM	**DCM**	**RCM**
↑ Creatine kinase	Mitochondrial diseases Glycogenosis Danon disease	Dystrophinopathies Sarcoglycanopathies Zaspopathies (*LDB3* gene) Laminopathies Myotonic dystrophy *FKTN* mutations Desminopathies Myofibrillar myopathies	Desminopathies
Proteinuria with/without ↓ glomerular filtration rate	Anderson–Fabry disease Amyloidosis		Amyloidosis
↑ Transaminase	Mitochondrial diseases Glycogenosis Danon disease		
High transferrin saturation/ hyperferritinaemia		Haemochromatosis	Haemochromatosis
Lactic acidosis	Mitochondrial diseases	Mitochondrial diseases	
Myoglobinuria	Mitochondrial diseases	Mitochondrial diseases	
Leucocytopenia	Mitochondrial diseases (*TAZ* gene/Barth syndrome)	Mitochondrial diseases (*TAZ* gene/ Barth syndrome)	

DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy.
Rapezzi C, *et al*. Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J.* 2013;**34**:1448–58 with permission from Oxford University Press.

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Chapter 36

Dilated cardiomyopathy

Definition

Dilated cardiomyopathy (DCM) is characterized by left ventricular dilatation and systolic dysfunction in the absence of hypertension, coronary artery disease, valve disease, congenital heart disease, and other overloading conditions. Left ventricular diastolic dysfunction may coexist, and atrial dilation as well as right ventricular dilation and dysfunction can also develop.

Epidemiology

Dilated cardiomyopathy is the most common cardiomyopathy worldwide and accounts for 25% of heart failure cases in the USA. Prevalence in adults is 1:2500, with an incidence of 7:100 000 per year.[1] This disorder develops at any age and in either sex but more commonly in men than in women. In children, two-thirds of cases are idiopathic.

Aetiology and pathophysiology

Familial and genetic

Inherited dilated cardiomyopathy accounts for 20–35% of all cases, with mutations identified in more than 30 genes.[2,3] Most mutations are private missense, nonsense, or short insertion/deletions. Autosomal dominant inheritance is the predominant pattern of transmission. X-linked, autosomal recessive, and mitochondrial inheritance are less common. On presentation, a family history and screening of first-degree relatives (for ventricular dilatation, conduction disturbances, and skeletal myopathy) should be considered.[3]

Causative genes in dilated cardiomyopathy seem to predominantly encode sarcomeric and desmosomic proteins, with subsequent defects of force generation and transmission (Table 36.1), but it seems that none of the known disease-associated genes has been shown to account for ≥5% of this disease.[4] Recently, however, titin gene truncating mutations were detected in approximately 25% of familial cases of idiopathic dilated cardiomyopathy and in 18% of sporadic cases.[5] A high overlap between mutations causing dilated and hypertrophic cardiomyopathies, and genetic channelopathies has been observed in recent next-generation sequencing studies.[6] In the case of sarcomere-encoding genes, the same genes identified for hypertrophic cardiomyopathy seem to be responsible and support the concept of a 'final common pathway' of genetically determined cardiomyopathies (Figure 36.1). Titin gene mutations are also common in families with both dilated and peripartum cardiomyopathy.[7] Metabolic abnormalities and disturbed calcium homeostasis are additional mechanisms for cardiomyopathy.

When the disease is associated with atrioventricular block, with or without limb girdle muscular dystrophy, the most frequently identified gene is the **LMNA** encoding

Table 36.1 Most common genetic causes of dilated cardiomyopathy

Gene	Protein	Location and Function
TTN	Titin	Sarcomere (giant filament)
PKP2	Plakophilin-2	Desmosome
MYBPC3	Myosin binding protein C	Sarcomere (thick filament)
DSP	Desmoplakin	Desmosome
RyR2	Cardiac ryanodine receptor	Ca kinetics
DSC 2	Desmocolin-2	Desmosome
DSG2	Desmoglein-2	Desmosome
SCN5A	$Na_v1.5$	Inward sodium current (I_{Na})

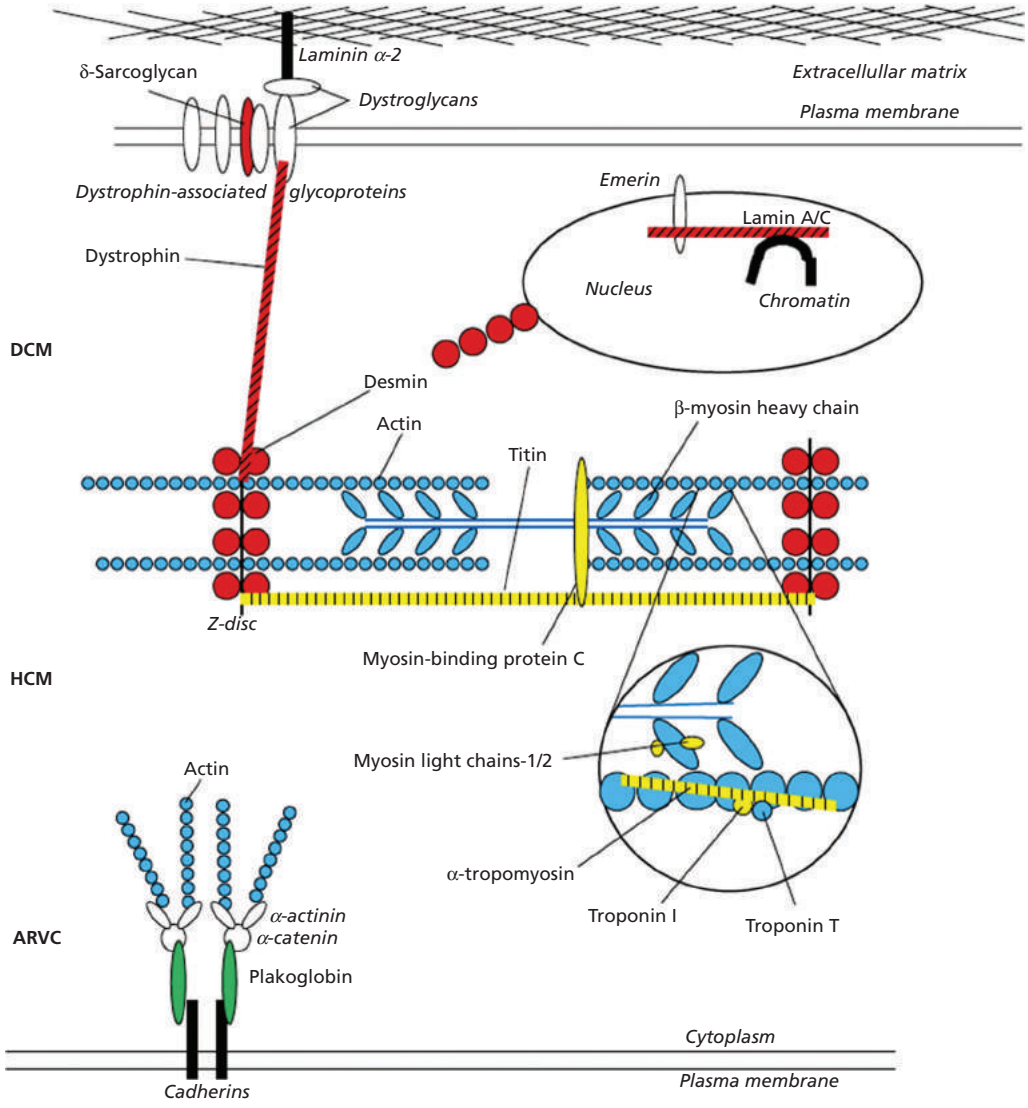

Figure 36.1 The final common pathway involved in cardiomyopathies. Cardiac myocytes are surrounded by the sarcolemma and contain myofibrils that are formed by repeating sarcomeres, the basic contractile units consisting of thin (actin, a–tropomyosin, and troponins) and thick (myosin and myosin-binding proteins) filaments. Titin is the supporting protein that extends from the Z disc (at the borders of the sarcomere in the thin filament) to the M disc (in the thick filament). Cardiac myocytes join each other at the intercalated discs that contain gap junctions (connexins), mechanical junctions (N-cadherin, catenins, vinculin), and desmosomes (desmin, desmoplakin, desmocolin, and desmoglein). As the dystrophin-associated protein complex links the basal lamina, sarcolemma, and sarcomere, mutant proteins (sarcomeric, cytosolic, or nuclear) cause dilated, hypertrophic, or a combined cardiomyopathy. Defective proteins in red cause DCM; those in yellow cause mainly HCM but may also cause DCM; those in blue cause either HOCM or DCM, and those in green cause ARVD.

Franz *et al*. Cardiomyopathies: from genetics to the prospect of treatment. *Lancet*. 2001;**358**:1627–37 with permission from Elsevier.

for lamin proteins A and C.[8] These mutations also cause Emery–Dreifuss muscular dystrophy and limb girdle muscular dystrophy (Erb's). Patients with the LMNA gene are also prone to AF and subsequently thromboembolism and ventricular arrhythmias and sudden death. **RBM20** mutation carriers with dilated cardiomyopathy also present with a fast progression of heart failure and high risk for arrhythmias.[6] Other mutations with pleiotropic cardiac manifestations such as of the **SCN5A gene** have been implicated in various arrhythmia syndromes (long QT, Brugada, idiopathic VF, conduction system disease, sick sinus syndrome, and AF).[9] Patients with **myotonic dystrophy** (type 1-Steinert's disease or type 2) due to mutations in DMPK gene also have a high risk of developing cardiac disorders such as cardiomyopathy and heart failure, conduction defects, and arrhythmias, both late and, especially, within the first years of diagnosis.[10] Mutations in the **tafazzin (TAZ) gene** are responsible for the Barth syndrome that presents in male infants (X-linked) as heart failure associated with cyclic neutropenia and cardiolipin abnormalities and mitochondrial dysfunction. The **dystrophin gene** is responsible for Duchenne and Becker muscular dystrophy and X-linked dilated cardiomyopathy that develops in young men, with rapid progression from heart failure to death due to ventricular tachycardia or ventricular failure. These patients are identified by raised amounts of the muscle isoform of serum creatine kinase. Polymorphisms in genes encoding HLA-D antigens,[11] and a single nucleotide polymorphism on chromosome 6p21,[12] have also been related to DCM susceptibility.

Mitochondrial diseases are a group of disorders caused by defects in the mitochondrial respiratory chain that impair oxidative phosphorylation. Therefore, organ systems that rely on aerobic metabolism are primarily affected. Myopathy, external ophthalmoplegia, and diabetes are the most common findings, and these patients are at risk of cardiac events predicted by intraventricular conduction block, ventricular ectopy and LV hypertrophy.[13] Respiratory gas profiles indicative of severe and premature lactic acidaemia can be the only diagnostic clue. Although once considered rare, these disorders are being increasingly recognized with a prevalence of up to 13.1 per 100 000 births based on some studies.[14]

Infectious causes

Myocarditis is characterized by pathological inflammation of the myocardium, leading to chronic heart failure in a substantial number of patients younger than 40 years. Bacterial, fungal, parasitic, rickettsial, and spirochetal infections may be implicated, but the more common cause in the western world is **viral** infection (see Chapter 45). Although the causative relationship between viral infection and myocarditis is not unequivocally established, identification of the causative virus with polymerase chain reaction (PCR) indicates that some cases of dilated cardiomyopathy are the result of chronic myocarditis and subsequent cardiac injury either due to autoimmune reactions or direct viral tissue injury. Viral persistence in the myocardium has been associated with progressive cardiac dysfunction.[15] The most common viruses are parvovirus B19, adenovirus, coxsackie B, and other enteroviruses.[15,16] Presentation of disease can vary, ranging from minor symptoms of malaise to acute heart failure. **Chagas' cardiomyopathy**, caused by the protozoan *Trypanosoma cruzi*, remains the leading cause of chronic systolic heart failure in endemic areas. Dilated cardiomyopathy is the most important and severe manifestation of human chronic Chagas disease and is characterized by heart failure, ventricular arrhythmias, heart blocks, thromboembolic phenomena, and sudden death.[17] The annual incidence of Chagas cardiomyopathy is 1.85% and is driven primarily by mild cardiomyopathy.[18] Approximately 25% of asymptomatic, *T cruzi*-seropositive persons will develop cardiomyopathy within the next 10 years.[18]

Autoimmunity

Diagnosis for both viral and non-viral causes is based on histological, immunological, and immunohistochemical criteria for endomyocardial biopsy samples. Autoimmune-mediated chronic myocarditis is characterized by autoantibodies to cardiac myosin and other heart antigens.[1] Whether patients develop heart disease because they possess harmful antibodies against this receptor or whether they develop these antibodies as a result of cardiac tissue injury remains unclear. However, circulating cardiac autoantibodies are identified in dilated cardiomyopathy and myocarditis patients at a higher frequency than in patients with non-inflammatory heart disease. Furthermore, in healthy relatives of dilated cardiomyopathy patients, serum antiheart autoantibodies are an independent predictor for development of this disease.[19]

Cytotoxicity

Chronic alcohol abuse (more than 3 units a day) is one of the most important causes of dilated cardiomyopathy in developed countries.[20,21] The exact mechanism is not known: direct toxicity and increased cellular apoptosis, acetaldehyde-mediated cardiac calcium regulation disruption, and neurohormonal activation have been proposed. A genetic background may also coexist. Recent data indicate that the outcome is worse than in idiopathic dilated cardiomyopathy, and the estimated 4-year mortality rate approaches 50% in patients without complete abstinence after diagnosis.[21] The cardiac toxicity of drugs, such as **cocaine**, **anthracyclines (doxorubicin and daunorubicin)**, **trastuzumab**, and **anti-vascular endothelial growth factor (VEGF)** chemotherapy agents (bevacizumab, sorafenib, sunitinib, pazopanib), is discussed in Chapter 32 on CCF.

HIV infection, hyper- and hypothyroidism, infiltrative disease, such as **haemochromatosis, rheumatological disease, mitochondrial dysfunction**, and **metabolic storage diseases**, are more rare causes.

Despite complete evaluation, including history, physical examination, echocardiography, coronary angiography, and endomyocardial biopsy, approximately 50% of patients with dilated cardiomyopathy have no aetiology identified.[22]

Peripartum cardiomyopathy and **tachycardiomyopathies** and **stress-induced cardiomyopathy** are discussed in relevant chapters.

Presentation

Patients present with **SOBOE** and **fatigue** or signs of **overt heart failure**. Signs and symptoms that raise suspicion of specific diagnoses are presented in Tables 32.1 to 32.4 of Chapter 32.

Physical examination

It may be unremarkable or reveal the signs of heart failure (see Chapter 32 on CHF).

Investigations

Laboratory tests

Haemoglobin, WBC, serum iron and ferritin, liver, renal, and thyroid function tests, and serum electrolytes should be taken at initial assessment. In cases of suspicion of underlying disease, specific tests are obtained.[23]

Electrocardiography No ECG abnormalities are specific for DCM (Table 36.2). First- or second-degree AV block, intraventricular block, ST–T wave changes, Q waves, atrial fibrillation, or ventricular arrhythmias may be seen. New-onset LBBB is associated with an increased risk of all-cause mortality.[24] New ventricular arrhythmias or second-degree or third-degree heart block in patients with apparently chronic dilated cardiomyopathy suggests sarcoidosis, muscular or myotonic dystrophy, or LMNA disease. AF may also be seen early in patients with the LMNA gene. Monomorphic sustained VT is due to bundle branch reentry but is rare and also suggests sarcoidosis, Chagas' disease, or LV-dominant arrhythmogenic cardiomyopathy.

Echocardiography The left ventricle is dilated and more spherical than usual due to raised wall stress, and systolic function is depressed with or without mitral regurgitation (Table 36.3). Usually, contractility is globally reduced without segmental abnormalities. Additionally, pericardial effusion (especially in myocarditis) and signs of right heart failure may be present.

MRI provides the most accurate estimate of ventricular structure and function and allows detection of inflammation and scarring (see Chapter 32 on CHF).

Table 36.2 Electrocardiographic abnormalities that suggest specific diagnoses

Finding	Specific diseases to be considered
AV block	Laminopathy
	Emery Dreifuss 1
	Myocarditis, particularly *Trypanosoma cruzi*, diphtheria and Lyme disease
	Sarcoidosis
	Desminopathy
Low P wave amplitude	Myotonic dystrophy
Atrial standstill	Emery Dreifuss 1 and 2
'Posterolateral infarction'	Emery Dreifuss 1 and 2
	Dystrophin-related cardiomyopathy
	Limb-girdle muscular dystrophy
	Sarcoidosis
Low QRS voltage + 'atypical RBBB'	ARVC with biventricular involvement
Extremely low QRS amplitude	PLN mutation (very rare)

Rapezzi C, *et al*. Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2013;**34**:1448–58 with permission from Oxford University Press.

Combined 18F-fluorodeoxyglucose (FDG) PET-CT is useful to rule out sarcoidosis.

Endomyocardial biopsy is controversial. It can be used to distinguish between disease processes that need alternative treatment strategies, such as storage diseases, sarcoidosis, and haemochromatosis (see Chapter 32 on CHF). It is reasonable in patients with new-onset cardiomyopathy and fulminant heart failure who may benefit from an early diagnosis. Usually, however, microscopic examination reveals areas of interstitial and perivascular fibrosis and sometimes areas

Table 36.3 Echocardiographic clues to diagnoses

Finding	Specific diseases to be considered
LV non-compaction	Genetic DCM (more frequently sarcomeric mutations)
Postero-lateral akinesia/dyskinesia	Dystrophin-related cardiomyopathy
Mid (absent) dilatation + akinetic/dyskinetic segments with non-coronary distribution	Myocarditis
	Sarcoidosis

Rapezzi C, *et al*. Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2013;**34**:1448–58 with permission from Oxford University Press.

Table 36.4 ESC 2015 GL on VA and SCD. Risk stratification and management of patients with dilated cardiomyopathy

Optimal medical therapy (ACE inhibitors, beta-blockers and MRA) to reduce the risk of sudden death and progressive HF.	I-A
Prompt identification and treatment of arrhythmogenic factors (e.g. pro-arrhythmic drugs, hypokalaemia) and co-morbidities (e.g. thyroid disease).	I-C
Coronary angiography in intermediate risk of CAD and new onset VA.	I-B
ICD[a] in haemodynamically not tolerated VT/VF.	I-A
ICD[a] in symptomatic HF (NYHA class II–III) and EF ≤35% despite ≥3 months of treatment with optimal pharmacological therapy.	I-B
Catheter ablation in bundle branch re-entry ventricular tachycardia refractory to medical therapy.	I-B
ICD in confirmed disease-causing LMNA mutation and clinical risk factors.[b]	IIa-B
Amiodarone in recurrent ICD appropriate shocks in spite of optimal device programming.	IIa-C
Catheter ablation in VA not caused by bundle branch re-entry refractory to medical therapy.	IIb-C
Invasive EPS with PES for risk stratification of SCD.	IIb-B
Amiodarone is not recommended for the treatment of asymptomatic NSVT.	III-A
Use of sodium channel blockers and dronedarone to treat VA is not recommended.	III-A

DCM, dilated cardiomyopathy; EPS, electrophysiological study; MRA, mineralocorticoid receptor antagonists; NSVT, non-sustained ventricular tachycardia.
a: expected survival >1 year, with good functional status.
b: Risk factors in patients with a confirmed LMNA mutation: NSVT during ambulatory electrocardiogram monitoring, LVEF <45% at first evaluation, male sex and non-missense mutations (insertion, deletion, truncations or mutations affecting splicing)
ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J. 2015;**36**:2793–2867 with permission from Oxford University Press.

of necrosis and cellular infiltrate. Myocardial fibrosis is the presumed substrate of VF in DCM. Myocardial biopsy for electron microscopic detection of myofilament changes in biopsy specimens may also be useful in determining the prognosis of DCM patients presenting initially as decompensated heart failure, since they are strongly associated with mortality and HF recurrence, regardless of the cause.[25]

Electrophysiology study is indicated in patients with sustained palpitations, wide-QRS-complex tachycardia, presyncope, or syncope, and to diagnose bundle-branch reentrant tachycardia and to guide ablation (ACCF/AHA/HRS 2013 GL on Device therapy, I-C).

Additionally, testing for secondary or specific causes that mimic dilated cardiomyopathy is suggested–with clinical suspicion of ***haemochromatosis, sleep apnoea, HIV infection, rheumatological disease, storage diseases, or phaeochromocytoma***. The diagnosis of ***Chagas' disease*** is generally based on serologic testing for IgG antibodies to *T. cruzi* antigens, but no one of the available assays (ELISA, immunofluorescence assay, and haemagglutination assay) has adequate sensitivity and specificity for the diagnosis. Two tests, in which different antigens or techniques are used, are required to make the diagnosis; when the results are discordant, additional testing must be performed.[26]

Risk stratification

Risk stratification of patients with DCM is discussed in Chapter 32 as well as in Table 36.4. The main risk stratifier is LVEF. As in other primary myocardial disorders, programmed ventricular stimulation has no role in predicting SCD, and the independent predictive ability of NSVT is not established.[27] Cardiac magnetic resonance may be a predictor of SCD by means of detecting myocardial fibrosis.[28] Right ventricular systolic dysfunction as assessed by cardiac magnetic resonance is also an independent and powerful prognostic factor.[29]

Genetic counselling

Familial dilated cardiomyopathy demonstrates incomplete penetrance (i.e. not all mutations carriers are affected by the disease), with variable phenotypic expression, and significant locus and allelic heterogeneity, making genetic diagnosis complex. For pure dilated cardiomyopathy the diagnostic yield of **genetic testing** is 20%.

Relatives of patients with DCM should undergo clinical examination, ECG, and echocardiographic screening, and, when a highly positive family history is present, referral to a cardiovascular genetics centre for genetic testing is indicated. Recent developments on TTN truncating mutations

Table 36.5 Genetic testing for DCM

HRS/EHRA 2011 statement on genetic testing. State of genetic testing for dilated cardiomyopathy	
Comprehensive or targeted (LMNA and SCN5A) DCM genetic testing for patients with DCM and significant cardiac conduction disease (i.e. first-, second-, or third-degree heart block) and/or a family history of premature unexpected sudden death.	I
Mutation-specific genetic testing for family members and appropriate relatives following the identification of a DCM causative mutation in the index case.	I
Genetic testing for patients with familial DCM to confirm the diagnosis, to recognize those who are at highest risk of arrhythmia and syndromic features, to facilitate cascade screening within the family, and to help with family planning.	IIa

ACCF/AHA 2013 GL on Heart failure. Screening of family members and genetic testing in patients with idiopathic or familial DCM		
	Screening for family members	**Genetic testing**
Familial DCM	First-degree relatives not known to be affected should undergo periodic, serial echocardiographic screening with assessment of LV function and size. Frequency of screening is uncertain, but every 3–5 y is reasonable.	Genetic testing may be considered in conjunction with genetic counselling
Idiopathic DCM	Patients should inform first-degree relatives of their diagnosis. Relatives should update their clinicians and discuss whether they should undergo screening by echocardiography.	The utility of genetic testing in this setting remains uncertain Yield of genetic testing may be higher in patients with significant cardiac conduction disease and/or a family history of premature sudden cardiac death.

HRS/EHRA Expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Europace*, 2011;**13**:1077–1109 by permission of Oxford University Press.
ACCF/AHA 2013 Guideline for the management of heart failure. *J Am Coll Cardiol*. 2013;**62**:e147–e239, with permission from Elsevier.

are exciting in this respect.[5] In the presence of premature conduction disturbances and ventricular arrhythmias, screening for mutations in the SCN5A or LMNA genes may be useful. The HRS/EHRA recommendations are presented in Table 36.5.

Therapy

Treatment of heart failure has been described in the section on Heart failure. Treatment of myocarditis is described in Chapter 44. Immunosuppresion with steroids and azathioprine may be useful only in dilated cardiomyopathy patients with evidence of HLA upregulation on biopsy samples or virus-negative myocarditis and chronic inflammatory cardiomyopathy.[30,31] Intravenous immunoglobulin is not effective in recent-onset dilated cardiomyopathy.[32] In chronic dilated cardiomyopathy and persistent viral genomes, treatment with interferon resulted in the elimination of the viral genomes and improved left ventricular function.[33] Immunoadsorption with subsequent immunoglobulin G substitution is another possibility for patients with cardiodepressant autoantibodies detected in myocardial biopsy specimens.[34]

Recommendations for the management of arrhythmias are presented in Table 36.4. Independent risk factors for malignant arrhythmias in lamin A/C mutation carriers are NSVT, LVEF <45% at the first clinical contact, male sex, and non-missense mutations (ins-del/truncating or mutations affecting splicing).[35,36] Patients with muscular dystrophies should be closely followed for consideration of the need of pacing or ICD. Benznidazole 150 mg bd for 60 days is the antiparasitic treatment of choice for Chagas' disease.[37] Beta blockers are avoided in cocaine-related cardiomyopathy (unopposed alpha receptors), and benzodiazepines are used to blunt adrenergic excess in cocaine-associated heart failure.[20] Left ventricular volume procedures (such as the Batista or Dor) have not offered improved survival whereas percutaneous mitral annuloplasty with new devices for functional MR is being studied.[38] Gene and stem cell therapy are also under investigation. Indications for ICD and cardiac resynchronization pacing (CRT) are presented in Chapters 32 and 56. Although meta-analyses have indicated potential benefit, no single trial has documented improved survival with primary ICD implantation in dilated, as opposed to ischaemic, cardiomyopathy (see Chapter 69). ICD might therefore be considered in this setting (ACCF/AHA/HRS 2012 GL on devices, IIb-C). ICD is clearly indicated in patients with sustained VT/VF (ACCF/AHA 2012 GL on Devices, I-C). It may also be indicated in patients with unexplained syncope and significant LV dysfunction (ACCF/AHA 2012 GL on Devices, IIa-B).

Prognosis

Prognosis is variable, depending on the cause of DCM, with an average annual mortality of 10–30%, which, however, becomes consistently lower with time (5-year mortality at 20%), and especially during the last decades.[39,40] SCD accounts for, at least, 30% of the overall mortality in DCM.[41] In a nationwide study in Denmark, a family history of premature cardiomyopathy death was associated with an increase in risk of clinically diagnosed cardiomyopathy ranging from 6- to 400-fold, and a 3- to 7-fold increase in risk of ventricular arrhythmia.[42] Approximately 30% of new-onset DCM cases may have substantial recovery. Patients with cardiomyopathy due to infiltrative myocardial diseases, HIV infection, or doxorubicin therapy have an especially poor prognosis.[22] Framingham data suggest that survival is worse in non-ischaemic than ischaemic cardiomyopathy,[43] although this is debatable.[22] The highest-risk period for children with dilated cardiomyopathy is in the first year after diagnosis, with death or transplantation occurring in 26% of patients, compared with ~1% per year in subsequent years. Survival is worse for subjects diagnosed before 4 weeks and after 5 years of age, those with familial cardiomyopathy, and those who failed to improve left ventricular function during follow-up.[44]

Pregnancy

It is not absolutely contraindicated any more, depending on the type of cardiomyopathy and underlying risk factors (Table 36.6).[45,46] Careful considerations to maintain normovolaemia and lumbar epidural anaesthesia are preferred. Caesarian delivery may be needed to avoid the undesirable circulatory effects of the Valsalva manoeuvre.

Table 36.6 ESC 2011 GL on CV during pregnancy

Recommendations for the management of cardiomyopathies and heart failure	
Anticoagulation in patients with intracardiac thrombus detected by imaging or with evidence of systemic embolism.	I-A
Women with HF during pregnancy should be treated according to current guidelines for non-pregnant patients, respecting contraindications for some drugs in pregnancy.	I-B
Women with DCM should be informed about the risk of deterioration of the condition during gestation and peripartum.	I-C
In patients with a past history or family history of sudden death, close surveillance with prompt investigation is recommended if symptoms of palpitations or presyncope are reported.	I-C
LMWH or vitamin K antagonists according to stage of pregnancy for patients with AF.	I-C
Delivery with beta-blocker protection in women with HCM.	IIa-C
β-blockers in all patients with HCM and more than mild LVOTO or maximal wall thickness >15mm to prevent sudden pulmonary congestion.	IIa-C
In HCM, cardioversion should be considered for persistent atrial fibrillation.	IIa-C
Due to high metabolic demands of lactation and breastfeeding, preventing lactation may be considered in post-partum cardiomyopathy (PPCM).	IIb-C
Subsequent pregnancy is not recommended if LVEF does not normalize in women with PPCM.	III-C

ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**: 3147–97 with permission from Oxford University Press.

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Chapter 37

Hypertrophic cardiomyopathy

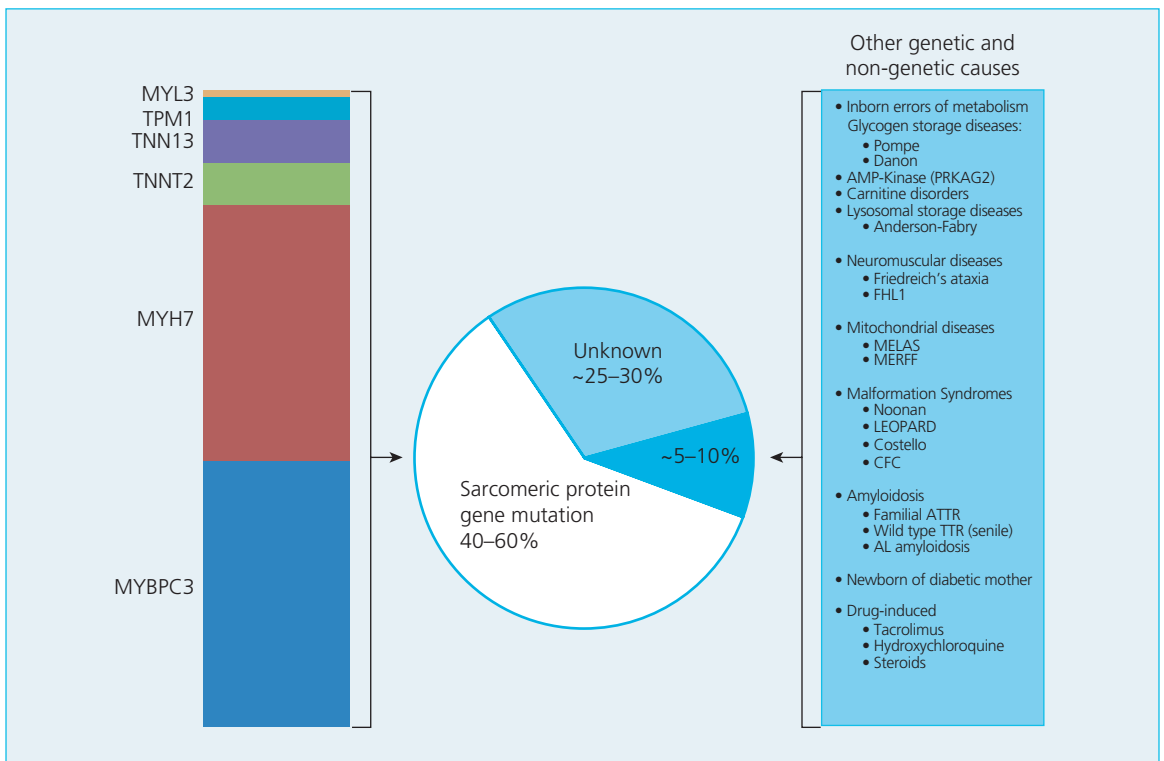
Definition

Hypertrophic cardiomyopathy (HCM) is a disease characterized by hypertrophy of the left ventricle in the absence of loading conditions and haemodynamic stress that is sufficient to account for the degree of hypertrophy.[1,2] Typically, HCM is usually recognized by maximal LV wall thickness ≥15 mm in one or more LV myocardial segments (or in children z-score >2, where z-score is the number of standard deviations from the population mean value), with wall thickness of 13 to 14 mm considered borderline.

Other typical findings such as LV wall thickness ≥15 mm due to basal septal hypertrophy with myocyte disarray, LVOT obstruction with gradient ≥30 mm Hg at rest or exercise (dynamic obstruction), and mitral valve systolic anterior motion, are common but not obligatory for the diagnosis of HCM.

There are several patterns of hypertrophy, such as asymmetrical septal hypertrophy with or without LVOT obstruction, mid-ventricular hypertrophy, apical hypertrophy, LV free wall hypertrophy, posterobasal left ventricular free wall hypertrophy, segmental hypertrophy with normal LV mass on MRI, and, rarely, concentric hypertrophy similar to that found in systemic hypertension.[3,4]

ACCF/AHA use the term HCM only for unexplained LV hypertrophy, i.e. hypertrophy that is not caused by detectable metabolic or storage disease in the context of multisystem disorders,[1] whereas ESC considers HCM as an 'umbrella' term that encompasses genetic and acquired disease (Figure 37.1).[2]



The majority of cases in adolescents and adults are caused by mutations in sarcomere protein genes. AL = amyloid light chain; ATTR = amyloidosis, transthyretin type. CFC = cardiofaciocutaneous; FHL-1 = Four and half LIM domains protein 1; LEOPARD = lentigines, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERFF = myoclonic epilepsy with ragged red fibres; MYL3 = myosin light chain 3; MYBPC3 = myosin-binding protein C, cardiac-type; MYH7 = myosin, heavy chain 7; TNN13 = troponin 1, cardiac; TNNT2 = troponin T, cardiac: TPM1 = tropomyosin 1 alpha chain; TTR = transthyretin.

Figure 37.1 ESC 2014 GL on HCM. Diverse aetiology of hypertrophic cardiomyopathy.

ACC/AHA do not consider conditions described under 'Other genetic and non-genetic causes' to represent typical HCM.

ESC 2014 Guidelines on diagnosis and management of hypertrophic cardiomyopathy, *Eur Heart J.* 2014;**35**:2733–79, with permission from Oxford University Press.

Epidemiology

HCM is the most common genetic cardiomyopathy. The prevalence of the disorder has been traditionally considered as 1 in 500 people, but it may be higher.[5] The prevalence of HCM in phenotype-negative children relatives at risk of developing HCM is 6% at 12 years follow-up.[6]

Aetiology

Sarcomeric protein gene mutations account for up to 60% of HCM cases in adults. Inheritance is autosomal dominant; every offspring has a 50% chance of developing the disease later in life (age-dependent penetrance), but with considerable heterogeneity in phenotypic expression and clinical course. Patients with new mutations (i.e. without any relatives with the disease) do exist. Familial disease is less frequent in children than in adults, with various modes of inheritance. In adults the majority of HCM cases are due to more than 1500 mutations in several genes that encode for sarcomeric or other myocyte proteins[7,8] Table 37.1 presents the most common genes implicated in HCM. Mutations in MYH7 and MYBPC3 that encode for the β-myosin heavy chain and the myosin binding protein C are responsible for 60–80% of sarcomeric protein gene mutations. Most of mutations are missence (substitution of one amino acid by another), but insertion/deletion mutations may also occur. Heterogenous expression of these mutations, as well as modifier genes and environmental factors, contribute to the characteristic diversity of HCM phenotype. The reasons for the development of hypertrophy due to sarcomeric mutations are not clear, and the same genes may be responsible for dilated, or other forms of, cardiomyopathies. Reduced contractile function and activation of various signalling pathways are speculated.

Inherited non-sarcomeric disease, such as mutations of genes encoding for other cytosolic proteins, metabolic storage diseases, and mitochondrial disease, may also result in similar cardiac hypertrophy (Figure 36.1). Although whether non-sarcomeric disease is typical HCM may be a matter of conjecture, proper differential diagnosis is important for both prognostic and therapeutic purposes. Left ventricular hypertrophy in the context of childhood neuropathy, corneal opacities, proteinuria, hearing loss, and small vascular lesions on the buttocks suggest **Fabry disease** (deficiency of a-galactosidase) that can be treated with primary enzyme replacement.[9] Other **lysosomal and glycogen storage diseases**, such as Danon disease, may also produce similar LV hypertrophy.[10] **Danon disease** (X-linked lysosome-associated membrane protein cardiomyopathy) is highly lethal and requires early recognition and referral for transplantation. **Friedreich ataxia** is an autosomal recessive neurodegenerative disease caused by a defect in the gene encoding for the mitochondrial protein frataxin. Myocardial involvement is well documented, with concentric left ventricular hypertrophy as the dominating cardiac finding. Average life expectancy in patients with cardiac involvement is considerably reduced to 29–38 years.[11] **Mitochondrial disease** includes clinical disorders that occur as a result of dysfunctional cellular oxidative phosphorylation due to defects in mitochondrial (or rarely nuclear) DNA. Symmetrical LV hypertrophy not fulfilling standard criteria for HCM and organ involvement, such as diabetes and deafness, suggests the possibility of mitochondrial DNA disease.[12] **Cardiac amyloidosis** may also result in concentric LV hypertrophy (see Chapter 38). Most cases of left ventricular hypertrophy in children are associated with congenital malformations, inherited metabolic disorders, and neuromuscular diseases.

Table 37.1 Most common genetic causes of hypertrophic cardiomyopathy

Gene	Protein	Location and function
MYH7 (30–40%)	β-myosin heavy chain	Sarcomere (thick filament)
MYBPC3 (30–40%)	Myosin binding protein C	Sarcomere (thick filament)
TNNT2 (1–7% of patients)	Cardiac troponin T	Sarcomere (thin filament)
TNNI3 (1–7% of patients)	Cardiac troponin I	Sarcomere (thin filament)
TPM1	α-tropomyosin	Sarcomere (thin filament)
MYL3	Essential myosin light chain	Sarcomere (thick filament)
TNNC1	Cardiac troponin C	Sarcomere (thin filament)
MYL2	Regulatory myosin light chain	Sarcomere (thick filament)
ACTC	Cardiac actin	Sarcomere (thin filament)
ACTN2	a-actinin 2	Z disk
MYOZ2	Myozenin 2	Z disk

Pathophysiology

Left ventricular hypertrophy is typically characterized by **myocyte disarray**, with cardiomyocytes varying in size and shape and forming abnormal intercellular connections, usually with expansion of the interstitial compartment and areas of replacement with fibrosis (Figure 37.2).[13] There is also small vessel disease, in which intramural coronary vessels are apparently narrowed by medial hypertrophy.[13] Myocyte disarray is characteristic of, but not confined to, HCM. It can be seen in patients with other diseases, such as Noonan's syndrome, Friedreich's ataxia, and congenital disorders.

Systolic septal bulging into the LVOT and hyperdynamic LV contraction (causing the Venturi effect) contribute to the creation of a variable **LVOT gradient** that increases with decreased afterload. Approximately 25% of patients have dynamic LVOT obstruction caused by contact between the anterior or, less commonly, the posterior mitral valve leaflet and the interventricular septum during systole **(systolic anterior motion—SAM)**. Severe LV hypertrophy results in increased chamber stiffness and diastolic dysfunction. Intrinsic abnormalities of the mitral apparatus, including fibrous leaflet thickening, prolapse, and malposition of the anterior papillary muscle, occur in an estimated 20% of patients with HCM and contribute to the obstruction. MRI may also detect mitral leaflet elongation that is independent of other disease variables.[14] Dyspnoea occurs with exertion and may result from limitation of cardiac output due to the low end-diastolic volume of a non-compliant LV, high pulmonary venous pressure due to diastolic dysfunction, and mitral regurgitation. Angina may result from an inability of the narrowed coronary microcirculation to supply the hypertrophied myocardium in the context of high myocardial oxygen demand associated with elevated LV systolic pressure. Atrial fibrillation or flutter is associated with a worsening of symptoms because these patients are dependent on atrial transport due to the concomitant diastolic dysfunction, an important pathophysiological feature of HCM. Presyncopal episodes and syncope are due to LVOT obstruction, myocardial ischaemia, inappropriate systemic vasodilation, and ventricular arrhythmias. Myocardial fibrosis and especially disarray are most probably the arrhythmogenic substrates. Abnormal blood pressure response during exercise, defined as fall or failure to rise >20 mmHg, may be seen in up to 25% of patients with HCM and is attributed to autonomic dysfunction. Approximately 10% of patients with HCM will develop end-stage morphology, with LV dilation and wall thinning, that is associated with worse outcome.[15]

Presentation and natural history

Patients may be asymptomatic or present with dyspnoea and angina, with a characteristic day-to-day variation in the activity needed to cause symptoms. Presyncope or syncope may also be the presenting symptom and is a marker for risk of sudden death.

There are three relatively discrete, but not mutually exclusive, pathways of clinical progression:[1]

1. **Sudden cardiac death (SCD)** due to unpredictable ventricular tachyarrhythmias, most commonly in young asymptomatic patients <35 years of age (including competitive athletes). The estimated rate of SCD is 1% per year in the overall HCM population but probably higher in those at greatest risk. Sex is not a major determinant of the risk of SCD. Most events, even in athletes, are not related to strenuous exercise.
2. **Heart failure** characterized by exertional dyspnoea (with or without chest pain) that may be progressive, despite preserved systolic function and sinus rhythm, or, in a small proportion of patients, heart failure may progress to the end stage, with LV remodelling and systolic dysfunction caused by extensive myocardial scarring.
3. **AF**, either paroxysmal or chronic, is also associated with various degrees of heart failure and an increased risk of systemic thromboembolism and both fatal and non-fatal stroke.
4. Patients surviving into the seventh decade with this genetic disease are at low risk for HCM-related mortality and morbidity, including sudden death (even when conventional risk factors are present).[16]
5. Thin filament mutations are associated with increased likelihood of advanced LV dysfunction and heart failure compared with thick-filament disease, whereas arrhythmic risk is the same.[17]

Signs and symptoms that raise suspicion of specific diagnoses are presented in Table 35.1 of Chapter 35.

Physical examination

Examination may be unremarkable or reveal:

Bisferiens pulse with dynamic obstruction.

Prominent **a wave** in JVP.

Systolic murmur at left sternal edge. It is distinguished from all other systolic murmurs (apart from this of mitral valve prolapse) by an increase in intensity with the Valsalva manoeuvre and during squatting-to-standing and by a decrease in intensity during standing-to-squatting action, passive leg elevation, and handgrip.

Pansystolic murmur of MR.

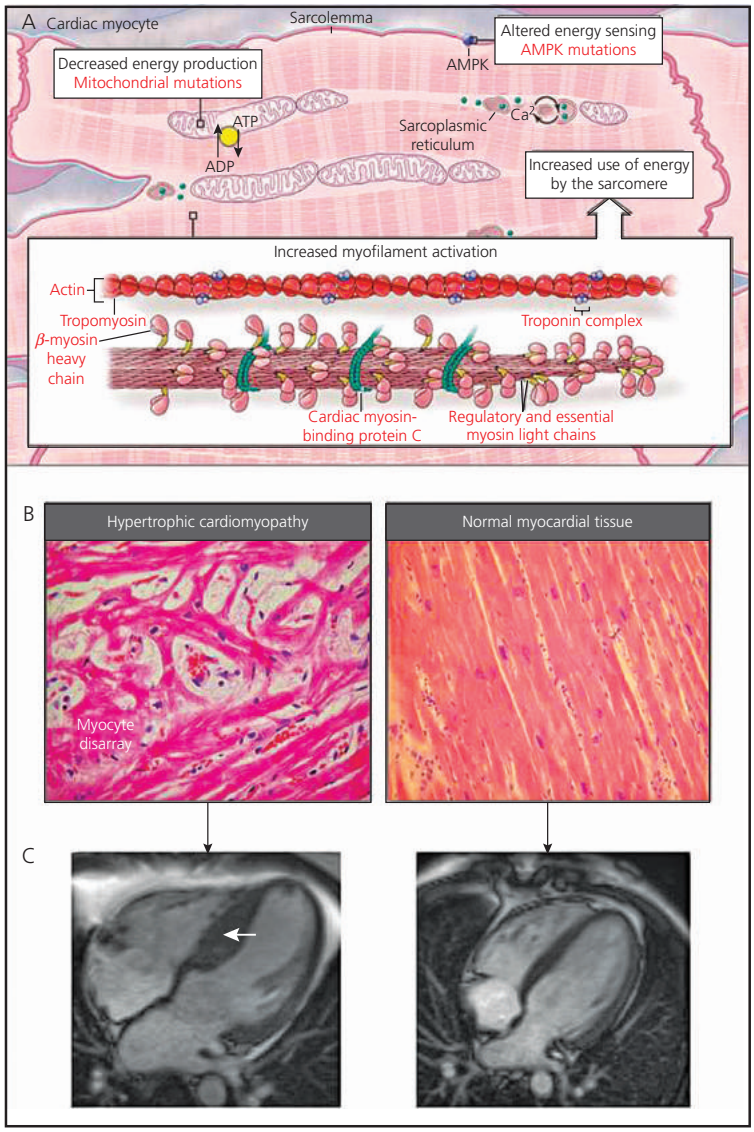


Figure 37.2 Pathogenesis of hypertrophic cardiomyopathy.
In hypertrophic cardiomyopathy, mutations in sarcomeric proteins generally increase myofilament activation and result in myocyte hypercontractility and excessive energy use (A). Alterations in myocardial energy status can also result from primary mutations affecting myocardial energy generation (e.g. mitochondrial transfer RNA mutations). These mitochondrial defects and mutations in the cardiac energy-sensing apparatus (e.g. AMP-activated protein kinase [AMPK]) recapitulate a hypertrophic cardiomyopathy-like phenotype. Alterations in myocardial energetics and in calcium handling combined with stimulation of signalling pathways (e.g. the Janus-associated kinase–signal transducers and activators of transcription [JAK-STAT] signalling pathway) diminish myocyte relaxation and promote myocyte growth, with aberrant tissue architecture (i.e. myofibrillar disarray and myocardial fibrosis) (B, haematoxylin and eosin). In patients with hypertrophic cardiomyopathy, these changes often result in gross hypertrophy, with especially prominent septal hypertrophy (arrow) as compared with the normal heart, as shown on the cardiac magnetic resonance images (C).
Watkins H, *et al*. Inherited cardiomyopathies. *N Engl J Med*. 2011;**364**:1643–56 with permission from Massachusetts Medical Society.

Investigations

Laboratory tests Liver and renal function tests and CK are mandatory. BNP, an independent predictor of survival in HCM, can identify patients who have poor cardiopulmonary exercise tolerance.[18] Other tests are indicated in Table 37.2. Abnormalities in tests that may suggest specific cardiomyopathies are presented in Table 35.2 of Chapter 35.

A **12-lead ECG** is abnormal in 75–95% of patients, and may show left atrial enlargement, repolarization abnormalities, and inferolateral Q waves. The PR may be short, and giant T waves may be present (apical hypertrophy—Japanese variant). QT prolongation (>480

ms) may be seen in 25% of patients.[19] ECG is essential (Table 37.3) and should be repeated every year once the diagnosis has been established to evaluate for asymptomatic changes in conduction or rhythm.

Holter monitoring is useful to detect paroxysmal AF or non-sustained VT, and should be repeated every 1–2 years. Frequent and prolonged (>10 beats) episodes of NSVT are a marker of sudden death.

Echocardiography LV wall thickness >15 mm in any segment could be diagnostic. In first-degree relatives of patients with unequivocal disease, LV ≥13 mm also indicates HCM. Patients with LVOT obstruction ≥30 mmHg at rest are at greater risk for heart failure or death in comparison with patients without obstruction.[20] LVOT obstruction is usually associated with variable degrees of mitral regurgitation, which, when due to SAM, is usually directed posteriorly, unless structural abnormalities of the mitral valve are present. Thickening of the mitral leaflets and anomalous papillary muscle origin may coexist and contribute to obstruction. LVOT flow gradient without SAM suggests other valvular or subvalvular causes of obstruction. Transthoracic echo is recommended in the initial evaluation of all patients with suspected HCM (Table 37.4) and should be repeated every 1–2 years. If the resting instantaneous peak LVOT gradient is ≤50 mmHg, it is reasonable to perform **exercise echocardiography** for detection of exercise-induced dynamic LVOT obstruction. Diastolic dysfunction is frequent and can dominate the clinical presentation to resemble restrictive cardiomyopathy.[1] **Tissue Doppler imaging** may identify mutation carriers prior to development of hypertrophy by detecting reduced long axis systolic and early diastolic velocities and velocity gradients.[21]

Transoesophageal echocardiography is useful if transthoracic echo is inconclusive for clinical decision-making about medical therapy and in situations, such as planning for myectomy, exclusion of subaortic membrane, mitral regurgitation secondary to structural abnormalities of the mitral valve apparatus, or in assessment for the feasibility of alcohol septal ablation. It is essential for intraoperative guidance of septal myectomy, and for the intraprocedural guidance of alcohol septal ablation with intracoronary contrast injection in the septal perforator(s).

Exercise testing with simultaneous respiratory gas analysis is useful for demonstration of exercise-induced obstruction, assessment of functional capacity and risk stratification, and for the differential diagnosis of unexplained hypertrophy (Table 37.5). Up to 25% of patients with HCM have an abnormal blood pressure response during upright exercise (systolic blood pressure fails to rise >20–25 mmHg from baseline or falls), either due to abnormal vasodilatation in non-exercising muscles or impaired cardiac output, and a reduction in peak oxygen consumption compared with healthy controls. However, respiratory gas profiles indicative of severe and premature lactic acidaemia can be the only clue to a diagnosis of mitochondrial myopathy.[12]

Cardiac magnetic resonance can identify focal hypertrophy as well as hypertrophy particularly in the anterolateral free wall and apex, which is not well appreciated by two-dimensional echocardiography (Table 37.6). It is essential in controversial cases. CMR can also provide detailed characterization of other myocardial structures, such as the papillary muscles, and enables an accurate assessment of total LV mass and extent of fibrosis. Extensive fibrosis assessed by late gadolinium enhancement measured by quantitative contrast enhanced CMR has been reported as a marker of increased risk for sudden cardiac death,[22,23] although its independent predictive ability regardless of LVEF is not established in all studies.[24] Apical-basal muscle bundles are a unique myocardial structure commonly detected in HCM by CMR.[25]

Myocardial perfusion studies are indicated only in the presence of chest pain or high likelihood of coronary artery disease, not as a routine test for detection of silent coronary disease (Table 37.7).

Coronary angiography is indicated in the presence of chest pain in patients with a high likelihood of coronary artery disease (Table 37.7). Angina may also be caused by myocardial bridging that is common in HCM[26] or supply/demand mismatch due to the hypertrophy.

Programmed ventricular stimulation has no role in risk stratification (Table 37.8, see also ICD therapy).[1]

Other potentially necessary tests are presented in Table 37.9.

Table 37.2 Recommended laboratory tests in adult patients with hypertrophic cardiomyopathy

Test	Comment
Haemoglobin	• Anaemia exacerbates chest pain and dyspnoea and should be excluded whenever there is a change in symptoms.
Renal function	• Renal function may be impaired in patients with severe left ventricular impairment.
	• Impaired GFR and proteinuria may be seen in amyloidosis, Anderson–Fabry disease and mitochondrial DNA disorders.
Liver transaminases	• Liver tests may be abnormal in mitochondrial disorders, Danon disease and β-oxidation defects.
Creatine phosphokinase	• Serum creatine phosphokinase is raised in metabolic disorders such as Danon and mitochondrial disease.
Plasma/leucocyte alpha galactosidase A (in men aged >30 years)	• Low (<10% normal values) or undetectable plasma and leucocyte alpha galactosidase is present in male patients with Anderson–Fabry disease.* • Plasma and leucocyte enzyme levels are often within the normal range in affected females and so genetic testing may be considered if clinically suspected.
Serum immunoglobulin free light chain assay, serum and urine immunofixation. and urine electrophoresis	• Should be considered if amyloidosis is suspected from history and non-invasive tests. Confirmation of the diagnosis usually requires histological analysis.
Fasting glucose	• May be elevated in some mitochondrial DNA disorders • May be low in fatty acid and carnitine disorders.
Brain natriuretic peptide and troponin T	• Elevated plasma levels of BNP, NT-proBNP, and troponin T are associated with higher risk of cardiovascular events, heart failure and death.
Thyroid function tests	• Should be measured at diagnosis and monitored every 6 months in patients treated with amiodarone.
Plasma lactate	• Elevated in some patients with mitochondrial disorders.

BNP = brain natriuretic peptide; DNA = deoxyribonucleic acid; GFR = glomerular filtration rate; NT-proBNP = N-terminal pro brain natriuretic peptide.
* Pseudo-deficiency may be seen in some genetic variants such as D313Y
ESC 2014 Guidelines on diagnosis and management of hypertrophic cardiomyopathy, *Eur Heart J*. 2014;**35**:2733–79, with permission from Oxford University Press.

Table 37.3 Electrocardiography

ACCF/AHA 2011 GL on HCM	
Electrocardiography	
12-lead ECG in the initial evaluation of patients with HCM.	I-C
24-hour ambulatory (Holter) electrocardiographic monitoring to detect ventricular tachycardia (VT) and identify patients who may be candidates for ICD therapy	I-B
24-hour Holter or event recording in patients who develop palpitations or lightheadedness	I-B
Repeat ECG when there is worsening of symptoms.	I-C
12-lead ECG every 12 to 18 months for adolescent first-degree relatives of patients with HCM who have no evidence of hypertrophy on echocardiography.	I-C
12-lead ECG for first-degree relatives of patients with HCM.	I-C
24-hour Holter, repeated every 1 to 2 years, in patients who have no previous evidence of VT to identify patients who may be candidates for ICD therapy	IIa-C
Annual 12-lead ECG in patients with known HCM who are clinically stable to evaluate for asymptomatic changes in conduction or rhythm (i.e., AF).	IIa-C
24-hour Holter in adults with HCM to assess for asymptomatic paroxysmal AF/atrial flutter.	IIb-C

(*continued*)

Table 37.3 Continued

ESC 2014 GL on HCM	
Electrocardiography	
Standard 12-lead ECG in suspected HCM	I-B
48-hour ambulatory ECG monitoring at initial clinical assessment, to detect atrial and ventricular arrhythmia.	I-B
Palpitations	
48-hour ambulatory ECG monitoring for frequent or sustained palpitations	I-C
Implantable loop recorder for frequent palpitations, when no cause is identified following prolonged ECG monitoring.	IIb-C
Unexplained syncope	
12-lead ECG, upright exercise test, resting and exercise 2D and Doppler echocardiography, and 48-hour ambulatory ECG monitoring	I-C
Implantable loop recorder in patients with recurrent episodes of syncope, who are at low risk of SCD.	IIa-C

Electrocardiographic abnormalities suggesting specific diagnoses or morphological variants

Finding	**Comment**
Short PR interval/pre-excitation	Pre-excitation is a common feature of storage diseases (Pompe, PRKAG2, and Danon) and mitochondrial disorders (MELAS, MERFF). A short PR interval without pre-excitation is seen in Anderson-Fabry disease.
AV block	Progressive atrioventricular conduction delay is common in mitochondrial disorders, some storage diseases (including Anderson-Fabry disease), amyloidosis, desminopathies and in patients with PRKAG2 mutations.
Extreme LVH (Sokolow score ≥50)	Extremely large QRS voltage is typical of storage diseases such as Pompe and Danon disease, but can be caused by pre-excitation alone.
Low QRS voltage (or normal voltages despite increased LV wall thickness)	Low QRS voltage in the absence of pericardial effusion, obesity and lung disease is rare in HCM (limited to cases with end-stage evolution) but is found in up to 50% of patients with AL amyloidosis and 20% with TTR amyloidosis. Differential diagnosis between HCM and cardiac amyloidosis is aided by measuring the ratio between QRS voltages and LV wall thickness.
Extreme superior ("North West") QRS axis deviation	Seen in patients with Noonan syndrome who have severe basal hypertrophy extending into the RV outflow tract.
Giant negative T wave inversion (>10 mm)	Giant negative T wave inversion in the precordial and/or inferolateral leads suggests involvement of the LV apex.
Abnormal Q waves ≥40 ms in duration and/or ≥25%of the R wave in depth and/or ≥3 mm in depth in at least two contiguous leads except aVR	Abnormally deep Q waves in the inferolateral leads, usually with a positive T wave, are associated with an asymmetrical distribution of LVH. Q waves of abnormal duration (≥40 ms) are associated with areas of replacement with fibrosis.
Coved ST segment elevation in lateral chest leads	Some patients with apical or distal hypertrophy develop small apical aneurysms, sometimes associated with myocardial scarring. These may only be detectable on CMR, ventriculography or contrast echo, and are occasionally associated with ST elevation in the lateral chest leads.

AV = atrioventicular,: AL = amyloid light chain; CMR = cardiac magnetic resonance; HCM = hypertrophic cardiomyopathy; LV = left ventricular; LVH = left ventricular hypertrophy; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERFF = myoclonic epilepsy with ragged red fibres; PRKAG2 = gamma-2 subunit of the adenosine monophosphate-activated protein kinase; RV = right ventricular; TTR = transthyretin.
ACCF/AHA 2011 Guidelines for the diagnosis and treatment of hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2011;**58**:2703–38 with permission from Elsevier.
ESC 2014 Guidelines on diagnosis and management of hypertrophic cardiomyopathy, *Eur Heart J*. 2014;**35**:2733–79, with permission from Oxford University Press.

Table 37.4 Echocardiography

ACCF/AHA 2011 GL on HCM	
Echocardiography	
Transthoracic echocardiogram (TTE) in the initial evaluation of all patients with suspected HCM	I-B
TTE for family members of patients with HCM unless the family member is genotype negative in a family with known definitive mutations	I-B
Periodic (12 to 18 months) TTE for children of patients with HCM, starting by age 12 years or earlier if a growth spurt or signs of puberty are evident and/or when there are plans for engaging in intense competitive sports or there is a family history of SCD	I-C
Repeat TTE for patients with HCM with a change in clinical status or new cardiovascular event	I-B
Transoesophageal echocardiogram (TOE) for the intraoperative guidance of surgical myectomy	I-B
TTE or TOE with intracoronary contrast injection of septal perforator(s) is recommended for the intraprocedural guidance of alcohol septal ablation	I-B
TTE to evaluate the effects of surgical myectomy or alcohol septal ablation for obstructive HCM	I-C
TTE every 1 to 2 years in symptomatically stable patients with HCM to assess myocardial hypertrophy, dynamic obstruction, and myocardial function	IIa-C
Exercise TTE for the detection and quantification of dynamic LVOT obstruction in the absence of resting outflow tract obstruction in patients with HCM	IIa-B
TOE if TTE is inconclusive about medical therapy and in planning for myectomy, exclusion of subaortic membrane or mitral regurgitation secondary to structural abnormalities of the mitral valve apparatus, or in assessment for alcohol septal ablation	IIa-C
TTE with intravenous contrast agent if the diagnosis of apical HCM or apical infarction or severity of hypertrophy is in doubt, particularly when other imaging modalities such as CMR are not available, not diagnostic, or are contraindicated.	IIa-C
Serial TTE for clinically unaffected patients who have a first-degree relative with HCM when genetic status is unknown. Every 12 to 18 months for children or adolescents from high-risk families and every 5 years for adult family members	IIa-C
TTE should not be performed more frequently than every 12 months in patients with HCM when it is unlikely that any changes have occurred	III-C
Routine TOE and/or contrast echocardiography is not recommended when TTE is diagnostic and/or there is no suspicion of fixed obstruction or intrinsic mitral valve pathology.	III-C
ESC 2014 GL on HCM	
Transthoracic echocardiography	
In all patients with HCM at initial evaluation 2D and Doppler echocardiography at rest and during Valsalva in the sitting and semi-supine positions-and then on standing if no gradient is provoked.	I-B
Measurement of maximum diastolic wall, using 2D short-axis views in all LV segments, from base to apex.	I-C
Comprehensive evaluation of LV diastolic function, Including pulsed Doppler of mitral valve inflow, tissue Doppler velocities at the mitral annulus, pulmonary vein flow velocities, pulmonary artery systolic pressure, and measurement of LA size and volume.	I-C
Detect provocable LVOT obstruction and exercise-induced mitral regurgitation in symptomatic patients with a resting or provoked* peak instantaneous LV outflow tract gradient <50 mm Hg, 2D and Doppler echocardiography during exercise in the standing, sitting or semi-supine position.	I-B
2D and Doppler echocardiography during exercise-in the standing, sitting or semi-supine positions when the presence of an LVOT gradient is relevant to lifestyle advice and decisions on medical treatment, in asymptomatic patients with a resting or provoked* peak instantaneous LV outflow tract gradient <50 mm Hg	IIb-C
In patients with sub-optimal images or with suspected LV apical hypertrophy or aneurysm, TTE with IV echocardiographic contrast as an alternative to CMR	IIa-C
Intracoronary contrast echocardiography in all patients undergoing septal alcohol ablation, to ensure correct localization of alcohol.	I-B
Transoesophageal echocardiography	
Perioperative TOE for septal myectomy, to confirm the mechanism of LVOT obstruction, to guide the surgical strategy, to assess post-surgical complications and to detect residual LV outflow tract obstruction.	I-C

(*continued*)

Table 37.4 Continued

TOE in patients with LVOT obstruction if the mechanism is unclear, or when assessing the mitral valve apparatus before a septal reduction procedure, or when severe mitral regurgitation, caused by intrinsic valve abnormalities, is suspected.	IIa-C
TOE with intracoronary contrast injection of the candidate septal perforator artery to guide septal alcohol ablation when transthoracic windows are insufficient for proper visualization of echo-contrast	IIa-C

Echocardiographic features that suggest specific aetiologies

Finding	Specific diseases to be considered
Increased interatrial septum thickness	Amyloidosis
Increased AV valve thickness	Amyloidosis; Anderson-Fabry disease
Increased RV free wall thickness	Amyloidosis, myocarditis, Anderson-Fabry disease, Noonan syndrome and related disorders
Mild to moderate pericardial effusion	Amyloidosis, myocarditis
Ground-glass appearance of ventricular myocardium on 2D echocardiography	Amyloidosis
Concentric LVH	Glycogen storage disease, Anderson-Fabry disease, PRKAG2 mutations
Extreme concentric LVH (wall thickness ≥30 mm)	Danon disease, Pompe disease
Global LV hypokinesia (with or without LV dilatation)	Mitochondrial disease, TTR-related amyloidosis, PRKAG2 mutations, Danon disease, myocarditis, advanced sarcomeric HCM, Anderson-Fabry disease
Right ventricular outflow tract obstruction	Noonan syndrome and associated disorders

* provocation with Valsalva, standing, or oral nitrate.
2D = two-dimensional; AV = atrioventricular; HCM = hypertrophic cardiomyopathy; LV = left ventricular; LVH = left ventricular hypertrophy; PRKAG2 = gamma-2 subunit of the adenosine monophosphate-activated protein kinase; RV = right ventricle; TTR = transthyretin.
ACCF/AHA 2011 Guidelines for the diagnosis and treatment of hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2011;**58**:2703–38 with permission from Elsevier
ESC 2014 Guidelines on diagnosis and management of hypertrophic cardiomyopathy, *Eur Heart J*. 2014;**35**:2733–79, with permission from Oxford University Press.

Table 37.5 Exercise testing

ACCF/AHA 2011 GL on HCM	
Stress testing	
Treadmill exercise testing (TET) to determine functional capacity and response to therapy	IIa-C
TET with monitoring of an ECG and blood pressure for SCD risk stratification	IIa-B
Exercise echocardiography for the detection and quantification of exercise-induced dynamic LVOT obstruction in patients without a resting peak instantaneous gradient ≥ 50 mm Hg	IIa-B
ESC 2014 GL on HCM	
Cardiopulmonary exercise testing	
Cardiopulmonary exercise testing, with simultaneous measurement of respiratory gases, in severely symptomatic patients with systolic and/or diastolic LV dysfunction evaluated for heart transplantation or mechanical support.	I-B
Cardiopulmonary exercise testing with simultaneous measurement of respiratory gases (or standard treadmill or bicycle ergometry when unavailable)	
Irrespective of symptoms to assess the severity and mechanism of exercise intolerance and change in systolic blood pressure.	IIa-B
In symptomatic patients undergoing septal alcohol ablation and septal myectomy to determine the severity of exercise limitation.	IIa-C

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ESC 2014 Guidelines on diagnosis and management of hypertrophic cardiomyopathy, *Eur Heart J*. 2014;**35**:2733–79, with permission from Oxford University Press.

Table 37.6 Cardiac magnetic resonance

ACCF/AHA 2011 GL on HCM	
CMR in suspected HCM when echocardiography is inconclusive	I-B
CMR in known HCM when additional information that may have an impact on management or decision making regarding invasive management, such as magnitude and distribution of hypertrophy or anatomy of the mitral valve apparatus or papillary muscles, is not adequately defined with echocardiography	I-B
CMR imaging to define apical hypertrophy and/or aneurysm if echocardiography is inconclusive	IIa-B
CMR imaging with assessment of late gadolinium enhancement (LGE) when SCD risk stratification is inconclusive	IIb-C
CMR in patients with LV hypertrophy and the suspicion of alternative diagnoses to HCM, including cardiac amyloidosis, Fabry disease, and genetic phenocopies such as LAMP2 cardiomyopathy	IIb-C
ESC 2014 GL on HCM	
CMR performed and interpreted by teams experienced in cardiac imaging and in the evaluation of heart muscle disease.	I-C
In the absence of contraindications, CMR with LGE in patients with suspected HCM and inadequate echocardiographic windows	I-B
CMR with LGE in patients with HCM, to assess cardiac anatomy, ventricular function, and the presence and extent of myocardial fibrosis.	IIa-B
CMR with LGE in suspected apical hypertrophy or aneurysm.	IIa-C
CMR with LGE in suspected cardiac amyloidosis.	IIa-C
CMR with LGE considered before septal alcohol ablation or myectomy.	IIb-C

LGE = late gadolinium enhancement
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ESC 2014 Guidelines on diagnosis and management of hypertrophic cardiomyopathy, *Eur Heart J*. 2014;**35**:2733–79, with permission from Oxford University Press.

Table 37.7 Myocardial perfusion and coronary angiography

ACCF/AHA 2011 GL on HCM	
Coronary arteriography (invasive or computed tomographic imaging-CTA) in patients with HCM with chest discomfort who have an intermediate to high likelihood of CAD	I-C
CTA for patients with chest discomfort and a low likelihood of CAD	IIa-C
Assessment of ischaemia or perfusion abnormalities suggestive of CAD with single photon emission computed tomography (SPECT) or positron emission tomography (PET) myocardial perfusion imaging (MPI; because of excellent negative predictive value) in patients with chest discomfort and a low likelihood of CAD	IIa-C
Routine SPECT MPI or stress echocardiography is not indicated for detection of "silent" CAD-related ischaemia in asymptomatic patients	III-C (no benefit)
Assessment for the presence of blunted flow reserve (microvascular ischaemia) using quantitative myocardial blood flow measurements by PET is not indicated	III-C (no benefit)
ESC 2014 GL on HCM	
Invasive coronary angiography in adult survivors of cardiac arrest, in patients with sustained ventricular tachyarrhythmia and in patients with severe stable angina (CCS Class ≥3)	I-C
Invasive or CTA in patients with typical exertional chest pain (CCS Class <3) who have an intermediate pre-test probability of atherosclerotic coronary artery disease based on age, gender and risk factors for atherosclerosis, or a history of coronary revascularization.	IIa-C
In all patients ≥40 years, invasive or CTA before septal reduction therapy	IIa-C

CTA = computed tomographic coronary angiography; CCS = Canadian Cardiovascular Society
ACCF/AHA 2011 Guidelines for the diagnosis and treatment of hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2011;**58**:2703–38 with permission from Elsevier.
ESC 2014 Guidelines on diagnosis and management of hypertrophic cardiomyopathy, *Eur Heart J*. 2014;**35**:2733–79, with permission from Oxford University Press.

Table 37.8 ESC 2014 GL on HCM

Invasive electrophysiological study	
In documented persistent or recurrent supraventricular tachycardia (atrial flutter, atrial tachycardia, AVNRT, AVRT) and in patients with ventricular pre-excitation, to guide ablation.	I-C
In documented, symptomatic, monomorphic, sustained (>30 s) ventricular tachycardia to guide ablation	IIb-C
Programmed ventricular stimulation is not recommended for sudden cardiac death risk stratification.	III-C

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Table 37.9 ESC 2014 GL on HCM. Other potentially necessary tests

Invasive haemodynamic studies	
Cardiac catheterization-to evaluate right and left heart function and pulmonary arterial resistance-in patients considered for heart transplantation or mechanical circulatory support.	I-B
In symptomatic patients with inconclusive, non-invasive cardiac imaging, left and right heart catheterization to assess the severity of LVOT obstruction and to measure LV filling pressures	IIb-C
Nuclear scintigraphy	
Bone scintigraphy (particularly with 99mTc-DPD) in symptoms, signs and non-invasive tests consistent with transthyretin-related amyloidosis.	IIa-B
Cardiac CT in patients with inadequate echocardiographic imaging and contraindications for CMR	IIa-C
Endomyocardial biopsy	
When the results of other clinical assessments suggest myocardial infiltration, inflammation or storage that cannot be confirmed by other means.	IIb-C

99mTc-DPD: 99mTechnetium-3,3-diphosphono-1,2-propano-di-carboxylic acid
ESC 2014 Guidelines on diagnosis and management of hypertrophic cardiomyopathy, *Eur Heart J*. 2014;**35**:2733–79, with permission from Oxford University Press.

Differential diagnosis

The likelihood of HCM can be determined by the identification of a diagnostic sarcomere mutation or inferred by marked LV thickness >25 mm and/or LVOT obstruction with systolic anterior motion and mitral-septal contact. However, in clinical practice, the most commonly encountered conditions that may resemble HCM are essential hypertension and the athletic heart. The **elderly** may also present with sigmoid or hypertrophied septum and make diagnosis difficult.[27] Symmetric LV hypertrophy, thickened valves, and moderately depressed LV function in males >65 years old suggest senile or transthyretin-related amyloidosis rather than HCM.[28] Long-standing **arterial hypertension** produces concentric hypertrophy of the LV, but wall thickness >15 mm (>20 mm in black patients) is rare. However, HCM can present with wall thickness <15 mm, and, particularly in black patients, diagnosis can be made by discovery of a non-hypertensive first-degree relative or by genetic testing. RV hypertrophy and late gadolinium enhancement at the interventricular junction or localized to segments of maximum LV thickening on CMR is indicative of HCM.[2]

Regression of LV hypertrophy following 6–12 months of antihypertensive therapy argues against HCM. The **athletic heart** results from intense training. Wall thickness resembling cardiomyopathy may occur in sporting disciplines that combine isometric and isotonic activity, such as cycling and rowing. Sudden cardiac death in young competitive athletes is an important, although rare, public health problem, and a common cardiovascular cause is HCM (see also Chapter 38). Since the phenotypic expression of HCM is variable, and not uncommonly includes patients with mild and localized left ventricular hypertrophy, the differential diagnosis with athlete's heart may be difficult. By contrast with most patients with HCM, athletes have increased left and right ventricular cavity dimensions and normal diastolic function and rarely have ECG changes suggestive of myocardial disease.[29] Physiological left ventricular hypertrophy can also be differentiated from hypertrophic cardiomyopathy by tissue Doppler imaging velocity measurements.[21] In some cases, protracted deconditioning may be the only way to establish a diagnosis. Other conditions associated with LV hypertrophy are presented in Figure 37.1 and discussed in 'Aetiology' of this chapter. The differential diagnosis between HCM and lysosomal and glycogen storage diseases is presented in Table 37.10.

Table 37.10 Differential diagnosis for HCM versus lysosomal and glycogen storage diseases in adolescents and adults

	HCM	Fabry	Danon	PRFAG2 Deficiency
Inheritance	Autosomal dominant	X-linked recessive	X-linked dominant	Autosomal dominant
Male to male transmission	Yes	No	No	Yes
Extra cardiac findings	No	Skin, renal and visual findings, but all absent in cardiac variant	Skeletal muscle, retinal and mental changes	Skeletal muscle rnyopathy
ECG	LVH, abnormal Q waves, LAE, ST-T changes	LVH, abnormal Q waves, LAE, ST-T changes	LVH, ST-T changes, WPW	WPW, high grade AV block, atrial fibrillation and flutter
LV changes	Preserved EF in most patients with asymmetrical LVH as the most frequent phenotype	Preserved EF in most patients with concentric LVH as the most frequent phenotype	Preserved EF early on, usually with the most severe concentric LVH seen in any of the 4 disorders, later development of moderate to severely depressed EF, dilated phenotype seen in 50% of females	Concentric LVH and normal EF in early disease, some series noted later decline in LVEF
LVOT obstruction	In 60% of patients	Rare but noted in case reports, in one series it occurred in 1 of 139 patients	Reported in 2 of 7 patients in one series, with gradient at 65 mmHg	Not reported

AV indicates atrioventricular; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; LAE, left atrial enlargement; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; PRKAG2, gamma 2 regulatory subunit of AMP-activated protein kinase; and WPW, Wolff–Parkinson–White syndrome.
Nagueh SF. Anderson–Fabry disease and other lysosomal storage disorders. *Circulation*. 2014;**130**:1081–90 with permission from Wolters Kluwer.

Risk stratification

HCM is one of the most common causes of sudden death in young people (≤1% annually and predominantly in patients <25 years), including competitive athletes. Sudden death is paradoxically low in patients >60 years of age.[16] It is caused by fast VT or VF due to reentry in the electrophysiological substrate of scarring and disarray. There is no evidence that bradyarrhythmias play a role.[30] High risk factors are (Table 37.11):

- Previous cardiac arrest (although most are lethal)
- Massive LV hypertrophy (≥30 mm)
- Family history of HOCM-related sudden cardiac death
- Non-sustained VT on Holter or during exercise.
- Unexplained syncope.

Recently, a new sudden cardiac death risk prediction model that provides individualized risk estimates was developed.[30] It considers age, maximal left ventricular wall thickness, left atrial diameter, left ventricular outflow tract gradient, family history of SCD, non-sustained ventricular tachycardia, and unexplained syncope. The derived HCM Risk-SCD formula is as follows:

$$\text{Probability}_{\text{SCD at 5 years}} = 1 - 0.998^{\exp(\text{Prognostic index})}$$

where Prognostic index = [0.15939858 × maximal wall thickness (mm)]^2 [0.00294271 × maximal wall thickness^2 (mm^2)] + [0.0259082 × left atrial diameter (mm)] + [0.00446131 × maximal (rest/Valsalva) left ventricular outflow tract gradient (mm Hg)] + [0.4583082 × family history SCD] + [0.82639195 × NSVT] + [0.71650361 × unexplained syncope]^2 [0.01799934 × age at clinical evaluation (years)]. It has been adopted by the ESC 2014 GL on HCM, and its ability to improve the risk stratification of patients with HCM for primary prevention of SCD has been recently verified (available online at http://www. doc2do.com/hcm/webHCM.html).[31]

LAMP2 cardiomyopathy is largely refractory to ICD therapy and has a poor prognosis.[32] The presence of LV apical aneurysm, end-stage disease with widespread LV scarring, and delayed gadolinium enhancement in MRI are probably additional important risk factors.[29] Sustained VT has a similar prognostic impact to SCD, although it is relatively uncommon in HCM and raises suspicion of a left ventricular apical aneurysm.[33] Three of the five principal risk predictors (NSVT, VT, abnormal blood pressure, response to exercise, and marked LV hypertrophy) have significantly higher predictive potential in young adult HCM patients than the >50 age group, and a family history of SCD is also considered less relevant with advancing years. Asymptomatic patients with none of these factors are at low risk (<0.5%/year), although risk factors are not identified in 3% of SCD victims.[33]

Table 37.11 Risk stratification

ACC/AHA 2011 GL on HCM. SCD risk stratification	
Comprehensive SCD risk stratification at initial evaluation to determine the presence of the following: a. A personal history for ventricular fibrillation, sustained VT, or SCD events, including appropriate ICD therapy for ventricular tachyarrhythmias.† b. A family history for SCD events, including appropriate ICD therapy for ventricular tachyarrhythmias.† c. Unexplained syncope. d. Documented NSVT (3 or more beats at ≥120 bpm on ambulatory (Holter) ECG). e. Maximal LV wall thickness ≥ 30 mm.	I-B
Assessment of blood pressure response during exercise as part of SCD risk stratification.	IIa-B
SCD risk stratification on a periodic basis (every 12 to 24 months) for patients who have not undergone ICD implantation but would otherwise be eligible in the event that risk factors are identified (12 to 24 months).	IIa-C
Potential SCD risk in selected patients for whom risk remains borderline after documentation of conventional risk factors: a. CMR imaging with LGE. b. Double and compound mutations (i.e., >1). c. Marked LVOT obstruction.	 IIb-C IIb-C IIb-B
Invasive electrophysiologic testing as routine SCD risk stratification.	III-C

ESC 2014 GL on HCM. Major clinical features associated with an increased risk of sudden cardiac death in adults	
Risk factor	**Comment**
Age	• The effect of age on SCD has been examined in a number of studies and two have shown a significant association, with an increased risk of SCD in younger patients • Some risk factors appear to be more important in younger patients, most notably, NSVT, severe LVH and unexplained syncope.
Non-sustained ventricular tachycardia	• NSVT (defined as >3 consecutive ventricular beats at ≥120 BPM lasting <30 seconds) occurs in 20–30% of patients during ambulatory ECG monitoring and is an independent predictor of SCD. • There is no evidence that the frequency duration or rate of NSVT influences the risk of SCD.
Maximum left ventricular wall thickness	• The severity and extent of LVH measured by TTE are associated with the risk of SCD. • Several studies have shown the greatest risk of SCD in patients with a maximum wall thickness of ≥30 mm, but there are few data in patients with extreme hypertrophy (≥35 mm).
Family history of sudden cardiac death at a young age	• While definitions vary, a family history of SCD is usually considered clinically significant when one or more first-degree relatives have died suddenly aged <40 years with or without a diagnosis of HCM, or when SCD has occurred in a first-degree relative at any age with an established diagnosis of HCM.
Syncope	• Syncope is common in patients with HCM but is challenging to assess as it has multiple causes. • Non-neurocardiogenic syncope for which there is no explanation after investigation is associated with increased risk of SCD. • Episodes within 6 months of evaluation may be more predictive of SCD
Left atrial diameter	• Two studies have reported a positive association between LA size and SCD. There are no data on the association between SCD and LA area and volume. Measurement of LA size is also important in assessing the risk of AF.
Left ventricular outflow tract obstruction	• A number of studies have reported a significant association with LVOTO and SCD. Several unanswered questions remain, including the prognostic importance of provocable LVOTO and the impact of treatment (medical or invasive) on SCD.
Exercise blood pressure response	• Approximately one-third of adult patients with HCM have an abnormal systolic blood pressure response to exercise characterized by progressive hypotension or a failure to augment the systolic blood pressure that is caused by an inappropriate drop in systemic vascular resistance and a low cardiac output reserve. • Various definitions for abnormal blood pressure response in patients with HCM have been reported; an abnormal blood pressure response is defined as a failure to increase systolic pressure by at least 20 mm Hg from rest to peak exercise or a fall of >20 mm Hg from peak pressure. • Abnormal exercise blood pressure response is associated with a higher risk of SCD in patients aged ≤40 years, but its prognostic significance in patients >40 years of age is unknown.

†Appropriate ICD discharge is defined as ICD therapy triggered by VT or ventricular fibrillation, documented by stored intracardiac electrogram or cycle length data, in conjunction with the patient's symptoms immediately before and after device discharge.
HCM = hypertrophic cardiomyopathy; LA = left ventricular hypertrophy; LVOTO = left ventricular outflow tract obstruction; NSVT = non-sustained ventricular tachycardia; SCD = sudden cardiac death; TTE = transthoracic echocardiography.
ACCF/AHA 2011 Guidelines for the diagnosis and treatment of hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2011;**58**:2703–38 with permission from Elsevier.
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Therapy

The management of patients with HCM is aimed at restricting extreme activity, with avoidance of volume depletion, symptomatic relief, prevention of sudden death, and screening of relatives. With the exception of ICD, no pharmacological or other strategies offer protection from sudden death.[29] Contemporary therapeutic interventions including ICD have resulted in a very low disease-related mortality: 0.5%/year.[34]

Medical therapy

In asymptomatic HCM patients, benefit from beta blockers or L-type calcium channel blockers has not been established, but beta blockers are first-line agents for the management of symptomatic (angina or dyspnoea) patients with HCM (Tables 37.12 and 37.13, and Figure 37.3). The addition of disopyramide to beta blocker therapy or the use of verapamil alone may be beneficial in those who do not respond to beta blockers. Vasodilators, including dihydropyridine calcium channel blockers and angiotensin-converting enzyme inhibitors, are potentially harmful in those with evidence of LVOT obstruction.

Beta blockers, particularly without intrinsic sympathomimetic activity and aimed at heart rate <60–65 bpm, improve ventricular relaxation, increase diastolic filling time, and should theoretically reduce susceptibility to ventricular arrhythmias. They are the mainstay of treatment for symptomatic improvement.

L-type calcium channel blockers, such as **verapamil** (starting in low doses and titrating up to 480 mg/day) and **diltiazem**, are beneficial due to negative inotropic and chronotropic effects and improved diastolic function and are used instead of, or with, beta blockers. They may, however, exacerbate LVOT gradient due to vasodilation. They are particularly useful in the non-obstructive form.

Disopyramide, in combination with beta blockers, reduces LVOT gradient and improves symptoms by its negative inotropic action. Although it has not been considered proarrhythmic in HCM,[35] concerns about the inherent proarrhythmia of Class IA agents cannot be ignored. Significant vagolytic side effects, such as dry mouth and prostatism, occur in 5% of patients.

Amiodarone is not considered a therapeutic option for prevention of sudden death in HCM any more.[1]

Table 37.12 ACCF/AHA 2011 GL on HCM. Management of HCM

Asymptomatic patients	
Comorbidities (hypertension, diabetes, hyperlipidaemia, obesity) should be appropriately treated	I-C
Low-intensity aerobic exercise	IIa-C
Usefulness of beta blockade and calcium channel blockers not well established	IIb-C
Septal reduction therapy should not be performed for asymptomatic adult and paediatric patients with HCM with normal effort tolerance	III-C
In patients with resting or provocable outflow tract obstruction, pure vasodilators and high-dose diuretics are potentially harmful.	III-C
Symptomatic patients	
Beta-blockers in adults for symptoms, with caution in sinus bradycardia or severe conduction disease.	I-B
If low doses ineffective, titrate to a resting heart rate < 60–65 bpm.	I-B
Verapamil (starting in low doses and titrating up to 480 mg/d) for symptoms. If no response or contraindication to beta blockers, with caution in high gradients, advanced heart failure, or sinus bradycardia.	I-B
IV phenylephrine (or another pure vasoconstricting agent) for the treatment of acute hypotension in patients who do not respond to fluid administration.	I-B
Disopyramide with a beta-blocker or verapamil in patients who do not respond to beta-blockers or verapamil alone.	IIa-B
Diuretics in non-obstructive HCM when dyspnoea persists despite the use of beta blockers or verapamil or their combination.	IIa-C
Beta-blockers in children or adolescents monitored for depression, fatigue, or impaired scholastic performance.	IIb-C
Diuretics in non-obstructive HCM when dyspnoea persists despite the use of beta blockers or verapamil or their combination.	IIb-C
ACEI or ARB with resting or provocable LVOT obstruction.	IIb-C
Diltiazem if verapamil is not tolerated.	IIb-C

(*continued*)

Table 37.12 Continued

Nifedipine or other dihydropyridine calcium channel-blockers	III-C
Verapamil in the setting of systemic hypotension or severe dyspnoea at rest.	III-C
Digoxin in the absence of AF.	III-B
Disopyramide alone without beta blockers or verapamil in AF	III-B
Dopamine, dobutamine, norepinephrine, and other IV inotropes for acute hypotension in patients with obstructive HCM.	III-B

ACCF/AHA 2011 Guidelines for the diagnosis and treatment of hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2011;**58**:2703–38 with permission from Elsevier.

Table 37.13 ESC 2014 GL on HCM. Medical therapy

Treatment of LVOT obstruction: General measures	
Arterial and venous dilators, including nitrates and phosphodiesterase inhibitors, should be avoided if possible in patients with resting or provocable LVOT obstruction.	IIa-C
Restoration of sinus rhythm or appropriate rate control before considering invasive therapies in patients with new-onset or poorly controlled AF	Iia-C
Digoxin is not recommended in patients with resting or provocable LVOT obstruction.	III-C
Medical treatment to improve symptoms of resting or provoked LVOT obstruction	
Non-vasodilating ß-blockers, titrated to maximum tolerated dose, as first-line therapy	I-B
Verapamil, titrated to maximum tolerated dose, in patients who are intolerant or have contraindications to β-blockers.	I-B
Disopyramide, titrated to maximum tolerated dose, is recommended in addition to a ß-blocker (or, if this is not possible, with verapamil)	I-B
Disopyramide, titrated to maximum tolerated dose, may be considered as monotherapy taking caution in patients with or prone to AF (increased ventricular rate response)	IIb-C
β-Blockers or verapamil in children and asymptomatic adults	IIb-C
Low-dose loop- or thiazide diuretics with caution to improve exertional dyspnoea.	IIb-C
Diltiazem, titrated to maximum tolerated dose, in intolerance or contraindications to ß-blockers and verapamil	IIa-C
Oral or i.v. ß-blockers and vasoconstrictors in patients with severe provocable LVOT obstruction presenting with hypotension and pulmonary oedema.	IIa-C
Chest pain on exertion in patients without LVOT obstruction	
β-Blockers and calcium antagonists in patients with no evidence for obstructive coronary artery disease.	IIa-C
Oral nitrates in patients with no evidence for obstructive coronary artery disease.	IIb-C

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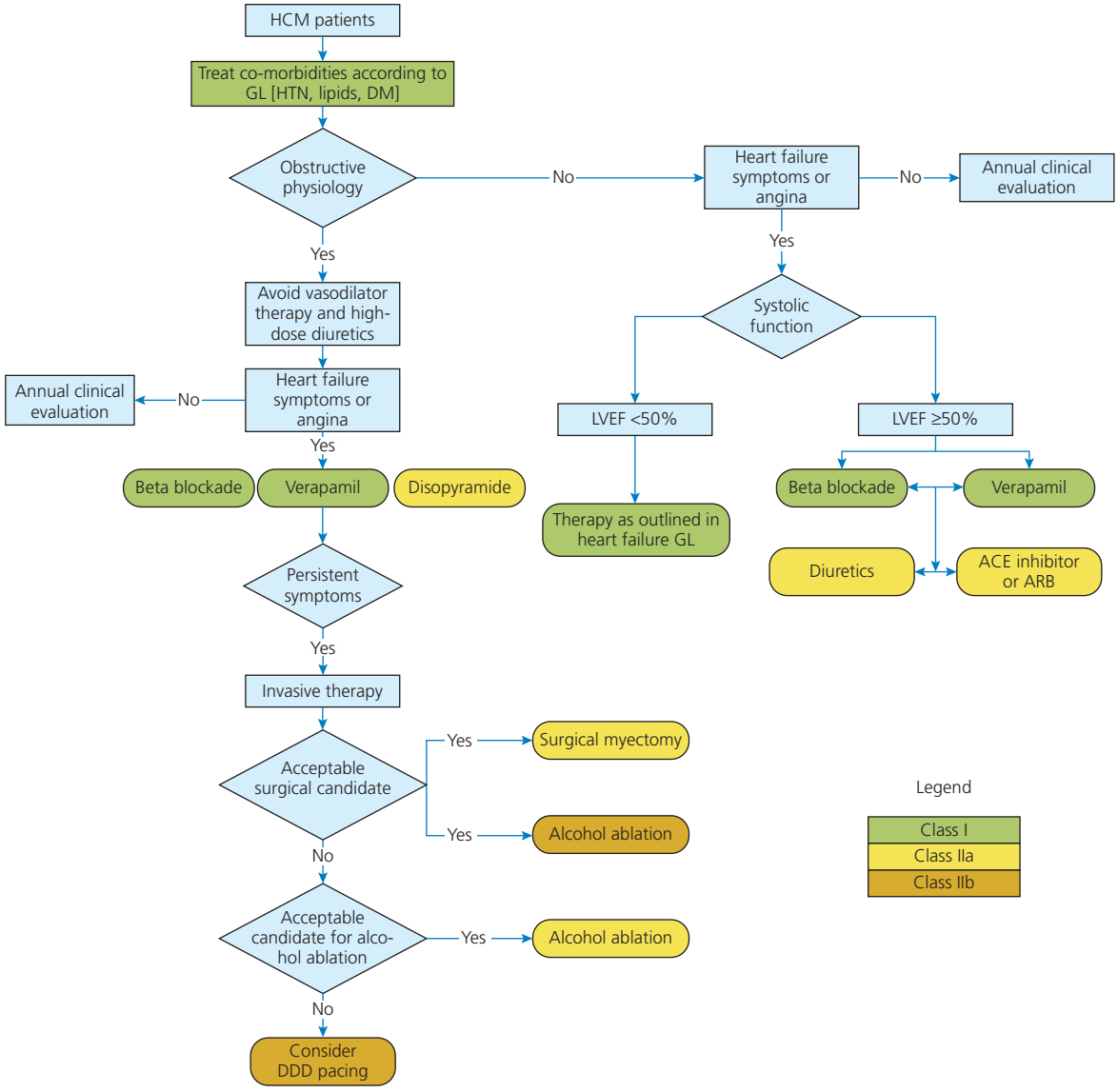

Figure 37.3 Treatment algorithm.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DM, diabetes mellitus; EF, ejection fraction; GL, guidelines; HCM, hypertrophic cardiomyopathy; HTN, hypertension; LV, left ventricular.

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Septal reduction

Septal myectomy is considered for patients with significant LVOT gradients (≥50 mmHg, Table 37.4) or ≥30 mmHg at rest or ≥50 mmHg during exercise, and symptoms refractory to medical therapy (Table 37.14).[36] Operative mortality in experienced centres is <1.5%, and the risk of VSD is 1% and of complete heart block 6%.[36,37] Mitral valve replacement has been used to manage HCM in the unusual patient whose septal thickness is 16–18 mm, if a significant mid-cavity gradient is present, or if a significant gradient or substantial mitral regurgitation persists after adequate myectomy.[36]

Transcatheter septal ablation with, usually, alcohol infusion or with radiofrequency, can be considered in

Table 37.14 Septal reduction

ACC/AHA 2011 GL on HCM. Invasive therapies	
Septal reduction therapy should be performed only by experienced Operators* in the context of a comprehensive HCM clinical program and only for the treatment of eligible patients with severe drug-refractory symptoms and LVOT obstruction.†	I-C
Consultation with centres experienced in performing both surgical septal myectomy and alcohol septal ablation.	IIa-C
Surgical septal myectomy, at experienced centres, is the first consideration for the majority of eligible patients with severe drug-refractory symptoms and LVOT obstruction.	IIa-B
Surgical septal myectomy, at experienced centres, in symptomatic children with severe resting obstruction (>50 mm Hg)	IIa-C
Alcohol septal ablation, at experienced centres, when surgery is contraindicated or high-risk and NYHA III/IV.	IIa-B
Patient's preference for septal ablation with severe drug-refractory symptoms and LVOT obstruction.	IIb-B
Alcohol septal ablation in patients with HCM with marked (i.e., >30 mm) septal hypertrophy is discouraged.	IIb-C
Septal reduction for patients minimally symptomatic or asymptomatic or controlled on optimal medical therapy.	III-C
Septal reduction therapy in inexperienced centres.	III-C
Mitral valve replacement for relief of LVOT obstruction in patients in whom septal reduction therapy is an option.	III-C
Alcohol septal ablation in patients in need of cardiac surgery (mitral or CABG).	III-C
Alcohol septal ablation in patients < 21 years of age and in adults < 40 years of age if myectomy is a viable option.	III-C
ESC 2014 GL on HCM. Septal reduction therapy in patients with resting or maximum provoked LVOT gradient ≥50 mmHg	
Septal reduction therapies should be performed by experienced operators, working as part of a multidisciplinary team expert in the management of HCM.	I-C
Septal reduction to improve symptoms in patients who are in NYHA III-IV, despite maximum tolerated medical therapy.	I-B
Septal reduction in patients with recurrent exertional syncope despite optimal medical therapy.	IIa-C
Septal myectomy, rather than alcohol ablation, in patients with an indication for septal reduction and other lesions requiring surgical intervention (e.g. mitral valve repair/replacement, papillary muscle intervention).	I-C
Mitral valve repair or replacement in symptomatic patients and moderate-to-severe mitral regurgitation not caused by systolic anterior motion of the mitral valve alone.	IIa-C
Mitral valve repair or replacement in patients with a maximum septal thickness 16 mm at the point of the mitral leaflet-septal contact or when there is moderate-to-severe mitral regurgitation following isolated myectomy.	IIb-C

*Experienced operators are defined as an individual operator with a cumulative case volume of at least 20 procedures or an individual operator who is working in a dedicated HCM program with a cumulative total of at least 50 procedures.

†Eligible patients are defined by all of the following:

a. Clinical: Severe dyspnoea or chest pain (usually NYHA functional classes III or IV) or occasionally other exertional symptoms (such as syncope or near syncope) that interfere with everyday activity or quality of life despite optimal medical therapy.

b. Haemodynamic: Dynamic LVOT gradient at rest or with physiologic provocation >50 mm Hg associated with septal hypertrophy and SAM of the mitral valve.

c. Anatomic: Targeted anterior septal thickness sufficient to perform the procedure safely and effectively in the judgment of the individual operator.

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symptomatic patients with accessible septal branch and septal thickness ≥15 mm, significant LVOT gradient (≥30 mmHg at rest or ≥50 mmHg on provocation), and in the absence of intrinsic abnormality of the mitral valve and of proximal left anterior descending coronary artery stenosis.[38–41] Septal ablation has uncertain effectiveness with marked septal hypertrophy (>30 mm). Mortality is <3% and the risk of permanent pacemaker 10–30%, but it is reduced with contrast echocardiography and slow ethanol injection.[40] There is an incompletely defined risk of ventricular arrhythmias arising at the borders of the iatrogenic scar,[3] and this option is not recommended in young patients. However, in recent non-randomized comparisons, long-term survival offered by septal ablation was similar to that of an age- and sex-matched general population, and to patients undergoing surgical myectomy as well, without an increased risk of sudden cardiac death.[42,43] So far, no mortality benefit has been detected with either transcatheter or surgical septal reduction compared to medical therapy,[38] and in patients with pre-existing risk factors for sudden death, an ICD should be implanted before septal ablation.

Pacing

DDD pacing with a short AV delay has been shown to decrease LVOT gradient and symptoms in some, but not all, randomized comparisons.[44,45] It may be useful in the elderly without short PR intervals (Table 37.15), and in medically refractory symptomatic patients with LVOT obstruction who are suboptimal candidates for septal reduction therapy.[1,46]

Table 37.15 Pacing

ACCF/AHA 2011 GL on HCM	
In patients with a dual-chamber device implanted for non-HCM indications, consider a trial of dual-chamber atrial-ventricular pacing (from the right ventricular apex) for the relief of symptoms attributable to LVOT obstruction.	IIa-B
Permanent pacing in medically refractory symptomatic patients with obstructive HCM who are suboptimal candidates for septal reduction therapy.	IIb-B
Permanent pacemaker implantation for the purpose of reducing gradient in asymptomatic or medically controlled patients.	III-C
Permanent pacemaker implantation as a first-line therapy to relieve symptoms in medically refractory symptomatic patients with HCM and LVOT obstruction who are candidates for septal reduction.	III-B
ESC 2014 GL on HCM	
Cardiac pacing in patients with resting or maximum provoked LVOT gradient ≥50 mmHg*	
Sequential AV pacing, with optimal AV interval to reduce the gradient or facilitate medical therapy in patients with sinus rhythm and drug-refractory symptoms, who have contraindications for septal alcohol ablation or septal myectomy or are at high risk of developing heart block following septal reduction.	IIb-C
In patients with sinus rhythm and drug refractory symptoms, in whom there is an indication for an ICD, a dual-chamber ICD instead of a single-lead device.	IIb-C
Recommendations on cardiac resynchronization therapy	
CRT to improve symptoms in patients with maximum LVOT gradient <30 mm Hg, drug refractory symptoms, NYHA II-IV, LVEF <50% and LBBB with QRS >120 ms.	IIb-C

* Similar recommendations by the ESC 2013 GL on pacing and CRT.

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ESC 2014 Guidelines on diagnosis and management of hypertrophic cardiomyopathy, *Eur Heart J*. 2014;**35**:2733–79, with permission from Oxford University Press.

ICD

Although no randomized studies exist in HCM populations (as in **ischaemic** cardiomyopathy), there is a consensus that, in high-risk patients defined as those with a history of cardiac arrest or with ≥2 risk factors, ICD are lifesaving (Table 37.16, Figure 37.4). Results from a recent multicentre registry indicated that an important proportion of appropriate ICD discharges occurred in high-risk patients who had undergone implantation for a single risk factor.[47] Potential complications of ICD therapy are pneumothorax, haematoma, lead revisions, and infection. The main concern, however, is inappropriate shocks that may occur in up to 36% of patients, with a rate of 5% per year.[48] Extreme LV hypertrophy is the most common risk factor in children and an ICD, when indicated, can be life-saving. However, the complication rate (inappropriate shocks and lead malfunction) may be up to 3-fold higher than interventions for VT/VF.[49]

Table 37.16 ICD indications

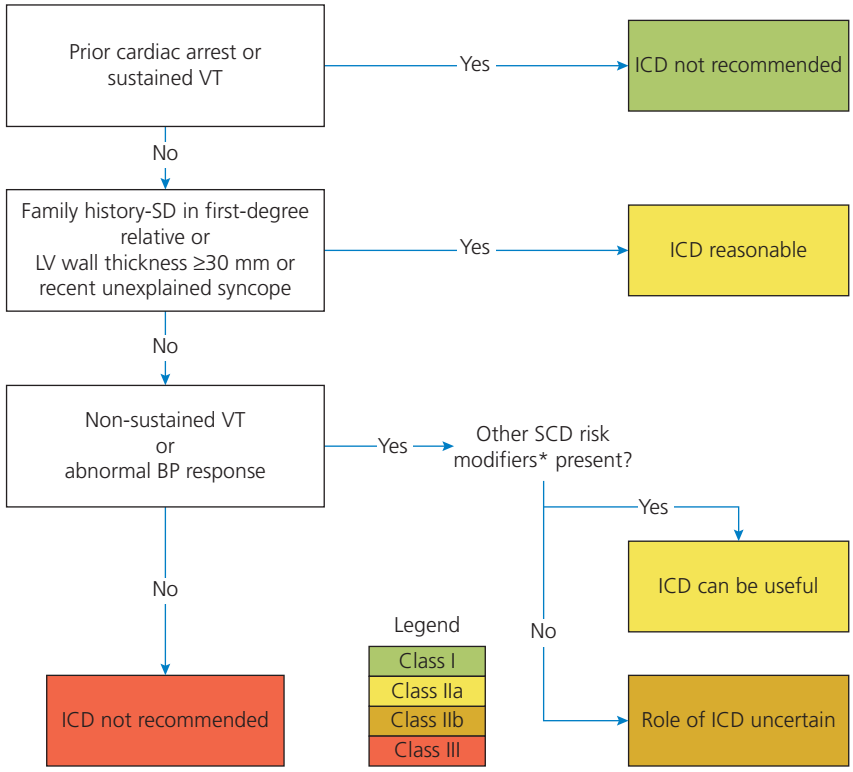
ACC/AHA 2011 GL on HCM	
Selection of patients for ICD*	
Application of individual clinical judgment, and discussion of the strength of evidence, benefits, and risks to allow the informed patient's active participation in decision making.	I-C
ICD placement is recommended for patients with HCM with prior documented cardiac arrest, VF, or haemodynamically significant VT.	I-B
ICD for patients with: a. Sudden death presumably caused by HCM in 1 or more first-degree relatives. b. A maximum LV wall thickness ≥ 30 mm. c. One or more recent, unexplained syncopal episodes.	IIa-C
Select patients with NSVT (particularly those <30 years of age) in the presence of other SCD risk factors or modifiers.	IIa-C
ICD in selected patients with an abnormal blood pressure response with exercise in the presence of other SCD risk factors or modifiers.	IIa-C
ICD for high-risk children with HCM, based on unexplained syncope, massive LV hypertrophy, or family history of SCD, after taking into account the relatively high complication rate of long-term ICD implantation.	IIa-C
ICD in patients with isolated bursts of NSVT in the absence of any other SCD risk factors or modifiers.	IIb-C
ICD in patients with an abnormal blood pressure response with exercise in the absence of any other SCD risk factors or modifiers, particularly in the presence of significant outflow obstruction.	IIb-C
ICD as a routine strategy in patients with HCM without an indication of increased risk is potentially harmful.	III-C
ICD as a strategy to permit patients with HCM to participate in competitive athletics.	III-C
ICD in patients who have an identified HCM genotype in the absence of clinical manifestations of HCM.	III-C
Selection of ICD device type	
Single-chamber devices in younger patients without a need for atrial or ventricular pacing.	IIa-B
Dual-chamber ICDs for patients with sinus bradycardia and/or paroxysmal AF.	IIa-C
Dual-chamber ICDs for patients with elevated resting outflow gradients > 50 mm Hg and significant heart failure symptoms who may benefit from RV pacing (most commonly, but not limited to, patients >65 years of age).	IIa-B
ACCF/AHA/HRS 2012 GL on device therapy	
Survivors of cardiac arrest	I-A
Spontaneous sustained VT	I-B
Patients with one or more major risk factors). (prior cardiac arrest, spontaneous sustained VT, spontaneous nonsustained VT, family history of SCD, syncope, LV thickness ≥ 30 mm, and an abnormal blood pressure response to exercise).	IIa-C
ESC 2014 GL on HCM	
Prevention of sudden cardiac death	
(Similar to those by the ESC GL on VA and SCD)	I-C
Practical aspects of implantable cardioverter defibrillator therapy	
Prior to ICD implantation, patients should be counselled on the risk of inappropriate shocks, implant complications and the social, occupational, and driving implications of the device.	I-C
ß-Blockers and/or amiodarone in patients with ICD, who have symptomatic ventricular arrhythmias or recurrent shocks despite optimal treatment and device reprogramming.	I-C
Electrophysiological study in patients with ICDs and inappropriate shocks due to regular supraventricular tachycardias, to guide ablation.	I-C
A subcutaneous ICD lead system (S-ICD™) may be considered in HCM patients who do not have an indication for pacing.	IIb-C
Implantation of cardioverter defibrillators in children	
ICD implantation in children who have survived a cardiac arrest or experienced documented sustained ventricular tachycardia.	I-B
ICD implantation in children after appropriate counselling and when an assessment of the lifelong risk of complications and the impact of an ICD on lifestyle and psychological health suggests a net benefit from ICD therapy:	
Two or more major paediatric risk factors**	IIa-C
Single major paediatric risk factors**	IIb-C
ESC 2015 GL on VA and SCD. Prevention of sudden death	
Avoidance of competitive sports	I-C
ICD in survived cardiac arrest due to VT or VF or spontaneous sustained VT causing syncope or haemodynamic compromise,	I-B

(*continued*)

Table 37.16 Continued

Risk stratification with the HCM Risk-SCD calculator to estimate the 5-year risk in patients ≥16 years of age without a history of resuscitated VT or VF or spontaneous sustained VT causing syncope or haemodynamic compromise. At first evaluation and at 1- to 2-year intervals, or when there is a change in clinical status.	I-B
ICD with an estimated 5-year risk of sudden death ≥6% following detailed clinical assessment that takes into account the lifelong risk of complications and the impact of an ICD on lifestyle, socioeconomic status and psychological health.	IIa-B
ICD with an estimated 5-year risk of SCD of ≥4 to <6% following clinical assessment as above.	IIb-B
ICD with an estimated 5-year risk of SCD <4% when they have clinical features that are of proven prognostic importance following clinical assessment as above	IIb-B
Invasive EPS with PVS is not recommended for stratification of SCD risk.	III-C

* All guidelines recommend ICD in patients with life expectancy >1 year.
** Major paediatric risk factors: Maximum left ventricular wall thickness ≥30mm or a Z-score ≥6, unexplained syncope, non-sustained ventricular tachycardia (≥3 consecutive ventricular beats at ≥120 BPM lasting <30 seconds), family history of SCD (one or more first-degree relatives with SCD aged <40 years with or without the diagnosis of HCM, or SCD in a first-degree relative at any age with an established diagnosis of HCM).
ACCF/AHA 2011 Guidelines for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy. *J Am Coll Cardiol.* 2011;**58**:2703–38 with permission from Elsevier.
ACCF/AHA/HRS 2012 Focused Update Incorporated Into the ACCF/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities. *J Am Coll Cardiol*. 2013;**61**: e6–e75 with permission for Elsevier.
ESC 2014 Guidelines on diagnosis and management of hypertrophic cardiomyopathy, *Eur Heart J.* 2014;**35**:2733–79, with permission from Oxford University Press.
ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015;**36**:2793–2867



Regardless of the level of recommendation put forth in these guidelines, the decision for placement of an ICD must involve prudent application of individual clinical judgement, through discussions of the strength of evidence, the benefits, and the risks (including but not limited to inappropriate discharges, lead and procedural complications) to allow active participation of the fully informed patient in ultimate decision-making.

Figure 37.4 Indications for ICDs in HCM.

*SCD risk modifiers include established risk factors and emerging risk modifiers. BP indicates blood pressure; ICD, implantable cardioverter-defibrillator; LV, left ventricular; SCD, sudden cardiac death; SD, sudden death; and VT, ventricular tachycardia.
ACCF/AHA 2011 Guidelines for the diagnosis and treatment of hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2011;**58**:2703–38 with permission from Elsevier.

Atrial fibrillation

AF occurs in 20% of patients with HCM (4-fold increase than in the general population).[20] AF can cause sudden, and sometimes severe, deterioration in symptoms and exercise capacity and is associated with a high risk of thromboembolism. Restoration of sinus rhythm usually results in a substantial improvement in symptoms, and amiodarone is effective in preventing recurrences.[50] Control of the ventricular rate with beta blockers, calcium antagonists, or both is almost as effective. Because of the potentially adverse effects of digoxin in patients with hypertrophic cardiomyopathy and normal systolic function, this drug is not routinely recommended for rate control. All patients with permanent or paroxysmal AF, in the context of an enlarged atrium, should be anticoagulated (Table 37.17 and Figure 37.5). Catheter ablation may offer restoration of sinus rhythm and improvement of symptomatic status in up to 50% of patients.[51]

Table 37.17 Atrial arrhythmias

AHA/ACC/HRS 2014 GL on AF. Hypertrophic cardiomyopathy	
Anticoagulation in HCM with AF independent of the CHA_2 DS_2 -VASc score	I-B
Amiodarone, or disopyramide combined with beta blockers or nondihydropyridine calcium channel antagonist to prevent recurrent AF	IIa-C
AF catheter ablation to facilitate a rhythm control strategy when antiarrhythmics fail or are not tolerated	IIa-B
Sotalol, dofetilide, and dronedarone for rhythm control	IIb-C
ESC 2014 GL on HCM. Atrial fibrillation/atrial flutter	
Unless contraindicated, oral anticoagulation with VKA (target INR 2.0–3.0) in patients who develop persistent, permanent or paroxysmal AF	I-B
Antithrombotic therapy for patients with atrial flutter, as for those with AF.	I-C
Assessment of the risk of bleeding with the HAS-BLED score when prescribing antithrombotic therapy (whether with VKA or antiplatelet therapy).	IIa-B
Restoration of sinus rhythm, by DC or pharmacological cardioversion with IV amiodarone in patients presenting with recent-onset AF.	IIa-C
Amiodarone for achieving rhythm control and to maintain sinus rhythm after DC cardioversion.	IIa-B
ß-Blockers, verapamil and diltiazem for controlling ventricular rate in permanent or persistent AF.	I-C
48-Hour ambulatory ECG monitoring every 6–12 months to detect AF in patients who are in SR and have an LA diameter of 45 mm	IIa-C
Catheter ablation for AF in patients without severe left atrial enlargement, who have drug refractory symptoms or are unable to take anti-arrhythmic drugs.	IIa-B
Ablation of the AV node to control heart rate when the ventricular rate cannot be controlled with drugs and when AF cannot be prevented by anti-arrhythmic therapy or is associated with intolerable side-effects.	IIb-C
Following AV node ablation in patients with an LVEF <50%, implantation of a DDD pacemaker with mode-switch function for patients with paroxysmal AF and a VVIR pacemaker for those in persistent or permanent AF.	I-C
In patients with any type of AF and LVEF <50%, implantation of a CRT pacemaker after AV node ablation.	IIb-C
Ablation procedures during septal myectomy in patients with symptomatic AF.	IIb-C
Antiplatelet therapy using aspirin 75–100 mg plus clopidogrel 75 mg daily (where there is a low risk of bleeding) when patients refuse the use of any OAC (whether VKAs or NOACs*).	IIa-B
When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF-due to failure to maintain therapeutic anticoagulation, side-effects of VKAs, or inability to attend or undertake INR monitoring-use a direct thrombin inhibitor (dabigatran) or an oral factor Xa inhibitor (e.g. rivaroxaban)	I-B
Unless there is a reversible cause of AF, lifelong OAC therapy with a VKA (INR 2.0–3.0), even if sinus rhythm is restored.	I-C

§Dabigatran should not be used in patients with prosthetic valves, haemodynamically significant valve disease, advanced liver failure, or severe renal failure (creatinine clearance <15 mL/min)

* NOACs: non-vitamin K dependent oral anticoagulants

AHA/ACC/HRS 2014 Guideline or the management of patients with atrial fibrillation. *J Am Coll Cardiol*. 2014;**64**:2246-80 with permission from Elsevier.

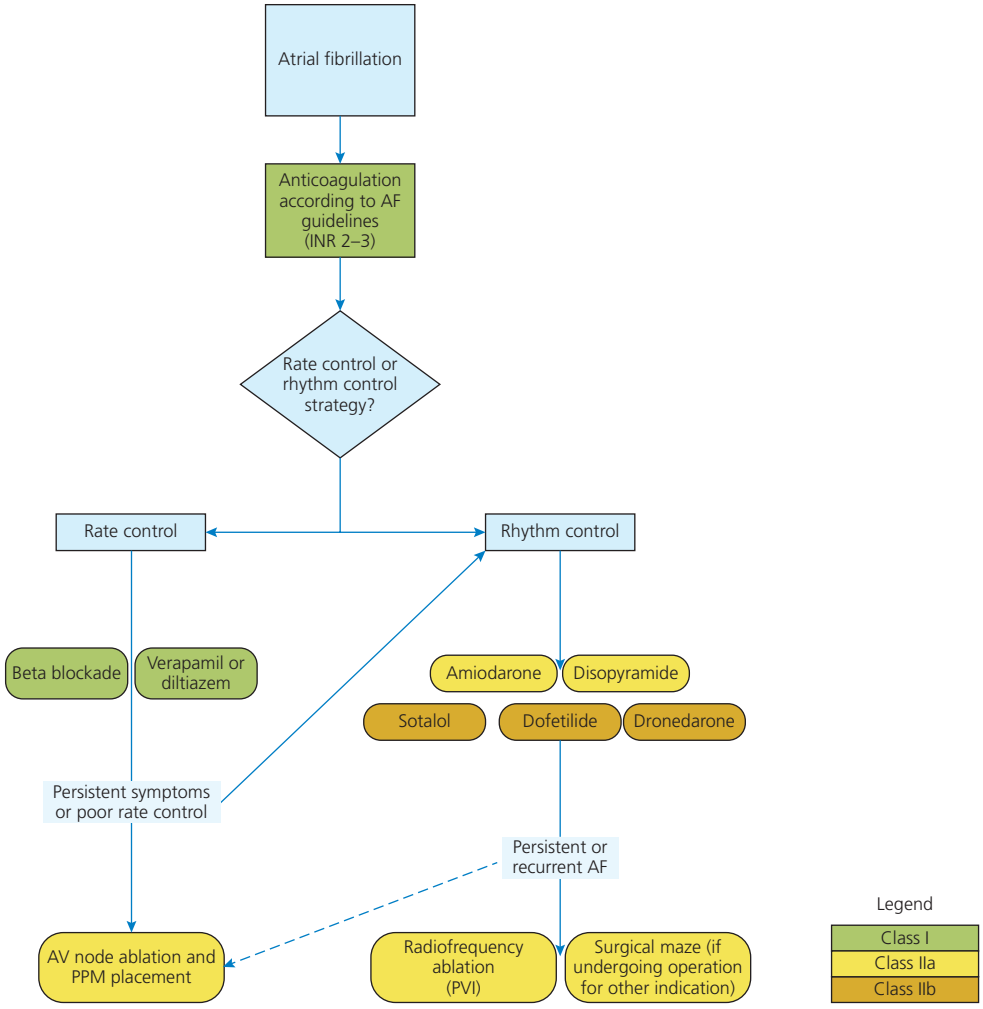


Figure 37.5 Management of AF in HCM.

AF indicates atrial fibrillation; AV, atrioventricular; INR, international normalized ratio; PPM, permanent pacemaker; and PVI, pulmonary vein isolation. ACCF/AHA 2011 Guidelines for the diagnosis and treatment of hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2011;**58**:2703–38 with permission from Elsevier.

LV dysfunction and heart failure

Recommendations are provided in Table 37.18. Heart transplantation is the last option for patients with irreversible heart failure due to systolic dysfunction.

Experimental therapies ARBs, aldosterone antagonists, statins, and N-acetylcysteine have been shown in animal models to achieve reversal or prevention of hypertrophy and fibrosis in HCM.[52] Pilot studies are being conducted.

Table 37.18 Heart failure

ACC/AHA 2011 on HCM	
Patients with LV systolic dysfunction	
Patients with systolic dysfunction with an EF ≤ 50% are treated as for adults with other forms of heart failure with reduced EF, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, and other indicated drugs.	I-B
Other concomitant causes of systolic dysfunction (such as CAD) are considered as potential contributors to systolic dysfunction in patients with HCM.	I-C
ICD in adult patients with advanced (as defined by NYHA III or IV), heart failure, nonobstructive HCM, on maximal medical therapy, and EF ≤50%, who do not otherwise have an indication for an ICD.	IIb-C
Reassess the use of negative inotropic agents (ie verapamil, diltiazem, or disopyramide), and consider discontinuing in patients who develop systolic dysfunction.	IIb-C
Selection of patients for heart transplantation	
Consideration for heart transplantation of patients with advanced heart failure (end stage*) and nonobstructive HCM not otherwise amenable to other treatment/interventions, with EF ≤ 50% (or occasionally with preserved EF).	I-B
Consideration for heart transplantation of symptomatic children with HCM with restrictive physiology who are not responsive to or appropriate candidates for other therapeutic interventions.	I-C
Heart transplantation in mildly symptomatic patients of any age.	III-C
ESC 2014 GL on HCM	
Patients with heart failure NYHA II-IV, LVEF ≥50%, and no evidence for resting or provocable LVOT obstruction	
ß-blockers, verapamil or diltiazem	IIa-C
Low-dose loop and thiazide diuretics	IIa-C
Patients with heart failure and LVEF <50%	
In patients without LVOT obstruction to reduce the risks of HF hospitalization and premature death.[a]	
An ACE inhibitor (or ARB if ACE inhibitor not tolerated), in addition to a ß-blocker	IIa-C
A ß-blocker in addition to an ACE inhibitor (or ARB if ACE inhibitor not tolerated)	IIa-C
Low-dose loop diuretics for symptomatic patients in NYHA II-IV, to improve symptoms and reduce the risk of HF hospitalization.[a]	IIa-C
A mineralocorticoid receptor antagonist to reduce the risks of HF hospitalization and premature death,[a] if NYHA Class II-IV and symptoms despite ACE inhibitor (or an ARB) and a ß-blocker	IIa-C
Low-dose digoxin for patients without LVOTO who are NYHA II-IV and have AF to control heart rate response.	IIb-C
Left ventricular assist devices	
Continuous axial flow LVAD in patients with end-stage HF despite optimal pharmacological and device treatment, who are otherwise suitable for heart transplantation, to improve symptoms, and reduce the risk of HF hospitalization from worsening HF and premature death while awaiting a transplant.	IIb-C
Orthotopic cardiac transplantation	
Eligible patients with LVEF <50% and NYHA III-IV despite optimal medical therapy, or intractable ventricular arrhythmia.	IIa-B
Eligible patients with normal LVEF (50%) and severe drug refractory symptoms (NYHA III-IV) caused by diastolic dysfunction.	IIb-B

*: Characterized by systolic dysfunction (EF ≤50%), often associated with LV remodelling, including cavity enlargement and wall thinning, and because of diffuse myocardial scarring.
a: In the absence of randomized trials in HCM, the benefit on hospitalization, symptoms and mortality is assumed but unproven.
ACCF/AHA 2011 Guidelines for the diagnosis and treatment of hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2011;**58**:2703–38 with permission from Elsevier.
ESC 2014 Guidelines on diagnosis and management of hypertrophic cardiomyopathy, *Eur Heart J*. 2014;**35**:2733–79, with permission from Oxford University Press.

Physical activity and sports

Patients are allowed to participate in low-intensity competitive sports (Class IIa-C, ACC/AHA 2011). Intensive competitive sports should be avoided, regardless of age, LVOT obstruction severity, or prior septal reduction intervention (Table 37.19). For sports classification, see also Chapter 83 on athlete's heart in Miscellaneous topics.

Follow-up

Recommendations are provided in Table 37.20 as well as in the discussion of Investigations.

Table 37.19 Physical Activity and Sports

ACC/AHA 2011 GL on HCM

Participation in Competitive or Recreational Sports and Physical Activity

Low intensity competitive sports (e.g., golf and bowling).	IIa-C
Recreational sporting activities.	IIa-C
Intense competitive sports regardless of age, sex, race, presence or absence of LVOT obstruction, prior septal reduction therapy, or implantation of a cardioverter-defibrillator for high-risk status.	III-C

ACCF/AHA 2011 GL on HCM

Recommendations for the acceptability of recreational (noncompetitive) sports activities and exercise in patients with HCM*

Intensity level Eligibility scale for HCM†

High		*Moderate*		*Low*	
Basketball (full court)	0	Baseball/softball	2	Bowling	5
Basketball (half court)	0	Biking	4	Brisk walking	5
Body building‡	1	Hiking	3	Golf	5
Gymnastics	2	Modest hiking	4	Horseback riding‡	3
Ice hockey‡	0	Motorcycling‡	3	Scuba diving§	0
Racquetball/squash	0	Jogging	3	Skating	5
Rock climbing‡	1	Sailing§	3	Snorkelling§	5
Running (sprinting)	0	Surfing§	2	Weights (nonfree weights)	4
Skiing (downhill)‡	2	Swimming (laps)§	5		
Skiing (cross-country)	2	Tennis (doubles)	4		
Soccer	0	Treadmill/stationary bicycle	5		
Tennis (singles)	0	Weightlifting (free weights)‡$‖	1		
Touch (flag) football	1				
Windsurfing§	1				

ESC 2014 GL on HCM. Recommendations for follow-up of mutation carriers without a phenotype

In definite mutation carriers who have no evidence of disease expression, sports activity may be allowed after taking into account the underlying mutation and the type of sport activity, and the results of regular and repeated cardiac examinations.	IIb-C

*Recreational sports are categorized according to high, moderate, and low levels of exercise and graded on a relative scale (from 0 to 5) for eligibility, with 0 to 1 indicating generally not advised or strongly discouraged; 4 to 5, probably permitted; and 2 to 3, intermediate and to be assessed clinically on an individual basis. The designations of high, moderate, and low levels of exercise are equivalent to an estimated >6, 4 to 6, and <4 metabolic equivalents, respectively.
†Assumes absence of laboratory DNA genotyping data; therefore, limited to clinical diagnosis.
‡These sports involve the potential for traumatic injury, which should be taken into consideration for individuals with a risk for impaired consciousness.
§The possibility of impaired consciousness occurring during water-related activities should be taken into account with respect to the individual patient's clinical profile.
$Recommendations generally differ from those for weight-training machines (nonfree weights), based largely on the potential risks of traumatic injury associated with episodes of impaired consciousness during bench-press manoeuvres; otherwise, the physiologic effects of all weight-training activities are regarded as similar with respect to the present recommendations.
‖Individual sporting activity not associated with the team sport of ice hockey.
ACCF/AHA 2011 Guidelines for the diagnosis and treatment of hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2011;**58**:2703–38 with permission from Elsevier.
ESC 2014 Guidelines on diagnosis and management of hypertrophic cardiomyopathy, *Eur Heart J.* 2014;**35**:2733–79, with permission from Oxford University Press.

Table 37.20 ESC 2014 GL on HCM. Routine follow-up

A clinical evaluation, including 12-lead ECG and TTE, every 12–24 months in clinically stable patients or whenever there is a change in symptoms.	I-C
48-Hour ambulatory ECG every 12–24 months in clinically stable patients, every 6–12 months in patients in sinus rhythm with left atrial dimension 45 mm, and whenever patients complain of new palpitations.	I-C
CMR every 5 years in clinically stable patients, or every 2–3 years in patients with progressive disease.	IIb-C
Symptom-limited exercise testing every 2–3 years in clinically stable patients, or every year in patients with progressive symptoms.	IIa-C
Cardiopulmonary exercise testing (when available) every 2–3 years in clinically stable patients, or every year in patients with progressive symptoms.	IIb-C

ESC 2014 Guidelines on diagnosis and management of hypertrophic cardiomyopathy, *Eur Heart J*. 2014;**35**:2733–79, with permission from Oxford University Press.

Family counselling and genetic testing

Family counselling is essential when the diagnosis of HCM is established (Table 37.21 and Figure 37.6). Clinical assessment of all first-degree relatives (particularly those <25 years) is necessary. It is recommended that clinical screening should start between 10 and 12 years, and then repeated every 2 years until the age of 20 and every 5 years until the age of 60.[53] However, the majority of child carriers of sarcomere gene mutations and child relatives with unknown genetic status do not develop HCM, at least within the next 12 years of follow-up.[6] Advances in DNA sequencing techniques (deep or massive parallel sequencing) have made genetic screening practical, with a diagnostic yield of approximately 50% with familial HCM but lower (<30%) when sporadic disease is considered (see http://www.genetests.org). In familial HCM, genetic screening of the clinically normal family members could lead to early identification of those with the causal mutation.[3,4] Although genetic testing is a powerful tool for both diagnosis and future treatment options, it has several limitations. Application of genetic testing is relevant whenever one of the known causal genes is responsible for HCM in the family. In addition, not all genetic variants, including non-synonymous variants in sarcomeric genes, cause HCM, and many could be benign variants. Therefore, identification of a non-synonymous variant in a known gene for HCM in an individual alone is not sufficient to establish the causal role, and a specific mutation in isolation has no prognostic utility.[54] There is no compelling evidence that genetically affected individuals without LV hypertrophy are at increased risk of sudden death.[5] Recent data suggest that the penetrance of the disease is much less than previously thought, and the SCD event rate in predictively tested mutation-carrying relatives is lower than in probands.[55] Whether gene-positive, phenotype-negative individuals carry a higher risk of sudden death is not known. Finally, the absence of a known mutation present in the family does not offer 100% security since there is possible presence of a second mutation and/or technical errors. Thus, the value of genetic screening is debatable.[56] Genetic testing may also be useful when metabolic storage disorders with either a very bad prognosis (LAMP2 cardiomyopathy) that may lead to heart transplantation or the possibility of therapy (Fabry's disease) are suspected. The potential association of double, triple or compound sarcomere mutations (5% of patients with HCM) with a higher risk is under study.[4]

Table 37.21 Genetic counselling and testing

ACCF/AHA 2011 GL on HCM Proposed clinical screening strategies with echocardiography (and 12-lead ECG) for detection of hypertrophic cardiomyopathy with left ventricular hypertrophy in families*
Age <12 y – *Optional unless:*
Malignant family history of premature death from HCM or other adverse complications
Patient is a competitive athlete in an intense training program
Onset of symptoms
Other clinical suspicion of early LV hypertrophy
Age 12 to 18–21 y† – *Every 12–18 mo*
Age >18–21 y – ***At onset of symptoms or at least every 5 y.*** More frequent intervals are appropriate in families with a malignant clinical course or late-onset HCM.

(*continued*)

Table 37.21 Continued

ACCF/AHA 2011 GL on HCM	
Genetic testing strategies/family screening	
Evaluation of familial inheritance and genetic counselling.	I-B
Patients who undergo genetic testing should also undergo counselling by someone knowledgeable in the genetics of cardiovascular disease so that results and their clinical significance can be appropriately reviewed with the patient.	I-B
Screening (clinical, with or without genetic testing) in first-degree relatives of patients with HCM.	I-B
Genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy is recommended in patients with an atypical clinical presentation of HCM or when another genetic condition is suspected to be the cause.	I-B
Genetic testing in the index patient to facilitate the identification of first-degree family members at risk for developing HCM.	IIa-B
The usefulness of genetic testing in the assessment of risk of SCD in HCM is uncertain.	IIb-B
Genetic testing in relatives when the index patient does not have a definitive pathogenic mutation.	III-B
Ongoing clinical screening in genotype-negative relatives in families with HCM.	III-B
Genotype-positive/phenotype-negative patients	
Serial ECG, TTE, and clinical assessment at periodic intervals (12 to 18 months in children and adolescents and about every 5 years in adults), based on the patient's age and change in clinical status, in individuals with pathogenic mutations who do not express the HCM phenotype.	I-B
ESC 2014 GL on HCM	
Genetic counselling	
When disease cannot be explained solely by a non-genetic cause, whether or not clinical or genetic testing will be used to screen family members.	I-B
Should be performed by professionals trained for this specific task working within a multidisciplinary specialist team.	IIa-C
Genetic testing in probands[a]	
In patients fulfilling diagnostic criteria for HCM, when it enables cascade genetic screening of their relatives.	I-B
Should be performed in certified diagnostic laboratories with expertise in the interpretation of cardiomyopathy-related mutations.	I-C
In the presence of symptoms and signs of disease suggestive of specific causes of HCM, to confirm the diagnosis.	I-B
In patients with a borderline diagnosis of HCM[b] only after detailed assessment by specialist teams.	IIa-C
Post-mortem genetic analysis of stored tissue or DNA in deceased patients with pathologically confirmed HCM, to enable cascade genetic screening of their relatives.	IIa-C
Genetic and clinical testing of adult relatives	
Cascade genetic screening, after pre-test counselling, in first-degree adult relatives of patients with a definite disease-causing mutation.	I-B
Clinical evaluation, ECG and echocardiography and long-term follow-up, in first-degree relatives who have the same definite disease-causing mutation as the proband.	I-C
First-degree relatives who do not have the same definite disease-causing mutation as the proband should be discharged from further follow-up but advised to seek re-assessment if they develop symptoms or when new clinically relevant data emerge in the family.	IIa-B
When no definite genetic mutation is identified in the proband or genetic testing is not performed, clinical evaluation with ECG and echocardiography should be considered in first-degree adult relatives and repeated every 2–5 years (or 6–12 months if non-diagnostic abnormalities are present).	IIa-C
Genetic and clinical screening in children	
Predictive genetic testing-following pre-test family counselling at age ≥ 10 years for children of patients with a definite disease-causing mutation	IIa-C
In first-degree child relatives aged ≥10 years, in whom the genetic status is unknown, clinical assessment with ECG and echocardiography should be considered every 1–2 years between 10 and 20 years of age, and then every 2–5 years thereafter.	IIa-C

(*continued*)

Table 37.21 Continued

If requested by the parent(s) or legal representative(s), clinical assessment with ECG and echocardiography may precede or be substituted for genetic evaluation after counselling	IIb-C
Clinical or genetic testing of first-degree child relatives before the age of 10 years when there is a malignant family history in childhood or early-onset disease or when children have cardiac symptoms or are involved in particularly demanding physical activity	IIb-C

*When pathologic mutations are not identified or genetic testing is either ambiguous or not performed.

†Age range takes into consideration individual variability in achieving physical maturity and in some patients may justify screening at an earlier age. Initial evaluation should occur no later than early pubescence.

a Proband: usually the first family member to be diagnosed with the condition.

b Borderline: left ventricular wall thickness 12–13 mm in adults; left ventricular hypertrophy in the presence of hypertension, athletic training, valve disease.

ACCF/AHA 2011 Guidelines for the diagnosis and treatment of hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2011;**58**:2703–38 with permission from Elsevier.

ESC 2014 Guidelines on diagnosis and management of hypertrophic cardiomyopathy, *Eur Heart J*. 2014;**35**:2733–79, with permission from Oxford University Press.

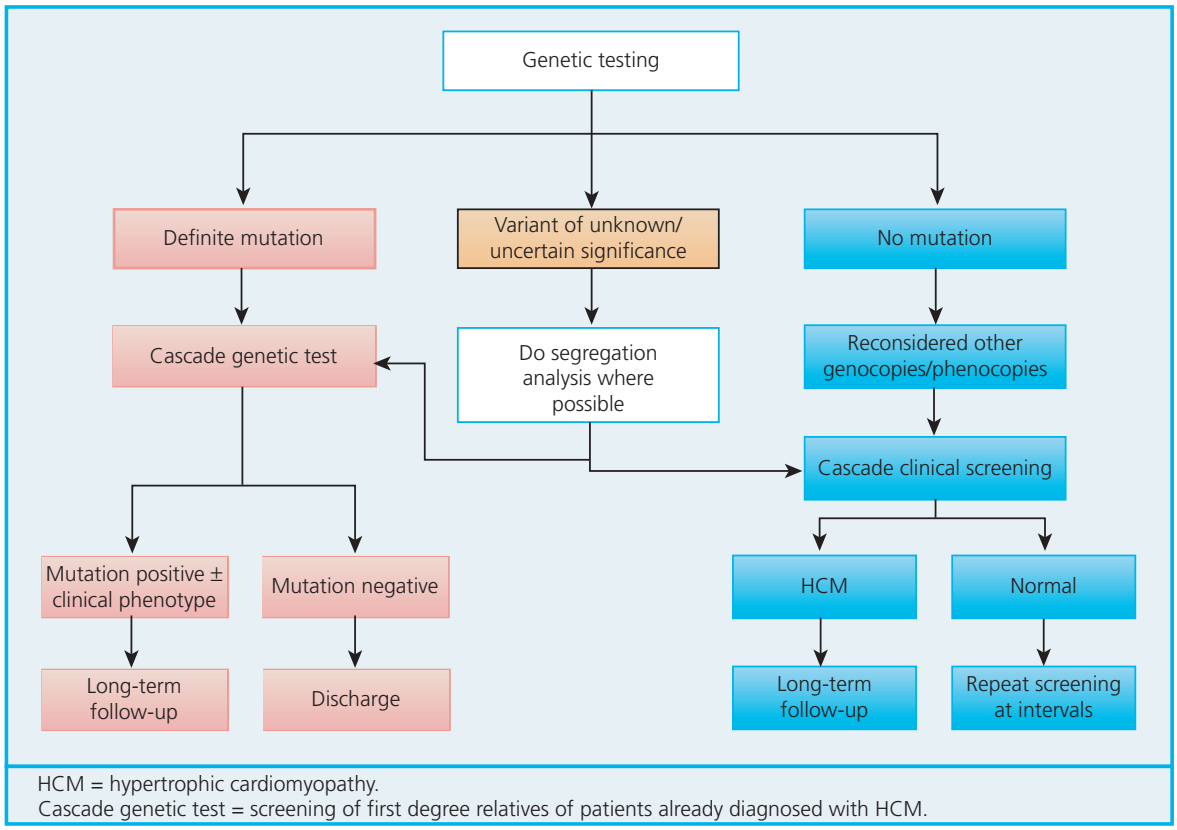


Figure 37.6 ESC 2014 GL on HCM. Flow chart for the genetic and clinical screening of probands and relatives.

ESC 2014 Guidelines on diagnosis and management of hypertrophic cardiomyopathy, *Eur Heart J*. 2014;**35**:2733–79, with permission from Oxford University Press.

Pregnancy

It is not contraindicated. Serious complications are rare (1–2%); caution is needed in patients with significant gradient when administering epidural anaesthesia that induces peripheral vasodilation (Table 37.22).[57,58]

Table 37.22 Pregnancy in HCM

ACC/AHA 2011 GL on HCM. Pregnancy/delivery	
In women who are asymptomatic or whose symptoms are controlled with beta-blocking drugs, the drugs should be continued during pregnancy, but increased surveillance for fetal bradycardia or other complications is warranted.	I-C
Genetic counselling before planned conception (for mother or father with HCM).	I-C
In women with HCM and resting or provocable LVOT obstruction ≥ 50 mm Hg and/or cardiac symptoms not controlled by medical therapy alone, pregnancy is associated with increased risk, and these patients should be referred to a high-risk obstetrician.	I-C
The diagnosis of HCM among asymptomatic women is not considered a contraindication for pregnancy, but patients should be carefully evaluated in regard to the risk of pregnancy.	I-C
For women whose symptoms are controlled (mild to moderate), pregnancy is reasonable, but expert maternal/fetal medical specialist care, including cardiovascular and prenatal monitoring, is advised.	IIa-C
For women with advanced heart failure symptoms and HCM, pregnancy is associated with excess morbidity/mortality.	III-C
ESC 2014 GL on HCM. Reproductive issues in women with hypertrophic cardiomyopathy	
Pre-pregnancy risk assessment and counselling in all women.	I-C
Counselling on safe and effective contraception in all women of fertile age.	I-C
Counselling on the risk of disease transmission for all men and women before conception.	I-C
β-Blockers (preferably metoprolol) should be continued in women who used them before pregnancy.	IIa-C
β-Blockers (preferably metoprolol) should be started in women who develop symptoms during pregnancy.	I-C
Monitoring of fetal growth and of the condition of the neonate whenever β-blockers are prescribed	I-C
Scheduled (induced) vaginal delivery as first choice in most patients	I-C
Therapeutic anticoagulation with LMWH or vitamin K antagonists depending on the stage of pregnancy for AF	I-C
Cardioversion for persistent AF atrial fibrillation.	IIa-C

ACCF/AHA 2011 Guidelines for the diagnosis and treatment of hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2011;**58**:2703–38 with permission from Elsevier.

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Chapter 38

Restrictive cardiomyopathy

Definition

Restrictive cardiomyopathy (RCM) is defined as heart muscle disease that results in impaired ventricular filling, with normal or decreased diastolic volume of either or both ventricles. Systolic function usually remains normal, at least early in the disease, and wall thickness may be normal or increased, depending on the underlying cause.[1,2] Restrictive cardiomyopathies are the least common of the cardiomyopathy disorders.

Pathophysiology

In typical RCM, systolic function is less affected than diastolic function, and usually there is an abnormality of filling rather than of relaxation. Thus, in most cases, there is rapid completion of filling of a poorly compliant ventricle in early diastole (E wave), with little or no further filling in late diastole (A wave). Though there is poor compliance of the ventricles, the early filling rate is higher than normal, possibly as a result of augmented ventricular diastolic suction. The situation is thus analogous to pericardial disease causing constriction or tamponade. Usually, patients with restrictive cardiomyopathy have normal ventricular volumes but raised filling pressures. In both constriction and restriction, there is characteristically rapid completion of ventricular filling in early diastole so that the ventricular diastolic waveform has a dip and plateau (square root sign) configuration, but this is not always present.[2] Since the condition affects either or both ventricles, it may cause symptoms and signs of right or left ventricular failure. Infiltrative cardiac diseases may also produce hypertrophic or dilated cardiomyopathy patterns. Some of them increase ventricular wall thickness, without actual myocyte hypertrophy and, occasionally, even produce dynamic left ventricular outflow obstruction (as may happen in amyloidosis), while others cause chamber enlargement with secondary wall thinning and global or regional wall motion abnormalities (as may happen in sarcoidosis).[3]

Aetiology

Conditions associated with restrictive cardiomyopathy are presented in Table 38.1. Infiltrative cardiomyopathies are characterized by the deposition of abnormal substances that cause the ventricular walls to become progressively rigid, thereby impeding ventricular filling.

Amyloidosis is the most common cause in the western world and, apart from diastolic, may also cause systolic ventricular abnormalities. Cardiac involvement is more

Table 38.1 Types of restrictive cardiomyopathy

Myocardial
Noninfiltrative
Idiopathic cardiomyopathy*
Familial cardiomyopathy (sarcomeric or other mutations)
Scleroderma
Pseudoxanthoma elasticum
Diabetic cardiomyopathy
Infiltrative
Amyloidosis*
Sarcoidosis*
Gaucher's disease
Mucopolysac charidoses (Hurler–Scheie syndrome)
Fatty infiltration
Storage diseases
Iron overload cardiomyopathy (primary haemochromatosis, beta thalassaemia, and other anaemias)
Fabry's disease
Glycogen storage disease
Myocardial oxalosis (primary hyperoxaluria)
Endomyocardial
Endomyocardial fibrosis*
Radiation*
Cardiotoxicity of anthracyclines*
Hypereosinophilic syndrome
Carcinoid heart disease
Metastatic cancers
Drugs causing fibrous endocarditis (serotonin, methysergide, ergotamine, mercurial agents, busulfan)

* the most common conditions.
Data sourced from Kushwaha SS, *et al*. Restrictive cardiomyopathy. *N Engl J Med*. 1997;**336**:267–76.

common in **primary amyloidosis**, which is caused by the production of immunoglobulin light chains (AL) by plasma cells, often in the context of multiple myeloma.[1,4] Restrictive cardiomyopathy results from replacement of normal myocardial contractile elements by infiltrative interstitial deposits that begin in the subendocardium and extend in the myocardium. Survival is poor in the presence of cardiac involvement and heart failure symptoms <1 year after diagnosis. **Secondary amyloidosis** is caused by the deposition of a non-immunoglobulin protein (AA) and can be **hereditary**, **senile**, or due to a **chronic inflammatory process**.[5,6] **Hereditary** transthyretin-related amyloidosis (ATTR) is due to amyloid derived from a mutation (usually V30M) in the gene encoding for the hepatically produced protein transthyretin. It can occur with or without peripheral neuropathy. It is autosomal dominant but sporadic mutations may also occur thus making a negative family history not a useful screening method. **Senile systemic amyloidosis** (wild type-non mutant) is probably due to age-related transthyretin misaggregation. Development of cardiomyopathy is less common with secondary amyloidosis and prognosis much better. Symmetric LV hypertrophy, thickened valves, and moderately depressed LV function in males >65 years old suggest ATTR or SSA rather than HCM.[7] Amyloid infiltration of the heart is common in the elderly and is typically subendocardial.

Sarcoidosis affects the basal septum, atrioventricular node and His bundle, focal regions in the ventricular free walls, and the papillary muscles. Two-dimensional echocardiographic characteristics of cardiac sarcoid vary according to disease activity, and include wall thickening (>13 mm) due to granulomatous expansion and wall thinning (<7 mm) due to fibrosis. With scar retraction, aneurysms may develop, especially if the patient has been treated with corticosteroids. Cardiac involvement is clinically apparent in only 5% of patients with systemic sarcoidosis, but, on autopsy, the prevalence of cardiac disease is approximately 25%.[8] In a recent study in Finland, the incidence of cardiac sarcoidosis was 5.3 cases per million.[9]

Fabry's disease is an X-linked autosomal recessive disease that results from the progressive accumulation of glycosphingolipids due to lysosomal alpha-galactosidase deficiency. Affected patients have microvascular disease of the kidneys, heart, and brain. Cardiac involvement is not manifested until the third or fourth decade of life and may mimic hypertrophic cardiomyopathy.

Primary (idiopathic) restrictive cardiomyopathy is expressed morphologically as myocyte hypertrophy and interstitial fibrosis.[10] It can be familial, with dominant inheritance and incomplete penetrance, and associated with skeletal myopathy and complete heart block.

Sarcomeric mutations There is now clinical and genetic evidence demonstrating that restrictive cardiomyopathy is part of the spectrum of sarcomeric disease and frequently coexists with hypertrophic cardiomyopathy in affected families.[11] To date, mutations have been identified in the cardiac genes for the sarcomeric proteins a-actin, troponin I and troponin T as well as for desmin (a cytosolic protein) (Figure 36.1 of Chapter 36 on DCM, Table 38.2).

Endomyocardial fibrosis and **Löffler's endocarditis** (eosinophilic cardiomyopathy) are the main causes of obliterative cardiomyopathy. They are both associated with eosinophilia (>1.5 × 10^9/L for, at least, 6 months) that is either primary (Loffler's) or secondary due to parasitic infections, lymphomas, or vasculitis.[1,2] The intracytoplasmic granular content of activated eosinophils is responsible for the toxic damage to the heart, with initial myocarditis and arteritis that are followed by a thrombotic stage and eventually formation of extensive fibrosis that promotes further thrombotic material formation. Endomyocardial

Table 38.2 Genetic causes of restrictive cardiomyopathy

Gene	Protein	Location and function
Autosomal		
MYH7 (5% of patients)	Beta-myosin heavy chain	Sarcomere
TNNI3 (5% of patients)	Cardiac troponin I	Sarcomere
DES	Desmin	Cytoskeleton, dystrophin-associated
TNNT2	Cardiac troponin T	Sarcomere
ACTC	Cardiac actin	Sarcomere

fibrosis is endemic in equatorial Africa, South America, and Asia.

Anthracyclines can cause dilated cardiomyopathy or endomyocardial fibrosis. Diastolic dysfunction may persist, even years, after therapy with anthracyclines. The risk is greatly increased when there is a history of **irradiation** that causes myocardial and endocardial fibrosis, particularly in the right ventricle.[1]

Carcinoid heart disease occurs as a late complication of the carcinoid syndrome in up to half of cases, with tricuspid regurgitation as the predominant lesion.[1] The development of cardiac lesions is correlated with circulating levels of serotonin and its principal metabolite 5-hydroxyindoleacetic acid. The pathological lesion consists of fibrous plaques involving the tricuspid and pulmonary valves and the right ventricular endocardium.

Chloroquine and **hydroxychloroquine** in large cumulative doses (kg) may cause skeletal myopathy and restrictive cardiomyopathy.[12]

Presentation

The diagnosis of restrictive cardiomyopathy should be considered in a patient presenting with **heart failure, but no evidence of cardiomegaly or systolic dysfunction**. Usually, patients present with **fatigue** and **dyspnoea**. Angina does not occur, except in amyloidosis in which it may be the presenting symptom.[2] Patients may also present with thromboembolic complications. Cardiac conduction disturbances and AF are particularly common in idiopathic restrictive cardiomyopathy and amyloidosis. Heart block and ventricular arrhythmias are also common in cardiac sarcoidosis (Table 38.3). Signs and symptoms that raise suspicion of specific diagnoses are presented in Tables 35.1 to 35.4 of Chapter 35.

Physical examination

JVP is elevated. A rapid 'x' descent and especially a prominent 'y' descent may be present in sinus rhythm.

Kussmaul's sign, i.e. a rise or failure of JVP to decrease with inspiration, may be present but typically occurs in constrictive pericarditis.

S_3 of LV or RV origin may be present.

Peripheral oedema or **ascites** and **enlarged and pulsatile liver** may be seen in progressed disease.

In advanced cases, all typical signs of heart failure are present, except cardiomegaly, although dilated ventricles may develop at later stages, particularly in patients with amyloidosis or sarcoidosis.

Investigations

Laboratory tests Haemoglobin, WBC, serum iron and ferritin, liver, renal, and thyroid function tests, and serum electrolytes should be taken at initial assessment. If suspicion of underlying disease, specific tests such as urine and plasma immunofixation and free light chains for amyloidosis are obtained.[7]

Chest X-ray reveals a normal cardiac size with possible atrial enlargement. Pulmonary congestion and pleural effusions may be present.

ECG shows non-specific ST-T changes with or without conduction abnormalities. The absence of increased voltage on ECG, despite the appearance of echocardiographic hypertrophy, can be the first clue to certain infiltrative diseases, such as cardiac amyloid or Friedreich's ataxia. Low voltage and prolonged PR interval and a pseudoinfarction pattern in the inferoseptal wall are typical signs of advanced amyloidosis. A decrease in QRS complex amplitude occurs because of myocyte atrophy, along with decreased conduction velocity and dyssynchronous activation resulting from amyloid deposition. However, infiltrative cardiomyopathies associated with increased size of cardiac myocytes may have increased voltage (e.g. Fabry's disease).[3] AV block suggests a desmin-related cardiomyopathy or amyloidosis.[13]

Two-dimensional echocardiography Ventricles are small, with normal or increased wall thickness, and the atria are usually dilated. Valvular regurgitation and atrial enlargement are more common in RCM than in constrictive pericarditis.

In **amyloidosis**, the ventricular walls are thickened, and pericardial effusion may coexist. In advanced cardiac amyloidosis, the typical ground glass (granular or sparkling) appearance of the myocardium as well as pericardial effusion may be seen.[14]

Table 38.3 HRS expert consensus statement on arrhythmias in cardiac sarcoidosis (CS)

Diagnosis of cardiac sarcoidosis	
There are 2 pathways to a diagnosis of CS: ***1. Histological Diagnosis from Myocardial Tissue*** CS is diagnosed in the presence of non-caseating granuloma on histological examination of myocardial tissue with no alternative cause identified (including negative organismal stains if applicable). ***2. Clinical Diagnosis from Invasive and Non-Invasive Studies:*** It is probable* that there is CS if: a) There is a histological diagnosis of extra-cardiac sarcoidosis *and* b) One or more of following is present: - Steroid +/– immunosuppressant responsive cardiomyopathy or heart block - Unexplained reduced LVEF (<40%) - Unexplained sustained (spontaneous or induced) VT - Mobitz type II 2nd degree heart block or 3rd degree heart block - Patchy uptake on dedicated cardiac PET (in a pattern consistent with CS) - Late Gadolinium Enhancement on CMR (in a pattern consistent with CS) - Positive gallium uptake (in a pattern consistent with CS) *and* c) Other causes for the cardiac manifestation(s) have been reasonably excluded	
Screening for cardiac involvement in patients with biopsy-proven extracardiac sarcoidosis	
Patients with biopsy-proven extracardiac sarcoidosis:	
Ask about unexplained syncope/presyncope/significant palpitations (complaint lasting >2 weeks) and screen with a 12-lead ECG	I
Echocardiogram	IIa
CMR or FDG-PET, at a centre with experience in CS imaging with one or more abnormalities detected on initial screening by symptoms/ECG/echocardiogram	IIa
Advanced cardiac imaging, CMR, or FDG-PET is not recommended for patients without abnormalities on initial screening by symptoms/ECG/echocardiogram.	III

* In general, 'probable involvement' is considered adequate to establish a clinical diagnosis of CS.
HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm*. 2014;**11**:1305–23 with permission from Elsevier.

Two-dimensional echocardiography is diagnostic in the **hypereosinophilic syndrome**, revealing the typical packing of both ventricular apices due to thrombus and usually significant MR.

Akinetic segments interspersed with normokinetic segments, resulting in an uneven wall motion abnormality, may be seen in **sarcoidosis**.

Doppler echocardiography The pattern of mitral inflow velocity reveals increased early diastolic filling velocity (E wave ≥1 m/s), decreased late filling velocity (A wave ≤0.5 m/s), increased E/A ratio (≥2), decreased deceleration time (≤150 ms), and decreased isovolumic relaxation time (≤70 ms). Pulmonary or hepatic vein patterns show that systolic forward flow is less than diastolic forward flow, with increased reversal of diastolic flow after atrial contraction during inspiration.

In patients with amyloidosis, Doppler variables of shortened deceleration time and increased early diastolic filling velocity to atrial filling velocity ratio are stronger predictors of cardiac death than were the two-dimensional echocardiographic variables of mean left ventricular wall thickness and fractional shortening.[15] New modalities, such as **strain rate** and **speckle tracking**, may be useful in diagnosing early amyloid infiltration.[14]

Cardiac catheterization The characteristic haemodynamic feature is a deep and rapid early decline in ventricular pressure at the onset of diastole, with a rapid rise to a plateau in early diastole. This is manifested as a prominent y descent, followed by a rapid rise to a plateau, i.e. the dip and plateau or square root sign. However, filling and the ventricular diastolic waveform are affected by heart rate, degree of hydration, and stage in the disease process so that, in some individuals, filling is more gradual. The right atrial pressure is elevated, and the wave form is M- or W-shaped, as in constrictive pericarditis. Usually, respiratory variation of venous pressure is absent, but the y descent may become deeper during inspiration.

Electrophysiology study may be used for risk stratification of sudden cardiac death in patients with cardiac sarcoidosis and LVEF >35%.[16]

Cardiac magnetic resonance has a higher resolution than echocardiography and detects the presence of myocardial fibrosis.[17] It is particularly useful in the diagnosis of infiltrative diseases such as sarcoidosis, amyloidosis, radiation-induced fibrosis, iron loaded cardiomyopathy, and constrictive pericarditis. In cardiac sarcoidosis, CMR may be used for risk stratification of sudden cardiac death.[16] Myocardial extracellular volume (bolus or

Table 38.4 HRS/EHRA 2011 statement on genetic testing

State of genetic testing for restrictive cardiomyopathy	
Mutation-specific genetic testing for family members and appropriate relatives following the identification of an RCM causative mutation in the index case.	I
Patients in whom a cardiologist has established a clinical index of suspicion for RCM based on examination of the patient's clinical history, family history, and electrocardiographic/echocardiographic phenotype.	IIb

HRS/EHRA 2011 Expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Europace*. 2011;**13**:1077–109 with permission from Oxford University Press.

infusion technique) and pre-contrast T1 in late gadolinium enhanced CMR are biomarkers for cardiac AL amyloid and they predict mortality in systemic amyloidosis.[18]

18 F-fluorodeoxyglucose (FDG) PET imaging, and particularly combined PET-CT is also useful in this respect.[6]

Serum or urine electrophoresis and **bone marrow biopsy** are useful for differentiation of various types of amyloidosis.[19]

Cardiac biopsy may be required in unexplained restrictive cardiomyopathy. A specific condition, such as amyloidosis, iron storage disease, Fabry's disease, sarcoidosis, or glycogen storage disease, may be diagnosed. However, non-specific histological features, such as interstitial fibrosis and myocyte hypertrophy, are common, and patchy infiltration, as typically occurs in sarcoidosis, may obscure the diagnosis. Voltage-guided (through electroanatomical mapping) or advanced imaging-guided biopsy may be useful in this setting.[16] Amyloidosis cannot be excluded purely on the basis of light microscopy. Electron microscopy of myocardial tissue can confirm the diagnosis when light microscopy is negative, though care should be taken to distinguish between recently formed perimyocyte collagen and amyloid. The presence or absence of amyloid deposits in other organs is not absolutely predictive of cardiac involvement. When cardiac amyloid is suspected, fat pad or rectal biopsies are easier and safer alternatives.[19]

Recommendations for genetic testing are presented in Table 38.4.[20]

Differential diagnosis

Restrictive haemodynamic characteristics may also be seen in cases of dilated or hypertrophic cardiomyopathy. However, the main problem is the distinction of RCM from constrictive pericarditis. Differences are summarized in Table 38.5, but no test is absolutely diagnostic. The two conditions may also coexist, as happens in the cases of radiation fibrosis.[2]

In the elderly, restrictive cardiomyopathy should be differentiated from age-related changes in diastolic compliance. Cardiac amyloidosis may mimic hypertrophic cardiomyopathy or hypertensive heart disease (Table 38.6).

Table 38.5 ESC 2015 GL on pericardial diseases. Differential diagnosis of restrictive cardiomyopathy and constrictive pericarditis

Diagnostic evaluation	Constrictive pericarditis	Restrictive cardiomyopathy
Physical findings	Kussmaul sign, pericardial knock	Regurgitant murmur. Kussmaul sign may be present. S3 (advanced).
ECG	Low voltages, non-specific ST/T changes, atrial fibrillation.	Low voltages, pseudoinfarction. possible widening of QRS. left-axis deviation, atrial fibrillation.
Chest X-ray	Pericardial calcifications (113 of cases).	No pericardial calcifications.
Echocardiography	◆ Sepal bounce. ◆ Pericardial thickening and calcifications. ◆ Respiratory variation of the mitral peak E velocity of >25% and variation in the pulmonary venous peak D flow velocity of >20% ◆ Colour M-mode flow propagation velocity (Vp) >45 cm/sec. ◆ Tissue Doppler: peak e^{t} >8.0 cm/s.	◆ Small left ventricle with large atria, possible increased wall thickness. ◆ E/A ratio >2. short DT. ◆ Significant respiratory variations of mitral inflow are absent ◆ Colour M-mode flow propagation velocity (Vp) <45 cm/sec. ◆ Tissue Doppler: peak e' <8.0 cm/s.

(*continued*)

Table 38.5 Continued

Cardiac catheterization	'Dip and plateau' or 'square root' sign, right ventricular diastolic, and left ventricular diastolic pressures usually equal, ventricular interdependence (i.e. assessed by the systolic area index >I.I)[a]	Marked right ventricular systolic hypertension (>50 mmHg) and left ventricular diastolic pressure exceeds right ventricular diastolic pressure (LVEDP >RVEDP) at rest or during exercise by 5 mmHg or more (RVEDP <1/3 RVSP).
CT/CMR	Pericarcial thickness >3–4 mm, pericardial calcifications (C1), ventricular interdependence (real-time Clne CMR).	Normal pericardial thickness (<3.0 mm). myocardial involvement by morphology and functional study (CMR).

CMR, cardiac magnetic resonance; CT, computed tomography; DT, deceleration time; LVEDP, left ventricular end-diastolic pressure; RVEDP, right ventricular end-diastolic pressure; RVSP, right ventricular systolic pressure; S3, third sound.
a: The systolic area index was defined as the ratio of the RV area (mmHg x s) to the LV area (mmHg x s) in inspiration versus expiration.
Specific diagnostic echocardiographic criteria for the diagnosis of constrictive pericarditis has been recently proposed by the Mayo Clinic and include: septal bounce or ventricular septal shift with either medial e' >8 cm/s or hepatic vein expiratory diastolic reversal ratio >0.78 (sensitivity 87%, specificity 91%; specificity may increase to 97% if all criteria are present with a correspondent decrease of sensitivity to 64%.
ESC 2015 Guidelines for the diagnosis and management of pericardial diseases. *Eur Heart J*. 2015;**36**:2921–64 with permission from Oxford University Press.

Table 38.6 Differential diagnosis of cardiac amyloidosis, HCM, and hypertensive heart disease

	Amyloidosis	**Hypertensive heart disease**	**Hypertrophic cardiomyopathy**
Distribution of LV thickening	Global	Global	Usually regional
LV cavity size	Normal to small	Normal; may dilate in end stage	Normal; may dilate in end stage
Ejection fraction	Low normal or mildly ↓	Ranges from hyperdynamic to low	Often hyperdynamic
RV thickness	Often ↑	Normal	Rarely ↑
Myocardial echogenicity	Often ↑	Normal	Normal
Longitudinal strain/tissue Doppler velocity	Severely ↓	Mildly to moderately ↓	Regionally ↓
Valve abnormalities	May be uniformly thickened	No specific abnormality	Mitral regurgitation if systolic anterior motion
	Mitral regurgitation rarely more than mild		
Diastolic function	Often restrictive (grade 3 or 4)	Grade 1 or 2 most common	No specific common pattern
ECG voltage	Frequently low in limb leads	LVH	LVH
Blood pressure	Normal to low; rarely elevated	High	Normal
Cardiac MRI	Frequent, widespread delayed gadolinium enhancement, including RV and atria	Mild or no late enhancement	Varying, often mild, late enhancement, usually localized to LV

LV indicates left ventricular; RV, right ventricular; MRI, magnetic resonance imaging; and LVH, left ventricular hypertrophy.
Falk RH. Cardiac amyloidosis: a treatable disease, often overlooked. *Circulation*. 2011;**124**:1079–85, with permission from Wolters Kluwer.

Therapy

Diuretics are used with caution to avoid inadvertent reduction of ventricular filling pressures. There may be also extreme sensitivity to **beta blockers**. **ACEI/ARBs** may also be used with caution.

In AL amyloidosis, possibly because of an associated autonomic neuropathy, ACEIs and ARBs are rarely tolerated and may provoke profound hypotension, even when prescribed in small doses. Beta-blockade is of no proven use and may aggravate hypotension whereas calcium channel blockers generally worsen congestive heart failure.[5]

Digoxin is potentially arrhythmogenic, particularly in amyloidosis.

Table 38.7 Indications for ICD*

ESC 2015 GL on VA and SCD	
Cardiac amyloidosis	
Light-chain amyloidosis or hereditary transthyretin cardiac amyloidosis and sustained ventricular arrhythmias causing haemodynamic instability	IIa-C
Restrictive cardiomyopathy	
Sustained ventricular arrhythmias causing haemodynamic instability	I-C
Chagas cardiomyopathy	
Chagas cardiomyopathy and LVEF <40%	IIa-C
HRS 2014 statement on arrhythmias in sarcoidosis	
Indications of ICD in cardiac sarcoidosis	
Spontaneous sustained ventricular arrhythmias, including prior cardiac arrest	I
LVEF <35%, despite optimal medical therapy and immunosuppression (if there is active inflammation).	I
An indication for permanent pacemaker implantation	IIa
Unexplained syncope or near-syncope, felt to be arrhythmic in etiology	IIa
Inducible sustained ventricular arrhythmias (>30s monomorphic or polymorphic VT) or clinically relevant VF (VF with triple premature beats of 220 ms is considered a non specific response)	IIa
If VT ablation is planned, an indicated ICD should be implanted after ablation	IIa
LVEF 36%–49% and/or an RVEF<40% despite optimal medical therapy and immunosuppression	IIb
No history of syncope, normal LVEF/RV ejection fraction, no LGE on CMR, a negative EP study, and no indication for permanent pacing	III
Incessant ventricular arrhythmias	III
Severe NYHA IV heart failure	III

* In patients who are expected to survive >1 year with good functional status.
ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015;**36**:2793–2867 with permission from Oxford University Press.
HRS 2014 Expert Consensus Statement on the Diagnosis and Management of Arrhythmias Associated With Cardiac Sarcoidosis. *Heart Rhythm*. 2014;**11**:1304-23 with permission from Elsevier.

Anticoagulation is recommended because of the propensity for thrombus formation in all types of RCM and particularly in endomyocardial fibrosis.

AF reduces cardiac output, and rhythm control is recommended. Cardioversion in amyloidosis should be performed under cover of ventricular or transthoracic pacing with patches.

Permanent pacing and/or **ICD** may be required in conduction disturbances (mainly in amyloidosis, idiopathic RCM, and sarcoidosis), sick sinus syndrome (mainly amyloidosis), and arrhythmias (mainly in sarcoidosis, see Table 38.7.

Transplantation may increase survival, but, in systemic disorders, such as amyloidosis or sarcoidosis, recurrences may be seen in the transplanted heart. **Autologous stem cell transplantation** may also be helpful in amyloidosis.

Amyloidosis has a poor prognosis, particularly in the presence of a monoclonal light chain in serum or urine, multiple myeloma, and hepatic involvement. Senile systemic amyloidosis has a better prognosis.[4] Untreated patients have a median survival of less than 6 months after the onset of heart failure.[21] Median survival is less than 50% in 2 years despite therapy with melphalan, steroids, immunomodulating agents (lenalidomide and/or bortezomib), and stem cell transplantation.[21,22] Bradyarrhythmias herald terminal cardiac decompensation in most patients with severe cardiac AL amyloidosis and prophylactic pacemaker insertion may be considered.[23]

Prognosis of ***idiopathic restrictive cardiomyopathy*** is better than in amyloidosis but relatively poor in children.[24] Transplantation is the only therapeutic option in advanced cases. Prednisone (30–80 md od) tapered over 6 months with or without additional immunosuppression with methotrexate, mycophenolate mofetil, ciclosporin or infliximab is used for ***cardiac sarcoidosis***. Half of the patients with cardiac sarcoidosis require an ICD and 25% of them need permanent pacing. Prognosis has improved but still when the condition presents with heart failure, the 10-year transplantation-free survival is only 53%.[9]

Loffler's endocarditis may respond to steroids at early stages. Surgical decortication may be required in advanced cases of endomyocardial fibrosis, but operative mortality is high (15–25%).[2] Most patients with this condition die within 2 years.[2]

Replacement of alpha-galactosidase reduces wall thickness in ***Fabry's disease***.[25]

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Chapter 39

Arrhythmogenic right ventricular cardiomyopathy/dysplasia

Definition

Arrhythmogenic right ventricular cardiomyopathy or dysplasia (ARVC/D) is predominantly a genetically determined heart muscle disorder that is characterized mainly by fibrofatty replacement of the right ventricular myocardium. This results in abnormalities ranging from regional wall motion abnormalities and aneurysms to global dilation and dysfunction, with or without left ventricular involvement.[1,2]

Epidemiology

The estimated prevalence of ARVC/D in the general population ranges from 0.1 to 0.02%.[3] ARVC/D is one of the most arrhythmogenic forms of human heart disease anda major cause of sudden death in the young.[1,4] The annual incidence of SCD is not known, with reported rates ranging from 0.08 to 1.5%, although, in ICD recipients, the annual rate of intervention is up to 5%.[4,5]

Aetiology

Several causative **desmosomal genes** (encoding for proteins of the cell adhesion complex) have been identified. Since only 30–50% of patients have one of these gene abnormalities, it is assumed that there are also other genes not yet identified. Frequently, patients with ARVC/D have more than one genetic defect in the same gene (compound heterozygosity) or in a second complementary gene (digenic heterozygosity).[6] In addition, a family member

may have an ARVC/D gene defect and develop the disease or have no or minimal manifestations of the disease.[6] ARVC/D is inherited as an autosomal dominant trait with variable, age-dependent penetrance, meaning that the risk of a family member inheriting an abnormal gene is 50% for all offspring of the genetically affected proband. Main responsible genes are presented in Table 39.1. There are also recessive forms such as **Naxos disease** (palmoplantar keratosis, woolly hair and ARVC/D due to plakoglobin mutations) and **Carvajal syndrome** that are associated with a cutaneous phenotype (desmoplakin mutations).[1]

Extradesmosomal gene mutations have also been described. In a recent extensive study in Dutch families, mutations mainly affected placophilin-2 (truncating PKP2 mutations).[7] PKP2 variants that reduce the sodium current may also yield a Brugada syndrome phenotype.[8] Radical mutations in apparently healthy subjects are high-probability ARVC-associated mutations, whereas rare missense mutations should be interpreted in the context of race and ethnicity, mutation location, and sequence conservation.[9] Recently, LMNA (encoding for lamin proteins A and C) and TMEM43 (encoding for the nuclear protein LUMA) mutations were also found in severe forms of ARVC thus indicating that it is not just a disease of desmosomal proteins.[10,11] In addition, DES-encoding desmin, TTN-encoding titin, and PLN-encoding phospholamban have been suggested as novel ARVC/D genes.[1] Mutations in RYR2 gene encoding the ryanodine receptor have been reported in ARVC/D in patients with an arrhythmic presentation resembling that of catecholaminergic polymorphic ventricular tachycardia.[12] However, they may all account for overlap syndromes characterized mostly by a dilated cardiomyopathy phenotype and a high prevalence of conduction disease. The exact role of inflammatory (viral myocarditis) or immune mechanisms that may be present is not known.

Compared with other familial cardiomyopathies and ion channelopathies associated with sudden death, arrhythmogenic cardiomyopathy has low penetrance and unusually variable disease expression, even within members of the same family who carry the same disease-associated mutation, presumably due to genetic and/or epigenetic modifiers that interact with environmental factors.[3] Thus, ARVC/D does not appear to be a monogenic disease, but rather a complex genetic disease, characterized by marked intrafamilial and interfamilial phenotype diversity.

Table 39.1 Main genetic causes of ARVC/D

Gene	Protein	Location and function
DSP	Desmoplakin	Desmosome
PKP2	Plakophilin-2	Desmosome
DSG 2	Desmoglein-2	Desmosome
DSC 2	Desmocollin-2	Desmosome
JUP	Plakoglobin	Desmosome

Pathophysiology

ARVC/D mainly affects proteins of the intercalated disc, particularly the desmosome, a large intercellular junctional protein complex responsible for the mechanical coupling of myocytes. Desmosomes are cellular complexes that primarily serve to link intermediate filaments to the plasma membrane and create strong intercellular linkages (intercellular cardiac glue) that allow transmission of force through the cardiac syncytium.[13] Intercellular junctions are composed of a core region, which mediates cell to cell adhesion, and a plaque region which provides attachment to the intermediate filament cytoskeleton (Figure 39.1). Three separate groups of proteins assemble to form the desmosome: transmembrane proteins, i.e. desmosomal cadherins, such as desmoglein and desmocollin; desmoplakin, a plakin family protein that binds directly to intermediate filaments; and linker proteins, i.e. armadillo proteins, such as plakoglobin and plakophilin, which mediate interactions between the desmosomal cadherin tails and desmoplakin.[1,3]

The mechanism whereby mutations affecting components of the cardiac desmosome result in ARVC/D is not known. It is believed that the lack of the protein or the incorporation of defective proteins into cardiac desmosomes may provoke detachment of myocytes at the intercalated discs, particularly under mechanical stress conditions. Histologically, there is presence of replacement type fibrosis and myocyte degenerative changes, together with substantial fat replacement. The replacement of the right ventricular myocardium by fibrofatty tissue is progressive, starting from the epicardium or mid-myocardium and then extending to become transmural. It eventually leads to wall thinning and aneurysms, typically located at the inferior, apical, and infundibular walls (so-called triangle of dysplasia), the hallmark of ARVC/D. The fibrofatty replacement interferes with electrical impulse conduction and is the key cause of epsilon waves, right bundle branch block, late potentials, and reentrant ventricular arrhythmias, also possibly due to gap junction remodelling. Left ventricular involvement, usually confined to the posterolateral subepicardium, is present in more than half of cases. Predominant LV disease is also recognized. Thus, the term ARVC/D refers to RV, biventricular, and LV dominant subtypes. Mechanical stress may impact cellular junctions, and exercise may exacerbate the progression of the disease.[13]

Presentation

Patients usually present between the second and fourth decades of life due to **palpitations with ventricular ectopic beats or runs of ventricular tachycardia**. Arrhythmias occur early in the natural history

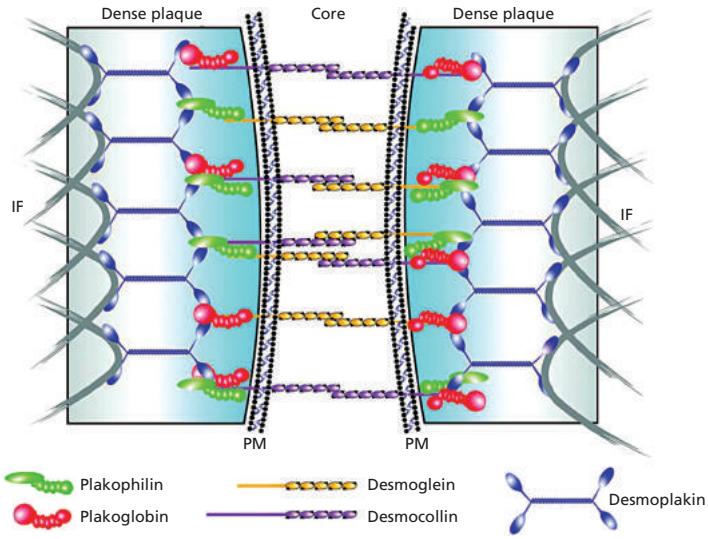

Figure 39.1 Schematic representation of the intracellular and intercellular components of the desmosomal plaque.

IF, intermediate filaments; PM, cytoplasmic membrane.

Basso C, *et al*. Arrhytmogenic right verntricular cardiomyopathy. *Lancet*. 2009;**373**:1289–1300 with permission from Elsevier.

of arrhythmogenic cardiomyopathy, often preceding structural remodelling of the myocardium, and **sudden death** by VF may also be seen in the asymptomatic young people and athletes. Presentation with SCD or VF occurs at a younger age compared to sustained monomorphic VT.[14] There is a predilection for the male sex in the second to the fourth decades of life.[1] Patients with ARVC/D may present with asymptomatic NSVT, despite only subtle RV abnormalities, and have a trend for an increased arrhythmic risk and a rate of appropriate ICD intervention of 3.7%/year.[5] Disease progression may occur during exacerbations that are usually clinically silent or characterized by the appearance of life-threatening arrhythmias and chest pain. Environmental factors, such as exercise or inflammation, might facilitate disease progression. **Progressive heart failure** may occur in <10% of patients.[15]

Investigations

Investigations and diagnostic criteria for ARVC/D are presented in Table 39.2 and Figure 39.2. Clinical diagnosis of ARVC/D may be difficult due to the broad spectrum of phenotypic manifestations, ranging from severe to concealed forms.

ECG depolarization abnormalities result from delayed right ventricular activation and include RBBB, prolongation of right precordial QRS duration (110 ms or more), and epsilon waves, defined as small amplitude potentials occurring after the QRS complex and before the onset of the T waves. Usually, these patients have inverted T waves over V_1–V_3. S wave duration >55 ms in V_1–V_3 is also a marker of the disease. Inverted T waves or epsilon waves in inferolateral leads suggest biventricular involvement.[16]

Exercise testing in asymptomatic PKP-2 mutation carriers may reveal new epsilon waves (Figure 39.3), premature ventricular contractions with superior axis, and new terminal activation duration ≥55 ms.[17]

Holter monitoring may reveal ventricular ectopic beats or runs of VT with LBBB morphology and inferior or superior axis. Non-sustained VT or >500 PVCs/24h on Holter precede structural abnormalities that are detected by CMR.[18]

On **echocardiography**, the more common structural changes in the right ventricle consist of wall motion abnormalities, trabecular derangement, and diastolic dilatation of the RVOT, but the ventricle may be normal in mild forms of ARVC/D. Typically, the inferior subtricuspid, antero-apical, and mid-outflow tract regions are affected **(triangle of dysplasia)**. In the early stages of ARVC/D, overall right ventricular function may be normal, with local or regional wall motion abnormalities, and these are difficult to quantify.[19] As the disease progresses, RV dilatation and failure may occur. Although ARVC was originally described as a right ventricular disease, it is now recognized to include a spectrum of biventricular and left dominant forms that may be misdiagnosed as dilated cardiomyopathy.

Table 39.2 Revised (2010) International Task Force Criteria for Diagnosis of ARVC/D

Definitive diagnosis: 2 major or 1 major, and 2 minor criteria or 4 minor from different categories

Borderline: 1 major and 1 minor or 3 minor criteria from different categories

Possible: 1 major or 2 minor criteria from different categories.

I. Global or regional dysfunction and structural alterations*

Major

By 2D echo:

Regional RV akinesia, dyskinesia, or aneurysm and one of the following (end diastole):

— PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m^2)

— PSAX RVOT ≥ 36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m^2)

— or fractional area change ≤33%

By MRI:

Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and one of the following:

— Ratio of RV end-diastolic volume to BSA ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female)

— or RV ejection fraction ≤40%

By RV angiography:

Regional RV akinesia, dyskinesia, or aneurysm.

Minor

By 2D echo:

Regional RV akinesia or dyskinesia and 1 of the following (end diastole):

— PLAX RVOT ≥29 to <32 mm (corrected for body size [PLAX/BSA] ≥16 to <19 mm/m^2)

— PSAX RVOT ≥32 to <36 mm (corrected for body size [PSAX/BSA] ≥18 to <21 mm/m^2)

— or fractional area change >33% to ≤40%

By MRI:

Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and one of the following:

— Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m^2 (male) or ≥90 to <100 mL/m^2 (female)

— or RV ejection fraction >40% to ≤45%

II. Tissue characterization of wall

Major

Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy.

Minor

Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy.

III. Repolarization abnormalities

Major

Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals.

>14 years of age (in the absence of complete right bundle-branch block, QRS ≥120 ms).

Minor

Inverted T waves in leads V1 and V2 in individuals >14 years of age (in the absence of complete right bundle-branch block) or in V4, V5, or V6.

Inverted T waves in leads V1, V2, V3, and V4 in individuals >14 years of age in the presence of complete right bundle-branch block.

IV. Depolarization/conduction abnormalities

Major

Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3).

(*continued*)

Table 39.2 Continued

Definitive diagnosis: 2 major or 1 major, and 2 minor criteria or 4 minor from different categories
Minor
Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG.
Filtered QRS duration (fQRS) ≥114 ms.
Duration of terminal QRS 40 mV (low-amplitude signal duration) ≥38 ms.
Root-mean-square voltage of terminal 40 ms ≤20 mV.
Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R′, in V1, V2, or V3, in the absence of complete right bundle-branch block.
V. Arrhythmias
Major
Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL).
Minor
Nonsustained or sustained ventricular tachycardia of RV outflow configuration, LBBB morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis.
>500 ventricular extrasystoles per 24 hours (Holter).
VI. Family history
Major
ARVC/D confirmed in a first-degree relative who meets current Task Force criteria
ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative
Identification of a pathogenic mutation† categorized as associated or probably associated with ARVC/D in the patient under evaluation
Minor
History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria
Premature sudden death (<35 years of age) due to suspected ARVC/D in a first-degree relative
ARVC/D confirmed pathologically or by current Task Force Criteria in second-degree relative

PLAX indicates parasternal long-axis view; RVOT, RV outflow tract; BSA, body surface area; PSAX, parasternal short-axis view; aVF, augmented voltage unipolar left foot lead; and aVL, augmented voltage unipolar left arm lead.
*Hypokinesis is not included in this or subsequent definitions of RV regional wall motion abnormalities for the proposed modified criteria.
†A pathogenic mutation is a DNA alteration associated with ARVC/D that alters or is expected to alter the encoded protein, is unobserved or rare in a large non-ARVC/D control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree.
Marcus FI, *et al.* Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. *Eur Heart J*. 2010;**31**:806–14 with permission from Oxford University Press.

Cardiac magnetic resonance is very useful by means of detecting fatty tissue and, with gadolinium, intramyocardial fibrosis. This is very important since intramyocardial fat without fibrosis is present in the right ventricular anterolateral and apical region, even in a normal heart, and increases with age and body weight.[20] Thus, caution is needed in individuals with misdiagnosis of ARVC/D mostly based on cardiac imaging/CMR features.[21] However, CMR abnormalities are indicative of high risk in the presence of ECG and/or Holter abnormalities.[18]

Isoproterenol testing has been found very sensitive for the diagnosis of ARVC/D. Continuous infusion of isoproterenol (45 micrograms/min) is given for 3 minutes, and induction of polymorphic premature ventricular contractions with ≥1 couplet or sustained or non-sustained ventricular tachycardia with LBBB configuration indicates ARVC/D.[22]

Electrophysiology study is useful for differential diagnosis between ARVC/D and idiopathic right ventricular outflow tract tachycardia, but the role of inducibility of sustained VT or VF for prediction of long-term arrhythmic outcome in ARVC/D patients is debatable.[23]

Electroanatomical mapping can reveal low-voltage areas, either endocardially or epicardially, that correspond to fibrofatty myocardial replacement and could assist in the differential diagnosis with idiopathic right ventricular outflow tract tachycardia.[24]

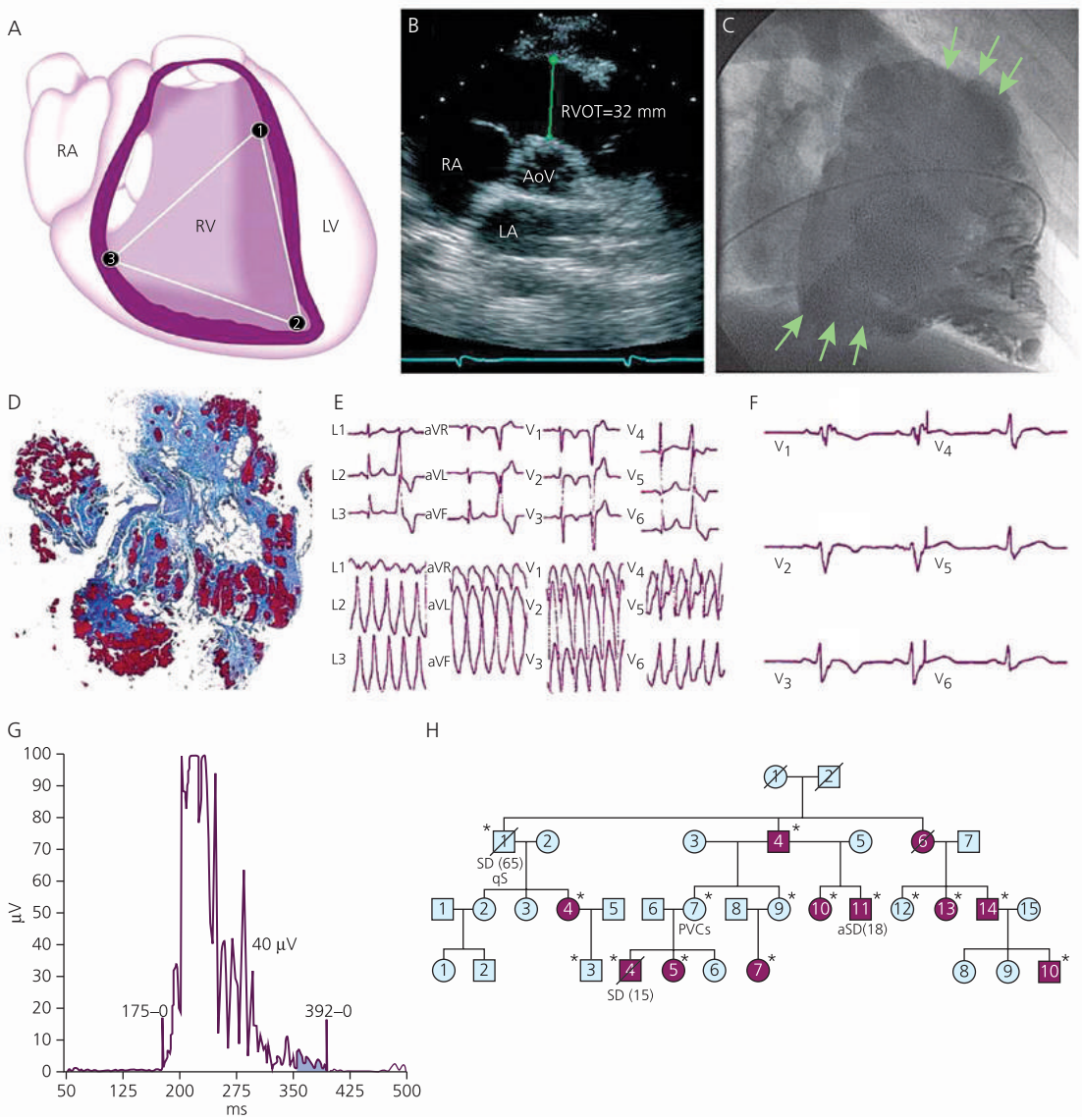

Figure 39.2 Features of arrhythmogenic right ventricular cardiomyopathy. Diagnostic morphofunctional, electrocardiographic, and tissue characteristic features of arrhythmogenic right ventricular cardiomyopathy. (A) Triangle of dysplasia, which shows the characteristic areas for structural and functional abnormalities of the right ventricle. RA, right atrium; RV, right ventricle; LV, left ventricle. (B) Two-dimensional echocardiography showing right ventricular outflow tract enlargement from the parasternal short axis view. AoV, aortic valve; LA, left atrium; RVOT, right ventricular outflow tract. (C) Right ventricular contrast angiography (30° right anterior oblique view) showing a localized right ventricular outflow tract aneurysm (arrows) and inferobasal akinesia (arrows) with mild tricuspid regurgitation. (D) Endomyocardial biopsy sample with extensive myocardial atrophy and fibrofatty replacement (trichrome; ×6). (E) 12-lead ECG with inverted T waves (V_1, V_2, V_3), with left bundle branch block morphology, premature ventricular complexes, and VT. (F) ECG tracing showing post-excitation epsilon wave in precordial leads V_1, V_2, V_3 (arrows). (G) Signal-averaged ECG with late potentials (40 Hz high-pass filtering); filtered QRS duration (QRSD) = 217 ms; low amplitude signal (LAS) = 107 ms; and root mean square voltage of terminal 40 ms (RMS) = 4 μV. (H) Family pedigree of arrhythmogenic right ventricular cardiomyopathy: note the autosomal dominant inheritance of the disease.

SD, sudden death; aSD, aborted sudden death; PVC, premature ventricular complexes; qS, qS in inferior leads. * Gene mutation carrier.
Basso C, *et al*. Arrhytmogenic right verntricular cardiomyopathy. *Lancet*. 2009;**373**:1289–1300 with permission from Elsevier.

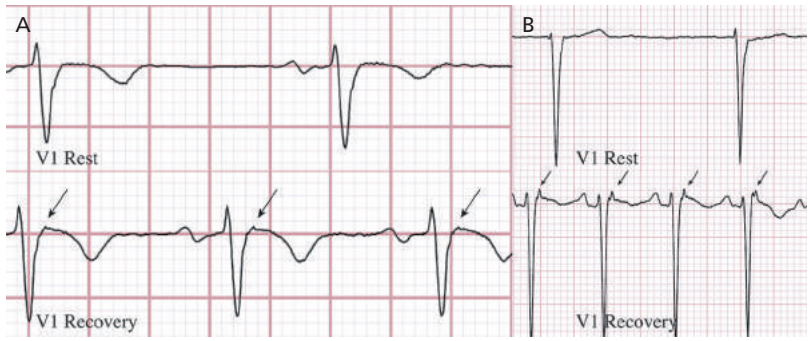

Figure 39.3 Epsilon waves appearing during exercise. (A) An epsilon wave appeared during early exercise and persisted during the recovery period (arrows). (B) A relatively large amplitude epsilon wave (arrows) was prominent late into the recovery period. Both asymptomatic subjects had normal results on rest electrocardiography and normal results on cardiac magnetic resonance imaging and harboured radical plakophilin 2 mutations.

Perrin MJ, *et al*. Exercise testing in asymptomatic gene carriers exposes a latent electrical substrate of arrhythmogenic right ventricular cardiomyopathy. *J Am Coll Cardiol*. 2013;**62**:1772–9 with permission from Elsevier.

Endomyocardial biopsy has not been consistently useful because the structural changes in ARVC/D tend to spare the subendocardium and do not typically involve the interventricular septum.

Immunohistochemical analysis of endomyocardial biopsy samples has been recently found to be a sensitive and specific diagnostic test for ARVC/D by means of detecting defective desmosomal proteins at intercalated discs.[25]

Differential diagnosis

It is aimed at exclusion of idiopathic right ventricular outflow tract tachycardia that is benign and displays LBBB morphology with inferior axis. The absence of ECG repolarization and depolarization abnormalities and of right ventricular structural changes, recording of a single VT morphology and non-inducibility at programmed ventricular stimulation, and a normal voltage map provide evidence for the idiopathic nature of the VT.[3] Table 39.3 and Figure 39.4 present proposed criteria for distinguishing idiopathic VT from VT in ARVC/D.[26] A score ≥5 suggests ARVC/D (see also Chapter 56 on VT). Older age of symptom onset, presence of cardiovascular comorbidities, nonfamilial pattern of disease, PR interval prolongation, high-grade atrioventricular block, significant left ventricular dysfunction, myocardial delayed enhancement of the septum, and mediastinal lymphadenopathy should raise the suspicion for **cardiac sarcoidosis**.[27] Other conditions to be excluded are **Ebstein's anomaly, Uhl's disease** (isolated right ventricular enlargement and failure, with partial or total absence of right ventricular myocardium due to apoptotic anomalies), **myocardis, dilated cardiomyopathy, pulmonary hypertension, right ventricular infarction, atrial septal defect, Chagas' disease**, and **Brugada syndrome**. In black athletes without concomitant symptoms or family history, T-wave inversion and RV enlargement may be a benign finding (see Chapter 83).[28]

Table 39.3 Electrocardiographic scoring system for distinguishing RVOT arrhythmias in patients with ARVC/D from idiopathic VT

ECG characteristic	Points
Anterior T wave inversions (V_1–V_3) in sinus rhythm	3
VT/PVC:	
Lead I QRS duration ≥120 ms	2
QRS notching (multiple leads)	2
V_5 transition or later	1

Anterior T wave inversion is defined as T wave negativity in, at least, leads V_1, V_2, and V_3.
Lead I QRS duration ≥120 ms is defined as the duration from the initial deflection of the QRS complex to the end of the QRS complex in lead I.
QRS notching in multiple leads is defined as a QRS complex deflection on the upstroke or downstroke of >0.5 mV that did not cross the baseline occurring in, at least, two leads (Figure 39.4).
The precordial transition point is designated as the earliest precordial lead where the R wave amplitude exceeded the S wave amplitude.
Hoffmayer KS, *et al*. An electrocardiographic scoring system for distinguishing right ventricular outflow tract arrhythmias. *Heart Rhythm*. 2013;**10**: 477–82, with permission from Elsevier.

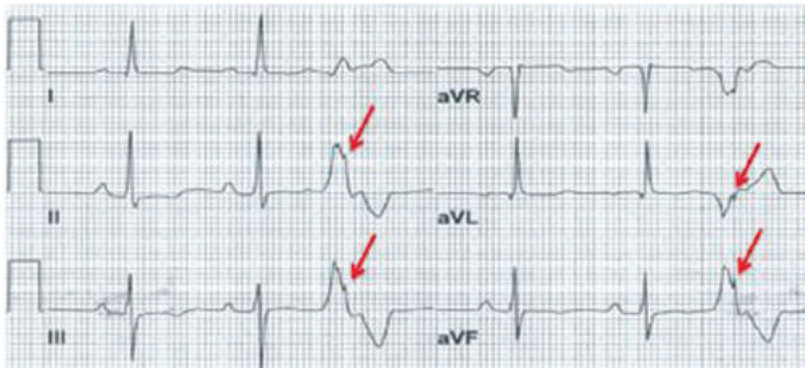

Figure 39.4 Example of QRS Notching. Arrows show QRS notching in lead II, III, aVF, and aVL.

Hoffmayer KS, *et al*. An electrocardiographic scoring system for distinguishing right ventricular outflow tract arrhythmias. *Heart Rhythm*. 2013;**10**: 477–82, with permission from Elsevier.

Risk stratification

Cardiac arrest due to VF can occur at any time during the disease course. Several risk factors, such as previous cardiac arrest, syncope, participation in competitive sports, young age, VT, severe right ventricular dysfunction, left ventricular involvement, and QRS dispersion of 40 ms or more, have been proposed, (Table 39.4), but in the North American ARVC/D Registry, the only risk factors for ventricular arrhythmias were spontaneous ventricular arrhythmias before enrolment and a younger age at ICD implantation.[29] The value of programmed ventricular stimulation is debatable, with both negative[19] and positive[24] results reported. Family history is of rather limited value in predicting SCD.[5] Although LV involvement has been considered for a long time as an expression of the advanced disease phase, it is now accepted that ARVC can start with isolated or predominant LV involvement since the early stages.[1] The genotype of ARVC/D mutation carriers affects disease expression and clinical course.[14]

Table 39.4 ESC 2015 GL on VA and SCD. Risk stratification and management of ARVC/D

Avoidance of competitive sports	I-C
Beta-blockers titrated to the maximally tolerated dose as first-line therapy to improve symptoms in patients with frequent PVC and NSVT.	I-C
ICD implantation in patients with a history of aborted SC and haemodynamically poorly tolerated VT.	I-C
Amiodarone to improve symptoms in patients with frequent PVC or NSVT who are intolerant of or have contraindications to beta-blockers.	IIa-C
Catheter ablation, in experienced centres, in patients with frequent symptomatic PVC or VT unresponsive to medical therapy to improve symptoms and prevent ICD shocks, respectively.	IIa-B
ICD in patients with haemodynamically well-tolerated sustained VT	IIa-B
ICD in patients with one or more recognized risk factors for ventricular arrhythmia	IIb-C
Invasive EPS with programmed electrical stimulation for stratification of SCD risk.	IIb-C

ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015;**36**: 2793–2867 with permission from Oxford University Press.

Therapy

Asymptomatic patients or healthy gene carriers do not require prophylactic treatment. They should undergo cardiac follow-up, including medical history, 12-lead ECG, 24-hour Holter monitoring, exercise testing, and echocardiography, on a regular basis. Data on antiarrhythmic drug therapy are limited. Amiodarone has been shown to prevent ventricular arrhythmias more effectively than beta blockers in ARVC/D patients treated with ICD.[30] Sotalol at high doses (320–480 mg daily) has also been found partially effective,[31] and beta blockers should, theoretically at least, be efficacious.[23] Treatment with ICD is indicated in patients with cardiac arrest, syncope, or haemodynamically poorly tolerated VT, or one or more risk factors for SCD (Table 56.6).[32,23] The majority of VT in ARVC/D are monomorphic, and antitachycardia pacing is highly successful in terminating VT independently of its cycle length. Thus, all ICDs should be programmed for antitachycardia pacing.[29] A potential problem with ICD in ARVC/D is that the disease is often progressive, leading to loss of myocardium and reduced ventricular R wave sensing over time. Catheter ablation of VT (endocardial or epicardial) when feasible is successful in reducing further episodes,[23] but cannot offer absolute protection without ICD backup since the progressive course of the disease precludes any curative role. Heart failure is treated according to standard recommendations (see Chapter 32). Cardiac transplantation may be needed in patients with intractable arrhythmias or heart failure.

Physical activity is restricted to mild cardiovascular sports for weight management with a low static component (see Chapter 83 for sports classification).[14] Competitive sports are prohibited, being associated with a two-fold increased risk of ventricular arrhythmias and/or sudden death; recreational sports may be allowed.[33]

Genetic testing

Molecular genotyping is currently applied to relatives of a proband with a known mutation probably associated with ARVC/D for risk assessment (presymptomatic test) while it is not routinely used in isolated cases with a borderline phenotype for confirming the diagnosis.[6] However, a negative genetic test does not exclude the possibility that the phenotype is due to a mutation of unknown, and thus untested, disease-causing genes. Approximately 50% of ARVC/D probands do not carry any known causative gene mutations.[34] The certainty of detecting causative mutation carriers is further limited by the difficulty in distinguishing causative mutations (mostly missense gene variants) from polymorphisms as well as by the potential presence of an undetected second pathogenetic mutation in the same or another gene. There is a low signal to noise ratio, with mutations in a recent series identified in 43% of ARVC/D cases and in 16% of controls.[9] There is no evidence that the genotype may help with management strategies. It has been shown, however, that almost one-third of at-risk relatives have electrical progression that precedes detectable structural changes that are rare.[35] Recommendations by HRS/EHRA are presented in Table 39.5.[36]

Table 39.5 HRS/EHRA statement. Genetic testing for ARVC/D

Family members and appropriate relatives following the identification of the ACM/ARVC causative mutation in an index case.	I
Comprehensive or targeted (DSC2, DSG2, DSP, JUP, PKP2, and TMEM43) ACM/ARVC genetic testing for patients satisfying Task Force diagnostic criteria for ACM/ARVC.	IIa
Patients with possible ACM/ARVC (1 major or 2 minor criteria) according to the 2010 Task Force criteria.	IIb
Patients with only a single minor criterion according to the 2010 Task Force criteria.	III

HRS/EHRA 2011 Expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Europace*. 2011;**13**:1077–109 with permission from Oxford University Press.

Pregnancy

It is well tolerated, but clinical follow-up is recommended in the last trimester and puerperium because of a reported increased risk of ventricular arrhythmias.

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Chapter 40

Peripartum cardiomyopathy

Definition

Peripartum cardiomyopathy is a distinct cardiomyopathy, the cardiac phenotype of which resembles dilated cardiomyopathy.[1]

National Heart, Lung, and Blood Institute and the Office of Rare Diseases (2000)

- Development of heart failure in the last month of pregnancy or within 5 months post-partum
- Absence of an identifiable cause of heart failure
- Absence of recognizable heart disease prior to the last month of pregnancy
- LVEF <45%, fractional shortening <30%, or both, with or without an LVEDD >2.7 cm/m^2 body surface area.[1]

Heart Failure Association of the European Society of Cardiology (2010)

Peripartum cardiomyopathy is an idiopathic cardiomyopathy, presenting with heart failure secondary to left ventricular systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found. It is a diagnosis of exclusion. The left ventricle may not be dilated, but the ejection fraction is nearly always reduced below 45%.[2,3]

Epidemiology

The incidence of peripartum cardiomyopathy varies from 1 in 2500–4000 in the USA to 1 in 1000 in South Africa, and 1 in 300 in Haiti.[3,4,5]

Aetiology

Peripartum cardiomyopathy continues to be a cardiomyopathy of unknown cause. Various pathophysiologic mechanisms have been proposed, such as excessive prolactin (reduced myocardial STAT3 protein levels and activated oxidative stress-cathepsin D-16 kDA prolactin cascade), cytokine-mediated inflammation, viral myocarditis, and autoimmune mechanisms. A genetic background has been suggested. Titin gene mutations are also common in families with both dilated and post-partum cardiomyopathy,[6] suggesting that peripartum cardiomyopathy may be a manifestation of familial dilated cardiomyopathy.

Prolonged tocolysis, advanced maternal age, high gravidity/parity, multipregnancy, race, socio-economic status, gestational hypertension, and cocaine abuse are risk factors associated with the development of peripartum cardiomyopathy.[5]

Presentation

Clinical presentation is extremely variable, from mild symptoms that can be attributed to pregnancy to acute heart failure. Elevated JVP, S_3, and basal rales can be normal in pregnancy. Most often, patients present with NYHA III or IV symptoms. Patients may also present with ventricular arrhythmias, systemic embolism due to LV thrombus, or pulmonary embolism. Most cases occur in the puerperium.[4]

Investigations

Diagnosis is being made by exclusion (Table 40.1). **ECG** is seldom normal, usually displaying ST-T abnormalities or LV hypertrophy voltage criteria. **Echocardiography** is essential for LV assessment. **MRI** allows more accurate measurements, but gadolinium crosses the placenta and is not recommended during pregnancy. **BNP** and **NT-pro-BNP** levels are raised. Differentiation between post-partum cardiomyopathy and severe gestational hypertensive complications may be difficult.[4]

Table 40.1 Differential diagnosis of peripartum cardiomyopathy (PPCM)

	Distinguishing features
Pre-existing idiopathic dilated cardiomyopathy (IDC) unmasked by pregnancy presents by the 2nd trimester	PPCM most commonly presents post-partum whereas IDC (unmasked by pregnancy) usually presents during pregnancy with larger cardiac dimensions than PPCM
Pre-existing familial dilated cardiomyopathy (FDC) unmasked by pregnancy. FDC usually presents during pregnancy with larger cardiac dimensions than PPCM	PPCM most commonly presents post-partum whereas FDC usually presents by 2nd trimester
HIV/AIDS cardiomyopathy ventricles	HIV cardiomyopathy presents often with non-dilated ventricles
Pre-existing valvular heart disease unmasked by pregnancy	Rheumatic mitral valve disease is often unmasked by pregnancy; PPCM most commonly presents post-partum whereas valvular heart disease usually presents by 2nd trimester
Hypertensive heart disease	Exclude pre-existing severe hypertension in those presenting before delivery
Pre-existing unrecognized congenital heart disease	Previously unrecognized congenital heart disease often has associated pulmonary hypertension; PPCM most commonly presents post-partum whereas congenital heart disease usually presents by 2nd trimester
Pregnancy-associated myocardial infarction	
Pulmonary embolus	

Therapy

After delivery, peripartum cardiomyopathy is treated conventionally (see Chapter 31 on CHF).

During pregnancy precautions are needed:

Furosemide in congestion—caution is needed in pre-eclampsia due to concern for decreased placental perfusion. **Thiazides** carry a possible risk of birth defects or fetal thrombocytopenia. **Spironolactone** may cause feminization of male fetus. No data for **eplerenone**.

Hydralazine and **nitrates** to maintain a systolic blood pressure <110 mmHg. **Amlodipine** can also be used. **ACEI** and **ARB** are teratogenic.

Beta 1-selective beta-blockers, such as **metoprolol**, that are compatible with breastfeeding are used. Neonates should be monitored for bradycardia, hypoglycaemia, and growth retardation. Beta 2 receptor blockade has anti-tocolytic action, and carvedilol may be teratogenic at high doses.[5]

Digoxin may be used.

Bromocriptine (2.5 mg twice daily for 2 weeks, followed by 2.5 daily for 4 weeks), a dopamine D2 receptor agonist, has prevented the onset of disease in experimental models of peripartum cardiomyopathy, and appears successful and safe in initial trials with patients.[7]

The addition of **pentoxifylline** to conventional therapy has also been shown to improve outcome in patients with peripartum cardiomyopathy.[8]

Subcutaneous **LMWH** may be used in LVEF <30% or AF.

In acute heart failure, **dobutamine** and **dopamine** may be used. **Norepinephrine** decreases placental blood flow.

Antiarrhythmic therapy is presented in Table 40.2.

CRT with or without ICD is considered in patients who fulfil criteria 6 months following presentation.

Therapy with standard heart failure medications should be continued probably for a minimum of 12 months.[9] If cardiac function does not normalize within 6–12 months, heart failure medications should likely be continued indefinitely.

Table 40.2 ESC 2015 GL on VA and SCD. Management of arrhythmias related to pregnancy induced cardiomyopathy.

Electrical cardioversion or defibrillation in pregnant women developing haemodynamically unstable	I-B
Standard management of heart failureF with avoidance of drugs contraindicated in pregnancy (ACE inhibitors, ARB and renin inhibitors).	I-C

ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J.* 2015;**36**:2793–2867 with permission from Oxford University Press.

Delivery

Unless there is deterioration in the maternal or fetal condition, there is no need for early delivery. Urgent delivery, irrespective of gestation, may need to be considered in women presenting or remaining in advanced HF with haemodynamic instability. In general, spontaneous vaginal birth is preferable in stable women, but assisted second stage is recommended to reduce maternal efforts and shorten labour. Caesarean section is preferred for patients who are critically ill and in need of inotropic therapy or mechanical support.[2]

Prognosis

The prognosis is better than with other causes of dilated cardiomyopathy, with normalization of LV function in >50% of patients, mostly occurring within 2 to 6 months after diagnosis, although later recovery is also possible.[10] With contemporary therapy, reported mortality is 4–6% at 4 to 5 years. More than 40% of patients experience recovery, and >20% of them complete recovery, but this is usually delayed (>6 months).[11] Up to 13% of patients may have major events or persistent severe cardiomyopathy.[12] Caucasians and those diagnosed postpartum are

most likely to recover. Outcomes for **subsequent pregnancies** after peripartum cardiomyopathy are better for women who have fully recovered heart function after their initial presentation. In general, a subsequent pregnancy carries a recurrence risk for post-partum cardiomyopathy of 30–50%.[3] Factors associated with lack of recovery at initial assessment are LVEDD >5.6 cm, the presence of LV thrombus, and African-American race. Pregnancy is discouraged in women with LVEF <25% at diagnosis that has not been normalized at 2 months.[2,10] However, even if the LVEF is normalized, there is still a need for counselling because of the risk of recurrence with a new pregnancy.[3,4,13] Patients who decide to become pregnant again should undergo baseline echocardiography and determination of serum BNP level before or early in pregnancy. Patients should be followed with repeated echocardiography during the early second and third trimesters, during the last gestational month, early after delivery, and at any time if new symptoms of heart failure develop. Early termination of an unintentional pregnancy should be considered to prevent worsening of LV function and potential maternal mortality, especially in patients with persistent LV dysfunction.

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Chapter 41

Tachycardiomyopathy

Definition

The term denotes tachycardia-induced cardiomyopathy. Tachycardia is a reversible cause of impaired left ventricular function that can lead to heart failure and death. Very frequent premature ventricular contractions may also be a cause of cardiomyopathy.

Epidemiology

The incidence of tachycardiomyopathy is unknown, but it has been reported in any age group, from the foetus to the elderly.

Aetiology

The syndrome has been initially described with the so-called persistent reciprocating junctional tachycardia, a term that denoted both atrioventricular reentry due to a septal decremental pathway and fast-slow atrioventricular nodal reentry. We know now that any chronic cardiac arrhythmia may cause tachycardia-induced cardiomyopathy: **incessant atrioventricular reentrant tachycardia due to septal accessory pathways, rapid atrial fibrillation, idiopathic ventricular tachycardia, inappropriate sinus nodal tachycardia, atrial flutter**, and **persistent**

ectopic beats are the most described causes.[1–4] In young patients <18 years of age, ectopic atrial tachycardia is the commonest cause.[5]

Pathophysiology

Rapid pacing in animal models have documented cytoskeletal changes and remodelling of the extracellular matrix attributed to abnormal calcium cycling, increased catecholamines and decreased beta 1-adrenergic receptor density, oxidative stress, depletion of myocardial energy stores, and myocardial ischaemia due to increased heart rate.[3,6] However, it is not known why the majority of patients with frequent PVCs have a benign course, whereas up to 30% of them may develop cardiomyopathy.[7]

Presentation

Patients present with possibly unexplained left ventricular dilatation and systolic dysfunction and a history of paroxysmal tachycardias or permanent AF. Heart failure develops slowly, but sudden death is possible.[2]

Diagnosis

No strict criteria exist. Diagnosis is established by excluding other causes of cardiomyopathy and demonstrating recovery of LV function after eradication of the arrhythmia or control of the ventricular rate. The ventricular rate that causes cardiomyopathy is not known, although rates >100 bpm for prolonged periods are considered to be responsible.[3] PVCs should be >20 000 beats/day to account for the cardiomyopathy (or alternatively a 24-hour burden of >24% on Holter),[8] although ectopy-induced cardiomyopathy has been reported in a patient with only 5502 beats/day.[9] Worsening of the LV function has been reported with >1000 beats/day,[10] but the clear-cut point that marks the critical frequency for cardiomyopathy is not known. PVC QRS duration (≥140-150 ms) is also predictive of impaired LV function.[4] Usually, LVEDD is <65 and LVESD <50 mm in patients with LVEF <30% due to tachycardia-induced cardiomyopathy.[1] Larger values suggest dilated cardiomyopathy, although overlapping exists.

Therapy

There is considerable evidence that LV function improves approximately 3 months following restoration of normal heart rate. In inappropriate sinus nodal tachycardia, beta-blockers are indicated. Sinus node modification with catheter ablation carries a 10% risk of sinus nodal damage and need of a permanent pacemaker. Catheter ablation is indicated in cases of accessory pathways, idiopathic VT, and monomorphic VPBs. In AF, both pulmonary vein isolation[11,12] and AV nodal modification[13] improve LV function, but PV isolation has been found superior to AV nodal ablation and biventricular pacing in this respect.[14]

Long-term medical therapy with beta-blockers and ACE inhibitors or ARBs is indicated before and after successful ablation attempts for LV remodelling purposes.

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Chapter 42

Stress cardiomyopathy

Definition

Stress cardiomyopathy, also referred as Takotsubo ("octopus pot" in Japanese) cardiomyopathy, transient apical ballooning, or broken heart syndrome, is a disorder associated with transient left ventricular dysfunction. It occurs usually in old women (50% of them with neurologic or psychiatric conditions) after emotional or physical stress, but it also happens in men <50 years old and in the absence of stress.[1,2] LV ballooning may be apical (81%), midventricular (15%), basal (2%), or focal (1.5%).[2]

Pathophysiology

The mechanisms of disease remain unclear, and the cause has not been established. An excessive release of catecholamines (stress, exogenous cathecholamines administered during diagnostic tests, and beta-receptor agonists) seems to have a pivotal role in the development of stress cardiomyopathy.[3]

Diagnosis

Usually, patients present with acute heart failure although the condition may also be asymptomatic.

The **ECG** typically shows signs of acute or anterior myocardial infarction.

Echocardiography reveals systolic and diastolic dysfunction almost indistinguishable from acute MI due to LAD occlusion.[4]

Troponin elevation (0.01–5.3 ng/mL) is the rule.[1]

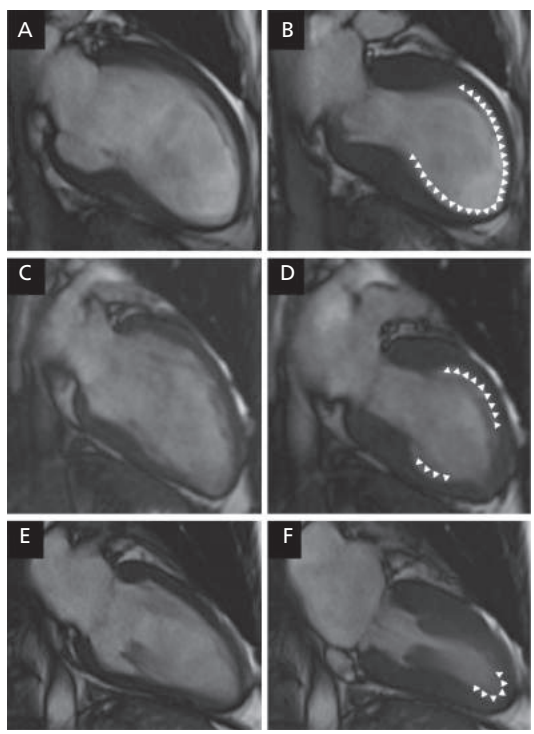

Figure 42.1 Diversity of LV contraction patterns in stress cardiomyopathy, as demonstrated by cardiac magnetic resonance in vertical long-axis view (A, C, and E) diastole; (B, D, and F) systole. Three types are depicted: (A, B) most common pattern of mid- and apical left ventricular (LV) akinesia (arrowheads); (C, D) mid-LV akinesia (arrowheads) with sparing of apical region; and (E, F) apical LV contraction abnormality only (arrowheads).

Sharkey SW, et al. Natural history and expansive clinical profile of stress (tako-tsubo) cardiomyopathy. *J Am Coll Cardiol*. 2010;**55**:333-41.

Cardiac MRI and **echocardiography** display characteristic features. Figure 42.1 depicts the most common types of stress cardiomyopathy. A focal type may also rarely occur.[2] Average LVEF is 32–36%.[1,5] Approximately 4% have right or left ventricular thrombus.

Therapy

Beta blockers are theoretically promising but they may not offer protection.[1,2] **ACE inhibitors or ARBs** are essential.[2]

Anticoagulation should be considered in the presence of ventricular thrombus or embolic events. Standard heart failure therapy is administered when needed. Early restoration of normal ventricular function is the rule, but in 5% of the patients, it can be delayed (>2 months). Approximately 5% of patients have a recurrence 3 weeks to 4 years after the first event.[1] In hospital mortality is 2–4% and during long-term follow up mortality is 5.6% per year.[1,2,5]

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Chapter 43

Iron overload cardiomyopathies

Definition

Iron overload cardiomyopathies are due to increased gastrointestinal (GI) iron absorption (haemochromatosis) or excess administration of exogenous iron by dietary sources or red blood cell (RBC) transfusions (haemosiderosis). They have either a restrictive or dilated phenotype that usually develops at later stages of the disease.[1]

Aetiology

The incidence of iron overload cardiomyopathy is increasing worldwide. Chronic blood transfusion is the main treatment for hereditary anaemias, such as thalassaemia and sickle cell disease, that, although prevalent in the Mediterranean basin, are also seen in other parts of the western world due to immigration. Causes of iron overload cardiomyopathy are presented in Table 43.1. Hereditary haemochromatosis is an autosomal disorder in which mutations, usually of the HFE gene, cause increased GI absorption of iron. Chronic transfusion is mandatory for the anaemias listed. A unit of packed RBCs consists of 200 to 250 mg of elemental iron that accumulates in the body because there is no active excretion of iron.

Table 43.1 Aetiology of iron overload disorders

Disease	Mechanism	Molecular correlate	Iron deposition
Primary			
Hereditary haemochromatosis	Increased GI absorption with normal diet	Missense mutation	Liver, heart, endocrine glands
Type 1 (*HFE*-related) (AR)		◆ C282Y homozygosity	
		◆ H63D homozygosity	
		◆ C282Y/H63D heterozygosity	
		◆ Other mutations of *HFE*	
Type 2 (juvenile haemochromatosis) (AR)	Increased GI absorption with normal diet	Mutation on *HJV* gene, which encodes haemojuvelin	Liver, heart, endocrine glands
		Rare form where hepcidin is inactivated	

(*continued*)

Table 43.1 Continued

Disease	Mechanism	Molecular correlate	Iron deposition
Type 3 (AR)	Increased GI absorption with normal diet	Mutation of transferrin receptor-2	Liver, heart, endocrine glands
Type 4 (AD)	Increased GI absorption with normal diet	Mutation of *SLC40A1*, which encodes ferroportin	Macrophages, liver, heart, endocrine glands
Secondary			
a. Iron-loading anaemias (transfusion-related)	Transfusion-related	Mutation causing defect in synthesis of alpha- and beta-globin chains of haemoglobin	Heart, pancreas, pituitary, liver
Thalassaemia	In severe thalassaemia, can have increased GI absorption		
Sickle cell anaemia	Transfusion-related	Substitution of a valine for glutamic acid as the 6th amino acid on the beta-globin chain (HbS)	Liver, heart
Sideroblastic anaemia	Transfusion-related	Hereditary or acquired	Neurons, heart, mitochondria
	Increased GI absorption with normal diet	Ineffective erythropoiesis	
Diamond–Blackfan anaemia	Transfusion-related	Congenital hypoplastic anaemia with decreased erythroid precursors	Heart, liver
Congenital dyserythropoiesis anaemia	Transfusion-related	Ineffective erythropoiesis	Liver, heart, endocrine
Post-stem cell transplant patients	Transfusion-related		Liver, heart
Chronic kidney disease/end-stage renal failure/dialysis	Oral and IV iron supplementation	Decreased erythropoietin	Heart, liver
	Transfusion-related		
b. Dietary overload	Increased dietary intake	Increased diet with predisposing genetic factors (proposed mechanism)	Heart, liver, endocrine
African iron overload			
c. Miscellaneous			
Aceruloplasminaemia (AR)	Inhibition of iron oxidation	Mutations of ceruloplasmin gene	Liver, heart, pancreas
Congenital atransferrinaemia (AR)	Inhibition of iron transportation	Mutations of transferrin gene	Liver, heart, pancreas
Chronic liver diseases			
Hepatitis C and B	In part, increased GI absorption	Not applicable	Liver
Alcohol-induced liver disease	In part, increased GI absorption	Not applicable	Liver
Porphyria cutanea tarda	In part, increased GI absorption	Not established, some are part AD	Liver
Fatty liver disease	In part, increased GI absorption	Not applicable	Liver

AD, autosomal dominant; AR, autosomal recessive; GI, gastrointestinal; IV, intravenous.
Gujja P, *et al*. Iron overload cardiomyopathy: Better understanding of an increasing disorder. *J Am Coll Cardiol*. 2010;**56**:1001–12 with permission from Elsevier.

Pathophysiology

Cardiac iron is regulated through transferrin-mediated uptake mechanisms. During iron overload, transferrin is saturated, and non-transferrin-bound iron is released into the circulation and enters cardiac myocytes in the ferrous form through L-type calcium channels. Iron is then bound to ferritin and transported to lysosomes for degradation and long-term storage in the cardiac myocyte. When the antioxidant capacity of the cell is exceeded, iron is catalyzed by the rapid Fenton reaction producing hydroxyl ions, which is an extremely reactive free radical species that causes cell damage and death. Pathologic iron deposition begins initially within the epicardium and extends to

the myocardium and then the endocardium, which helps explain the preservation of systolic function until very late in the disease. Thus, iron deposition is probably due to reversible storage than infiltration.[1,2]

A restrictive pattern with LV diastolic dysfunction is usually seen, and the condition may later progress to dilated cardiomyopathy, although both forms may be independently seen. Iron accumulation occurs initially at the ventricular myocardium and then the conduction system and the atrial myocardium, thus creating both conduction disorders and tachyarrhythmias due to inhomogeneity of conduction and refractoriness. Right heart failure can also be present early in the course of disease and be independent of left heart failure.

Presentation

Patients may be asymptomatic or present with **exertional shortness of breath**. Severely overloaded patients develop **advanced heart failure** if left untreated, and average survival is less than a year. Paroxysmal **atrial fibrillation** is the most common form of arrhythmia seen and is invariably associated with myocardial damage.

Diagnosis

Iron overload is considered when plasma **transferrin saturation is >55%** and **serum ferritin >200 ng/mL in women or 300 ng/mL in men**.[1,3,4] Myocardial overload cannot be detected based upon these measurements.

Liver biopsy is the gold standard for diagnosing haemochromatosis, but cardiac biopsy may be negative due to the patchy nature of the disease.

Echocardiography may reveal restrictive or dilated pattern.

Cardiac magnetic resonance is the only non-invasive method, with the potential to assess quantitatively myocardial iron load by using techniques, such as special small magnetic fields called gradients (gradient echo-GE) at specific time intervals (echo time-TE). The time constant of decay for GE-induced relaxation time is known as T2*. The following stratification scheme has been proposed:[5]

- T2* >20 ms indicates low risk for the imminent development of congestive heart failure
- T2* = 10–20 ms indicates intermediate risk of cardiac failure
- T2* <10 ms indicates high risk that needs intensification of chelation therapy.

Therapy

Dietary interventions to minimize or eliminate iron ingestion are not feasible or useful.

Phlebotomy removes 400–500 mL of blood (200–250 mg of iron) at each session, thus mobilizing iron from the organs where it is stored for the production of haemoglobin. Early in the disease, this procedure is done up to 1–2 times a week to obtain a target ferritin below 20 ng/mL, and then maintenance phlebotomy is performed 2–4 times a year.[6] Routine monitoring of haemoglobin, ferritin, and haematocrit is essential during maintenance phlebotomy.

Chelation therapy is used in patients not suitable for required phlebotomy, such as those with significant anaemia or malignancy. It removes iron by binding to it and then excreting the compound in urine and bile. Presently available chelators include deferoxamine (subcutaneous or IV) and oral deferiprone.[1,7]

New therapeutic modalities being studied are: erythrocytapheresis, novel chelating agents, calcium channel blockers, hepcidin induction (a gene regulating iron homeostasis in the body), gene therapy in beta thalassaemia or sickle cell disease (genetically modulating autologous stem cells implanted by a vector into the target cell), and donor-matched healthy stem cell transplantation.

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Chapter 44

Left ventricular non-compaction

Definition

Left ventricular non-compaction (LVNC) (spongy myocardium or foetal myocardium) represents an arrest in the normal process of myocardial compaction, the final stage of myocardial morphogenesis, resulting in persistence of many prominent ventricular trabeculations and deep intertrabecular recesses.[1–4] Whether left ventricular noncompaction (LVNC) is a distinct cardiomyopathy or a morphologic trait shared by different cardiomyopathies remains controversial.[3]

Epidemiology

Its prevalence is estimated to be 0.01–0.05% in adults,[2,4] but uncertainty about the assessment of trabeculations that can occur as a response to increased LV loading conditions makes true diagnosis difficult to be established.[5] Myocardial trabeculations can be seen in athletes, patients with sickle cell anemia, and during pregnancy and may be a benign finding.[6,7]

Aetiology

Left ventricular non-compaction is predominantly a genetic cardiomyopathy with variable presentation, ranging from asymptomatic to severe, and has mostly an autosomal dominant mode of inheritance. Mutations have been reported in at least 11, mainly sarcomere, genes but also genes encoding for such as TBX5 or SCN5A.[1,2,3,8] Mutations in the hyperpolarization-activated cyclic nucleotide channel 4 (HNC4) that results in bradycardia and LV noncompaction with or without mitral valve prolapse,[9,10] and the RYR2 gene that causes CPVT,[11] have also been associated with non-compaction. Sporadic forms also exist.

Presentation

The classical clinical presentation is heart failure, arrhythmias, and embolic events. However, LVNC may present in several subtypes, such as isolated LVNC with or without arrhythmias, dilated LVNC, hypertophic LVNC, restrictive LVNC, and in association with congenital defects, such as ASD, VSD, AS, and coarctation. There is a bilayered LV wall consisting of a thick endocardial layer with prominent intertrabecular recesses with a thin, compact epicardial layer. Trabeculations are typically most evident in the apical portion of the LV (Figure 44.1). Histology is not specific.

Clinical features include **heart failure, arrhythmias**, and **thromboembolic events**.[8] In infancy, LVNC presents with heart failure.

Diagnosis

Myocardial trabeculations even fulfilling the diagnostic criteria for non-compaction cardiomyopathy can be seen in athletes, patients with sickle cell anemia, and in pregnant women in whom they resolve within the next 2 years.[6] LV trabeculation measured in end-diastole in asymptomatic individuals recruited in the MESA study were not associated with deterioration in LV volumes or function during a 10-year period.[7]

The **ECG** is typically abnormal and may show giant voltages.

Echocardiographic diagnosis is based on the presence of:[2,12]

1. At least three trabeculations, with a ratio of the distance from the epicardial surface to the trough of the trabecular areas divided by the distance from the epicardial surface to the trough of the trabecular areas ≤5
2. A two-layer structure and a maximal end-systolic ratio of non-compacted to compacted layers of >2
3. Colour Doppler evidence of deep perfused intertrabecular recesses.

Such findings, however, can also be found in up to 8% of normal subjects.[5]

Cardiac MRI offers better spatial resolution than echocardiograpy. Proposed basic criteria for diagnosis of non-compaction include:[2,13,14]

1. Noncompacted LV myocardial mass >25%;
2. Total noncompacted LV myocardial mass index >15 g/m^2;
3. Noncompacted/compacted myocardium ratio ≥3:1 in at least 1 segment, excluding the apical segment; and
4. Trabeculation in segments 4 to 6 ≥2:1 (noncompacted/compacted).

Recommendations for **genetic testing** are provided in Table 44.1.[15]

Therapy

Aspirin is administered in all patients while anticoagulation is indicated in patients with dilated LV and LVEF <40% or history of thromboembolism. If LV dysfunction is present,

the management is that of heart failure. Arrhythmias that occur in up to 20% of patients,[2] managed as in other cardiomyopathies, and ICD may be considered (ACC/AHA 2012 GL on device therapy, IIb-C).

The diagnosis of LVNC requires genetic counselling, DNA diagnostics, and cardiological family screening. Prognosis depends on the degree of ventricular dysfunction; reported 3- and 6-year survival is 53 to 85%.[2,4]

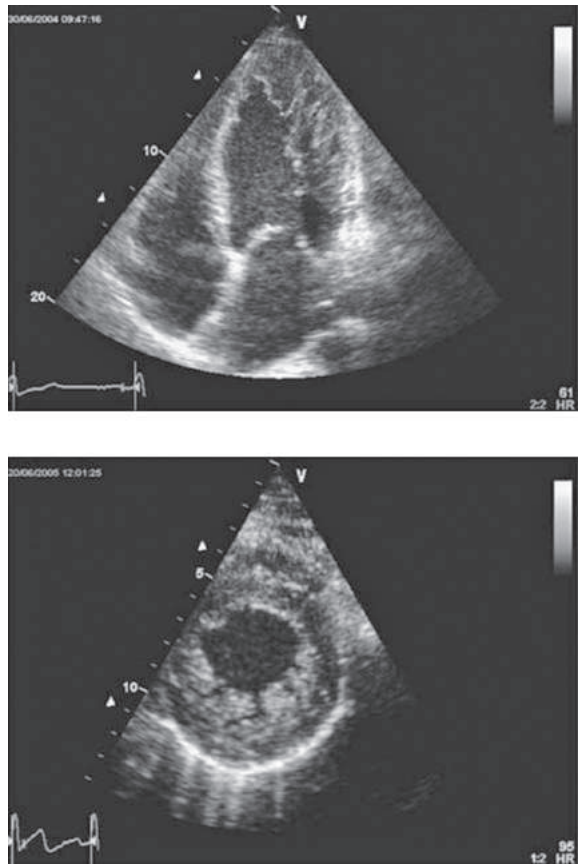

Figure 44.1 Apical echocardiographic view of a non-compacted left ventricle with extended and prominent trabeculations in the apical region and in the lateral wall. Two-layered appearance of the myocardium in a short-axis view of the left ventricle.
Pantazis AA, Elliott PM. Left ventricular noncompaction. *Curr Opin Cardiol*. 2009;**24**:209–13 with permission from Wolters Kluwer.

Table 44.1 HRS/EHRA 2011 statement on genetic testing

State of genetic testing for left ventricular non-compaction (LVNC)	
Family members and appropriate relatives following the identification of a LVNC causative mutation in the index case.	I
Patients in whom a cardiologist has established a clinical diagnosis of LVNC, based on examination of the patient's clinical history, family history, and electrocardiographic/echocardiographic phenotype.	IIa

HRS/EHRA 2011 Expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Europace*. 2011;**13**:1077–109 with permission from Oxford University Press.

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Part VII

Myocarditis

Relevant guidelines

AHA/ACC/ESC 2007 Scientific statement on endomyocardial biopsy

The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. *Eur Heart J*. 2007;**28**:3076–93.

ACC/AHA/HRS 2012 Guidelines for device-based therapy of cardiac rhythm abnormalities

ACCF/AHA/HRS 2012 Focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2013;**61**:e6–75.

ESC 2015 Guidelines on ventricular arrhythmias and prevention of sudden cardiac death

ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015 Aug 29. pii: ehv316. [Epub ahead of print] PubMed PMID: 26320108.

Chapter 45

Acute myocarditis

Definition and classification

Myocarditis refers to inflammation of the heart muscle due to exposure to external or self-antigens. Diagnosis is currently based on an unexplained rise of cardiac troponins, ECG changes suggestive of acute myocardial injury, and non-invasive imaging findings, such as cardiac magnetic resonance.[1,2,3] Although pathological confirmation of myocardial inflammation is still required for a definitive diagnosis of myocarditis,[3] endomyocardial biopsy is subject to sampling error, and the conventional Dallas criteria have been abandoned.[4] Immunohistochemical staining for characterization of inflammation and polymerase chain reaction (PCR) for viral genome detection are more sensitive criteria with prognostic significance.[5]

Clinicopathological classifications were based on early studies that used myocardial biopsies and conventional histology. Lymphocytic infiltration was the more common finding, usually in myocarditis due to viral, immune, or systemic disorders. Eosinophilic (hypereosinophilic syndrome or allergic reactions) and giant cell myocarditis (autoimmune) are also seen. **Fulminant lymphocytic myocarditis** is characterized by fever, rapid onset of symptoms (within 2 weeks), and severe heart failure with haemodynamic compromise. It is thought to be due to high cytokine production, and aggressive treatment with haemodynamic support leads to recovery and good prognosis in most patients.[6] **Acute (non-fulminant) lymphocytic myocarditis** does not have a distinct onset and haemodynamic compromise. The mild form has good prognosis but often results in death or the need for cardiac transplantation when presented with symptoms and LVEF <45%.[7] **Giant cell myocarditis** leads to severe heart failure, ventricular tachycardia or block, and has an ominous prognosis, with a mean survival less than 6 months without a transplant.[8] It is important to distinguish it from **cardiac sarcoidosis** that may present with similar clinical features. Atrial giant cell myocarditis represents a more benign form.[9] **Acute necrotizing eosinophilic myocarditis** is an aggressive form of eosinophilic myocarditis with acute onset and ominous prognosis.[10] We know now that these well-defined conditions are rare, and patients without distinct clinical pathological manifestations encompass a much broader category.[4,10]

Epidemiology

The true incidence of myocarditis is difficult to determine and is basically unknown, with estimates ranging from 0.12 to 12%.[1] It can be the cause of sudden death in approximately 10% of adults.[1,11]

In patients with human immunodeficiency virus infection, myocarditis was observed in >50% of performed autopsies.[12]

Aetiology

Several infectious and non-infectious diseases can cause myocarditis. Table 45.1 presents the most common ones. In the western world, the most common cause is viral infections. The predominant viral cause of this disease seems to change every decade (Coxsackie in the 1980s, adenovirus in the 1990s, and parvovirus B19 since 2000).[13,14] PCR analysis of viral genomes in myocardial tissue from endomyocardial biopsy samples has now replaced viral culture and serial serological testing. The most common viruses identified by this method are parvovirus B19, adenovirus, coxsackie B and other enteroviruses, human herpesvirus 6, cytomegalovirus, hepatitis C, influenza A virus, and HIV. The question of whether these viruses are innocent bystanders or pathological agents still remains. Autoimmune and systemic diseases may also rarely cause acute myocarditis (Table 45.1). Lupus myocarditis can affect approximately 10% of patients with lupus, and typically presents with an indolent course, but can present acutely as well. Concomitant systemic lupus erythematosus is also seen in 40% of antiphospholipid antibody syndrome (APLAS) patients. APLAS is a disorder of thrombotic events or obstetric complications, such as repeated miscarriages in the presence of sustained high titres of antiphospholipid antibodies. A catastrophic form characterized by clotting in multiple vascular beds may also present as acute myocarditis.[15]

Table 45.1 Aetiology of myocarditis

Viral infections
Parvovirus B19
Adenoviruses
Enteroviruses (Coxsackie B)
Human herpesvirus 6
Hepatitis C
CMV
Influenza A
EBV
HIV
Bacterial infections
Corynebacterium diphtheriae
Mycobacterium
Streptococcus A
Streptococcus pneumoniae
Spirochetal infections
Borrelia burgdorferi (Lyme disease)
Rickettsial infections
Coxiella burnetii (Q fever)
Protozoal infections
Trypanosoma cruzi (Chagas' disease)
Toxoplasma gondii
Drugs
Anthracyclines
Clozapine
Mesalamine
Ethanol
Hypersensitivity reactions
Smallpox vaccination
Autoimmune diseases
Giant cell myocarditis
Systemic lupus erythematosus
Antiphospholipid antibody syndrome (APLAS)
Churg–Strauss syndrome
Systemic diseases
Coeliac disease
Hypereosinophilic syndrome with eosinophilic endomyocardial disease
Sarcoidosis (idiopathic granulomatous myocarditis)

Pathophysiology

It is not completely understood. Acute infection results in myocyte death and activation of the innate immune response, including interferon gamma, and mobilization of natural killer cells with phagocytosis of released viral particles and cardiac proteins.[1,3] The immune reaction in the heart causes structural and functional abnormalities in cardiomyocytes with consequent regional or global contractile impairment, diastolic dysfunction, or conduction system disease. Most patients recover, but a subset has progression to a second phase, consisting of an adaptive immune response. In this response, antibodies to viral proteins and to some cardiac proteins (including cardiac myosin and β1 or muscarinic receptors) are produced, and effector T cells proliferate. Eventually, the immune response is downregulated, and fibrosis replaces a cellular infiltrate in the myocardium. Under neurohumoral stimulation and haemodynamic stress the ventricles dilate and may lead to chronic cardiomyopathy.

Presentation

Presentation of disease can vary, ranging from minor symptoms of malaise to acute heart failure. In adults, symptoms of viraemia, such as fever, myalgias, arthralgias, fatigue, and respiratory or gastrointestinal symptoms, frequently, but not always, precede the onset of myocarditis by several days to a few weeks. Children, particularly infants, have a more fulminant presentation than adults. Patients may present with dyspnoea, chest pain, palpitations, and decreased exercise tolerance. Fulminant cases are relatively rare. Ocasionally, the condition resembles myocardial infarction. Patients who present with apparently chronic dilated cardiomyopathy and new ventricular arrhythmias or second-degree or third-degree heart block or who do not have a response to optimal care, are more likely to have cardiac sarcoidosis, a granulomatous myocarditis, or, rarely, Chagas' or Lyme disease.[10] Myocarditis may also occur concomitantly with other cardiomyopathies, such as arrhythmogenic right ventricular dysplasia, hypertrophic cardiomyopathy and amyloidosis, or myocardial infarction.[10] Atrial giant cell myocarditis is a more benign form and patients may present with atrial dilatation.[9]

Physical examination

Physical examination may be unremarkable. Fever, tachycardia, S_3 or S_4 gallop, and pulmonary congestion may be present.

Investigations

ECG findings are usually non-specific ST-T changes. Occasionally, ECG changes may mimic myocardial infarction or display arrhythmias or LBBB. Q waves or new LBBB are ominous prognostic signs.[16]

Echocardiography may show global or segmental hypokinesia with or without pericardial effusion.

Patients with fulminant myocarditis usually have small cardiac chambers and thickened walls, whereas in acute myocarditis there is marked left ventricular dilation and normal wall thickness.[17] Diastolic filling patterns are abnormal in most patients, and the presence of right ventricular dysfunction is an ominous prognostic sign. Atrial dilatation with atrial wall thickening may suggest atrial giant cell myocarditis.[9]

Cardiac biomarkers of myocardial injury are elevated in up to 35% patients with myocarditis. Increased serum concentrations of troponin T (TnT), and especially troponin I (TnI), are more common than increased levels of CK-MB in both adults and children with acute myocarditis.[18] Serum level of interleukin-10 on admission is a prognostic predictor of human fulminant myocarditis.[1]

Cardiac MRI provides information about tissue necrosis and fibrosis, hyperaemia, and interstitial oedema, and is a useful prognostic tool.[19] The T2-weighted oedema imaging is used as a tool for evaluating the presence of acute myocardial inflammation. Proposed criteria are presented in Table 45.2.

Endomyocardial biopsy The usefulness of biopsy is limited by sampling error but is necessary in certain conditions, such as suspicion of giant cell or fulminant myocarditis (Table 45.3). There is a reported mortality risk of 0.3% with cardiac biopsy,[20] but in experienced centres complication rates such as perforation or embolization (but no deaths) have been reported as 0.33% with LV and 0.45% with RV biopsy. Perforation is higher with RV biopsy, but TIAs as well as diagnostic yield are higher with LV biopsy (under 1g IV aspirin).[21]

Myocardial gene expression profiling is a novel method that has been proposed to predict the presence of multinuclear giant cells in the myocardium in single biopsy sections even without a direct histological proof, thus reducing the risk of sampling errors.[22] If established, it could be of particular help to distinguish between giant cell myocarditis and cardiac sarcoidosis.

Table 45.2 Lake Louis CMR diagnostic criteria for myocarditis

In the setting of clinically suspected myocarditis, cardiac MRI findings are consistent with myocardial inflammation if, at least, two of the following criteria are present:
1. Regional or global myocardial signal intensity increase in T2-weighted images
2. Increased global myocardial early enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images
3. There is at least one focal lesion with non-ischaemic regional distribution in inversion recovery-prepared gadolinium-enhanced T1-weighted images (late gadolinium enhancement)
Cardiac MRI study is consistent with myocyte injury and/or scar caused by myocardial inflammation if criterion 3 is present
Repeat cardiac MRI study between 1 to 2 weeks after the initial cardiac MRI study if one of the criteria is present or none of the criteria is present, but onset of symptoms is very recent, and there is strong clinical evidence for myocardial inflammation
The presence of left ventricular dysfunction or pericardial effusion provides additional, supportive evidence for myocarditis

Friedrich MG, *et al*. International consensus group on cardiovascular magnetic resonance in myocarditis. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. *J Am Coll Cardiol*. 2009;**53**:1475–87 with permission of Elsevier.

Table 45.3 AHA/ACC/ESC 2007 scientific statement on endomyocardial biopsy

Indications for endomyocardial biopsy	
New-onset heart failure of <2 weeks' duration associated with a normal-sized or dilated LV and haemodynamic compromise	I-B
New-onset heart failure of 2 weeks' to 3 months' duration, associated with a dilated LV and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 weeks	I-B
Heart failure of <3 months' duration, associated with a dilated LV and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1 to 2 weeks	IIa-C
Heart failure associated with a DCM of any duration, associated with suspected allergic reaction and/or eosinophilia	IIa-C
Heart failure associated with suspected anthracycline cardiomyopathy	IIa-C
Heart failure associated with unexplained restrictive cardiomyopathy	IIa-C
Suspected cardiac tumours	IIa-C
Unexplained cardiomyopathy in children	IIa-C
New-onset heart failure of 2 weeks to 3 months' duration, associated with a dilated LV, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1 to 2 weeks	IIb-B
Heart failure of <3 months' duration, associated with a dilated LV, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1 to 2 weeks	IIb-C
Heart failure associated with unexplained HCM, suspected ARVC/D, unexplained ventricular arrhythmias	IIb-C
Unexplained atrial fibrillation	III-C

Cooper LT, *et al*. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. *Eur Heart J*. 2007;**28**:3076–93 with permission from Oxford University Press.

Therapy

Because of the high incidence of LV dysfunction, standard therapy for heart failure is administered. **Beta-blocker** treatment should be avoided in the acute phase of

decompensated heart failure and in the very early treatment of fulminant myocarditis.[23] In patients with suspected myocarditis, however, the lack of beta-blocker treatment is associated with poor outcome.[5] Digitalis is contraindicated, whereas dihydropyridines may be beneficial but not in acute heart failure.[1] In animal studies, NSAIDs have increased inflammation and mortality and should be given at the lowest required dose in patients with perimyocarditis in whom LV function is clearly normal and who have prominent chest pain from pericarditis.[23]

Physical activity is avoided in the acute phase.

Antiviral therapy (ribavirin) has not been proven effective. Interferon has resulted in the elimination of the viral genomes and improved left ventricular function in patients with chronic dilated cardiomyopathy and persistent viral genomes.[24]

Immunosuppressive therapy has not proved useful in patients with acute myocarditis and reduced LV function.[7] However, immunosuppression with steroids and azathioprine for 3–6 months has been found effective in patients with chronic dilated cardiomyopathy, and biopsy-proven virus-negative myocarditis,[25,26] or HLA upregulation on biopsy.[27] It may also be useful in giant-cell myocarditis, eosinophilic myocarditis, and sarcoidosis.[23,28]

In recent-onset dilated cardiomyopathy or myocarditis, **intravenous immune globulin** did not improve LV function.[29] However, in children with acute myocarditis, high-dose gamma-globulin (2 g/kg over 24 hours) resulted in improvement of LV function and a tendency to better survival in the first year after treatment.[30] ICD implantation is indicated in patients with giant cell myocarditis, regardless of LVEF.[31] Recommendations on arrhythmia management are provided in Chapter 56.

Prognosis

It is excellent for adult patients with mild acute lymphocytic myocarditis with preserved LV function. Both LVEF and left atrial size at presentation and at 6-month re-evaluation carry prognostic significance.[32] Presentation with heart failure and LVEF <45% carries a bad prognosis, with mortality of 50% at 4 years. NYHA class, immunohistological signs of inflammation, and lack of beta-blocker therapy, but not histology (positive Dallas criteria) or viral genome detection, have been related to poor outcome within the next 5 years.[5] Recently, the presence of late gadolinium enhancement on cardiac MRI was found to be the best independent predictor of mortality in biopsy-proven viral myocarditis.[19] Viral persistence in the myocardium has been associated with progressive cardiac dysfunction,[13] and biopsy-proven myocarditis is associated with a 19% mortality over the next 4.7 years.[19] Patients with fulminant viral myocarditis with severe haemodynamic compromise have an excellent long-term prognosis and are more likely to experience complete recovery than patients with acute (non-fulminant) myocarditis;[6] aggressive haemodynamic support is warranted for patients with this condition.[33] In patients with cardiac sarcoidosis or giant cell myocarditis, prognosis depends probably on an early initiated treatment (immunosuppressive therapy or heart transplantation).

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Part VIII

Pericardial disease

Relevant guidelines

ESC 2015 Guidelines on pericardial disease

2015 ESC Guidelines for the diagnosis and management of pericardial diseases. *Eur Heart J*. 2015;**36**:2921–64.

Chapter 46

Pericardial anatomy and congenital pericardial defects

Pericardial anatomy

The pericardium consists of two layers: the **visceral pericardium** or epicardium, a serous layer that is adjacent to the heart and proximal great vessels, and the **parietal pericardium** which is formed by the outer fibrous sac and the continuation of the visceral pericardium as it reflects back near the origin of the great vessels to form the inner layer of the parietal pericardium. The visceral and parietal layers are separated by the pericardial cavity, which, in healthy people, contains 15–50 mL of a plasma ultrafiltrate.[1,2] Intrapericardial pressure is normally similar to pleural pressure, varying from –6 mmHg at end inspiration to –3 mm Hg at end expiration. Apart from restraining the heart, the normal pericardium is an important determinant of cardiac filling by limiting chamber dilation and equalizing compliance between the right and left ventricle.

Congenital pericardial defects

They comprise partial left (70%) or right (17%) pericardial absence and have a prevalence of 0.001%. **Total pericardial absence** is rare but predisposes the patient to traumatic aortic dissection. **Partial left side defects** can be complicated by herniation and strangulation of the heart and the coronaries and may require surgical pericardioplasty. On echocardiography, there are prominent right cardiac chambers that may lead to the erroneous diagnosis of RV volume overload or ASD. Cardiac hypermobility (cardioptosis) may be seen, and rarely strangulation of the myocardium and coronary arteries may occur.[3] However, most patients are asymptomatic. Diagnosis is made by cardiac CT or MRI. A **pericardial cyst** is a benign abnormality that is detected as an incidental mass lesion on chest radiography, usually at the right cardiophrenic angle. The differential diagnosis includes tumours, cardiac chamber enlargement, and diaphragmatic hernia, as well as inflammatory (tuberculosis, cardiac surgery) and echinococcal cysts.

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Chapter 47

Acute and relapsing pericarditis

Acute pericarditis

Definition

Pericarditis indicates inflammation of the pericardium due to various causes.

Epidemiology

Pericarditis is diagnosed in 0.1% of hospitalized patients and in 5% of patients seen in the emergency room with chest pain but without myocardial infarction.[1,2]

Aetiology

Causes and estimated incidence of acute pericarditis are presented in Table 47.1. In 80–90% of patients, the cause is either viral or unknown (idiopathic). Idiopathic pericarditis is thought to be very common because the yield of diagnostic tests to confirm aetiology is relatively low. The major specific causes to be ruled out are tuberculous pericarditis, metastatic neoplasia, and connective tissue disorders.[3]

Table 47.1 Aetiology and estimated incidence of acute pericarditis in developed countries

Condition	Estimated incidence (%)
Idiopathic	Most common (>75)[1]
Infectious	
Viral Echovirus and Coxsackie virus, influenza, EBV, CMV, adenovirus, varicella, rubella, mumps, HBV, HCV, HIV, parvovirus B19, and human herpesvirus 6	Most common[1]
Bacterial	5–10
Tuberculous,[2] *Coxiella burnetii*, and rarely: *Pneumococcus, Meningococcus, Gonococcus, Haemophilus,* staphylococci, *Chlamydia, Mycoplasma, Legionella, Leptospira, Listeria, Providencia stuartii*	
Fungal *Histoplasma* and in immunosuppressed patients: aspergillosis, blastomycosis, *Candida*	Rare
Parasites *Echinococcus*, toxoplasma	Very rare
Autoimmune *Systemic sclerosis, SLE, Rheumatoid arthritis, systemic vasculitides, sarcoidosis*	<10
Myocarditis	
Myocardial infarction	
Post-cardiotomy, Post-ablation	
Neoplastic disease	5–9
Metastatic Lung, breast, lymphoma	
Primary Pericardial mesothelioma	Rare
Metabolic	5–10
Uraemia	
Before dialysis	
After initiation of dialysis	
Myxoedema	
Chest wall trauma	Rare
Aortic dissection	Rare
Irradiation	Rare
Drug-related Procainamide, hydralazine, isoniazid, phenytoin (lupus-like syndrome), penicillins (hypersensitivity pericarditis with eosinophilia), doxorubicin, and daunorubicin	Rare

Estimated incidence is derived from studies excluding patients with renal failure, neoplasia, trauma, or radiation.
[1] Most idiopathic cases are thought to be viral. [2] In developing countries, the prevalence of tuberculous pericarditis is high: 70–80% of pericarditis in sub-Saharan Africa and ≥90% when associated with HIV infection.
HBV, hepatitis B; HCV, hepatitis C; CMV, cytomegalovirus; HIV, human immunodeficiency virus, SLE, systemic lupus erythematosus; RA, rheumatoid arthritis.
Khandaker MH, *et al*. Pericardial disease: diagnosis and management. *Mayo Clin Proc*. 2010;**85**:572–93 with permission from Elsevier.
2015 ESC Guidelines for the diagnosis and management of pericardial diseases. *Eur Heart J*. 2015;**36**:2921–64 with permission from Oxford University Press.
Imazio M, *et al*. Controversial issues in the management of pericardial diseases. *Circulation*. 2010;**121**:916–28 with permission from Wolters Kluwer.

Presentation

Fever, myalgia, and malaise may occur as a prodromal phase. Body temperature >38°C is uncommon and may indicate purulent pericarditis.

Chest pain is usually sudden in onset, retrosternal, typically accentuated by inspiration and attenuated by leaning forward. Radiation of the pain to trapezius muscle ridges is probably due to pericarditis because the phrenic nerve that innervates these muscles traverses the pericardium.[4] Dull pain, imitating myocardial ischaemia, may also occur.

Pericardial friction rub is a high-pitched, scratchy sound heard at the left sternal border. It is present in up to 85% of patients but may be transient (repeated examinations are required), and mono-, bi-, or triphasic (corresponding to atrial systole, ventricular systole, and rapid ventricular

filling). It is audible throughout the respiratory cycle, whereas a pleural rub is absent when respiration is suspended.

Investigations

Diagnostic criteria for pericarditis are:

Typical **chest pain**
Pericardial **friction rub**
Suggestive **ECG changes** (typically widespread ST segment elevation, PR depression)
New or worsening **pericardial effusion** (not necessary)
Elevated **CRP** (not specific).

ECG Four stages have been described:

Stage 1: diffuse ST segment elevation (epicardial inflammation) and PR segment depression, with reciprocal ST segment depression in the aVR and V_1 leads, within the first hours to days (present in 80% of patients with pericarditis). There can also be PR segment elevation in the aVR (atrial injury)
Stage 2: the ST and PR segments normalize
Stage 3: T wave inversion
Stage 4: ECG normal or T wave inversion persists indefinitely.

Differential diagnosis from myocardial infarction

In MI:

ST segment elevation is often convex, rather than concave, and regional, rather than widespread

Q wave formation and loss of R wave voltage often occur
T wave inversion appears before the ST segments return to baseline
PR segment depression is uncommon
Atrioventricular block or **ventricular arrhythmias** may be seen.
A ratio of the height of the ST segment junction to the height of the apex of the T wave of more than 0.25 in lead V_6 is suggestive of pericarditis (Figure 47.1).[1,5]
Chest X-ray shows cardiomegaly only with effusions >250 mL.
Echocardiography may be normal or show a small effusion. A paediatric transoesophageal echo probe inserted into a chest drain in the pericardial space allows rapid assessment of post-operative effusions.[5]
Cardiac CT and MR provide excellent visualization of the pericardium and pericardial space. Normal pericardial thickness is usually 1–2 mm (<4 mm). Delayed gadolinium enhancement on CMR is the most sensitive method for diagnosis of acute pericarditis.[4] It is also useful for the assessment of myocardial involvement (Table 47.2).
Troponin concentrations are elevated in 30–50% of cases (CK-MB less often) due to epicardial inflammation. Persistence for more than 2 weeks suggests myocarditis. Unlike acute coronary syndromes, troponin elevation is not a negative prognostic marker in myopericardial inflammatory syndromes. Myopericardial inflammatory syndromes (myopericarditis/perimyocarditis) are rather benign clinical syndromes that can be frequently encountered in patients with an initial suspicion of pericarditis.[6]

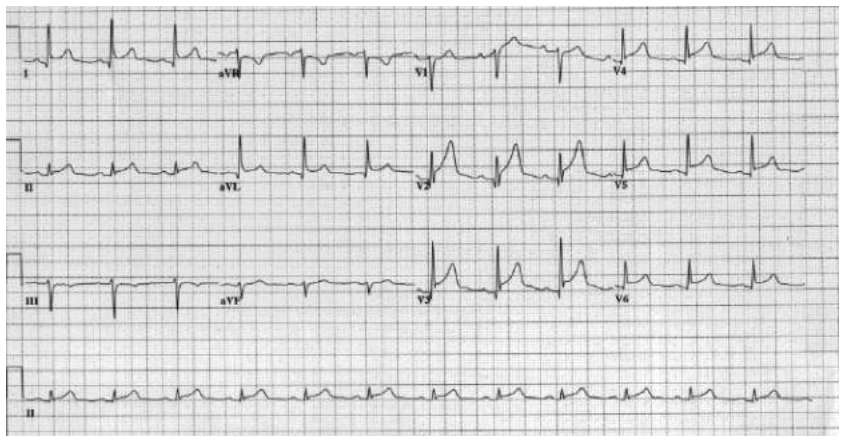

Figure 47.1 Apparently idiopathic acute pericarditis: nearly ubiquitous J (ST) elevations, with corresponding J (ST) depression in aVR. As is common in III and aVF when the QRS axis is horizontal (or these leads are of small voltage), the J (ST) is not elevated. The height of J (ST) is >25% of the height of the T wave peak in V5 and V6. Most PR segments are slightly depressed with respect to the T-P baseline (corresponding PR elevation in aVR). In the clinical setting, a spectrum of myopericardial inflammatory syndromes can be encountered, ranging from pure pericarditis to forms with increasing myocardial involvement (sometimes mimicking an acute coronary syndrome).

Imazio M, *et al*. Controversial issues in the management of pericardial diseases. *Circulation*. 2010;**121**:916–28 with permission from Wolters Kluwer.

Table 47.2 ECS 2015 GL on pericardial diseases. General diagnostic work-up of pericardial diseases

In all cases of suspected pericardial disease a first diagnostic evaluation with:	I-C
– auscultation	
– ECG	
– transthoracic echocardiography	
– chest X-ray	
– routine blood tests, including markers of inflammation (i.e., CRP and/or ESR), white blood cell count with differential count, renal function and liver tests and myocardial lesion tests (CK, troponins)	
Search for independent predictors of an identifiable and specifically treatable cause of pericarditis (i.e. bacterial, neoplastic, systemic inflammatory diseases). Major factors include:	I-B
– fever >38°C	
– subacute course (symptoms developing over several days or weeks)	
– large pericardial effusion (diastolic echo-free space >20 mm in width)	
– cardiac tamponade	
– failure of aspirin or NSAIDs	
CT and/or CMR as second-level testing for diagnostic workup in pericarditis	I-C
Pericardiocentesis or surgical drainage for cardiac tamponade or suspected bacterial and neoplastic pericarditis	I-C
Percutaneous or surgical pericardial biopsy in selected cases of suspected neoplastic or tuberculous pericarditis	IIb-C
Further testing is indicated in high-risk patients (defined as above) according to the clinical conditions	I-C

CK, creatine kinase; CMR, cardiac magnetic resonance; CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate.
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Viral cultures and **antibody** testing are not useful clinically, with the possible exception of HIV and HCV.[7]

WBC, ESR, and CRP are usually elevated. Marked WBC elevation may suggest purulent pericarditis.

Antinuclear antibody and **rheumatoid factor**, **tuberculin skin test** or **QuantiFERON-TB assay**, and **HIV** testing should be ordered only if the clinical presentation is suggestive of these diseases.

Pericardiocentesis is indicated in tamponade or if purulent, tuberculous, or neoplastic pericarditis is suspected.[3] Pericardial fluid is analysed for cell count, microscopy (including Gram and Ziehl–Neelsen stain), bacterial culture, and cytological examination. PCR techniques can identify causative viruses and *M. tuberculosis* (see also Chapter 48). Immunohistochemistry techniques can identify antibodies to myolemma and sarcolemma in immune-mediated pericarditis.[5] Concentrations of adenosine deaminase activity >30 U/L in pericardial fluid are specific for *M. tuberculosis* and can predict constriction. Carcinoembryonic antigen concentrations are higher (5 ng/mL) in neoplastic than in benign effusions. Measurements of pH, glucose, protein, and lactic dehydrogenase are also routinely done, but no accepted criteria link such measures to specific causes of pericarditis.[1]

Pericardial biopsy should be considered for patients who have recurrent tamponade despite treatment. In subjects with tamponade of unknown cause, pericardiocentesis and pericardial biopsy provided a diagnosis in 29% and 54% of cases, respectively.[1]

A diagnostic flowchart for some common conditions in high risk patients is presented in Table 47.3.

Table 47.3 ECS 2015 GL on pericardial diseases. Suggested diagnostic flowchart in some common conditions in high risk patients

Clinical condition	Blood tests	Imaging	Pericardial fluid[a]	Others
Probable autoimmune condition	– ANA, ENA_ANCA (ACE and 24 h urinary calcium – If sarcoidosis Is suspected) – Ferritin if Still disease Is suspected.	Consider PET if large vessel arteritis (Horton or Takayasu) or Sarcoidosis is suspected.		Specialist consultation may be useful. Hypereosinophilia (Churg Strauss), oral and genital apthae (Behcet): difference in blood pressure between two arms (Takayasu), dry eyes Sjogren, Sarcoidosis) macroglossia (amyloidosis)
Probable TB	IGRA test (i.e Quantiferon, ELISpot, etc).	Chest CT Scan	– Acid-fast bacilli staining, mycobacterium cultures, – PCR for genome Adenosine deaminase >40 U/I, unstimulated IFN-gamma.	– Culture and PCR in sputum and other biological fluids – Consider pericardial biopsy.
Probable neoplasm	Specif neoplastic markers not specific or. Sensitive (CA I25 is often non-specifically elevated in the blood when serosal effusions are present).	Chest and abdomen CT scan, consider PET	Cytology (higher volumes of fluid, centrifugation, and rapid analysis improve diagnostic yield). Tumour markers (e.g. CEA >5 ng/ml or CYFRA 2I-I >100 ng/ml).	Consider pericardial biopsy.
Probable viral Infections	– Genome search with PCR Is now preferred to serology for most viruses[b] – Consider serology for HCV and HIV		Genome search with PCR. for specific infectious agents, e.g. enteroviruses, adenoviruses,parvovirus BI9, HHV-6. CMV, EBV[b].	Infectious specialist consultation In case of positivity.
Probable bacterial infections	– Blood cultures before antibiotics. – Serology for *Coxiella burnetii* if Q-fever is suspected. – Serology for *Borrelia spp*. if Lyme disease is suspected.	Chest CT scan	– Aerobic and anaerobic cultures. – Grucose	Consider pericardial biopsy.
Probable autoinflammatory conditions (periodic fevers)	FMF and TRAPS mutations.			Possible clues for TRAPS are familial forms and poor response to colchicine.
Chronic pericardial effusion	TSH Renal function tests.			Consider appropriate tests for suspected neoplasms and TB.
Probable constriction	ENP (near-normal)	Cardiac MR, chest CT scan. biventricular catheterization.		Al the tests for suspected TB.

ACE, angiotensin-converting enzyme; ANA, anti-nuclear antibodies; ANCA, anti-neutrophil cytoplasm antibodies; BNP, brain natriuretic peptide; CEA, carcinoembryonic antigen; CMV, cytomegalovirus; CT, computed tomography; EBV, Epstein-Barr virus; ENA, anti-extractable nuclear antigens; FMF, familial Mediterranean fever; HCV, hepatitis C virus; HHV, human herpesvirus; HIV, human immunodeficiency virus; IGRA, interferon-gamma release assay; MR, magnetic resonance; PCR, polymerase chain reaction; PET, positron emission tomography; spp, species; TB, tuberculosis; TRAPS, tumour necrosis factor receptor-associated periodic syndrome; TSH, thyroid stimulating hormone.

a: Consider storage of a sterile sample for further analyses.

b: See viral pericarditis section—at present, these investigations have no therapeutic or prognostic implications.

IGRAs are whole-blood tests that can aid in diagnosing mycobacterium tuberculosis infection. They do not help to differentiate latent TB infection from TB disease.

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Therapy

When the aetiology is identified, therapy is directed towards treating the underlying cause. Patients with idiopathic pericarditis and without predictors of poor prognosis can be managed as outpatients.[7]

Predictors of poor prognosis are:

Major: Fever >38°C, subacute onset, large effusion, tamponade, lack of response to aspirin or NSAID after 1 week;

Minor: myopericarditis, immunosuppression, trauma, oral anticoagulation.

Aspirin (750–1000 mg tds for 7 days, with 500 mg tds for 1 additional week) or an NSAID such as **ibuprofen** (600 mg tds for 7 days, followed by 200–400 mg tds for another week), or **naproxen** (500–1000 mg bd) with gastroprotection, usually with proton pump inhibitors, are preferred (Table 47.4). Indomethacin should be avoided in patients with coronary artery disease because it decreases coronary blood flow.[3]

Colchicine (1.0 to 2.0 mg for the first day and then 0.5 mg od (patient weighing <70 kg) or bd (patient weighing >70 kg) for 3 months with tapering not mandatory) is now considered a first-line therapy as an adjunct to aspirin or NSAIDs. It reduces recurrences and the risk of tamponade or constriction,[8] and its efficacy is greatest in Familial Mediterranean Fever and Bechet's disease. In the recent ICAP trial, in patients with acute pericarditis, colchicine, when added to conventional anti-inflammatory therapy, significantly reduced the rate of incessant or recurrent pericarditis.[9] It is generally well tolerated during long-term administration, and most common side-effects are diarrhoea, nausea, and vomiting (<10%). Reversible alopecia, hepatic or bone marrow toxicity are very rare.

It is avoided in patients with severe renal insufficiency, hepatobiliary dysfunction, blood dyscrasias, and gastrointestinal motility disorders.[4] Reduced dosage is recommended with advanced renal dysfunction or concurrent therapy with moderate to strong inhibitors of CYP3A4 (eg, protease inhibitors, ketoconazole, fluconazole, erythromycin, diltiazem, verapamil) or P-glycoprotein inhibitors (eg, ciclosporin). In patients undergoing cardiac surgery, perioperative use of colchicine reduces the incidence of postpericardiotomy syndrome but not of postoperative AF or postoperative pericardial/pleural effusion.[10]

Corticosteroids increase the risk of relapsing pericarditis and should be used, together with colchicine, only if aspirin/NSAID are contraindicated. Prednisone (0.25–0.5 mg/kg/day with gradual tapering by 20% of the dose every 1–2 weeks) is given for 4 weeks. As initial treatment steroids may be used only when the underlying cause is an immune-mediated disease, a connective tissue disorder, or uraemic pericarditis. Despite promising initial indications, corticosteroids do not seem to reduce the incidence of constriction in tuberculous pericarditis.[11]

Exercise restriction recommendations are provided in Table 47.4. In case of myocardial involvement restriction should be extended to 6 months.

In **pregnancy**, both aspirin and NSAIDs are avoided after the 20th week, whereas colchicine is rather contraindicated, although in women with Familial Mediterranean Fever no adverse events on fertility, pregnancy, or fetal or child development have been reported even during prolonged exposure to the drug.[7]

Recommendations for pericarditis of specific aetiology are presented in Table 47.5.

Table 47.4 ECS 2015 GL on pericardial diseases. Treatment of acute pericarditis

Aspirin or NSAIDs as first-line therapy with gastroprotection	I–A
Colchicine as first-line therapy as an adjunct to aspirin/NSAID therapy	I–A
Serum CRP to guide the treatment length and assess the response to therapy	IIa–C
Low-dose corticosteroids (added to colchicine) in cases of contraindication/failure of aspirin/ NSAIDs and colchicine, and when an infectious cause has been excluded, or when there is a specific indication such as autoimmune disease	IIa–C
Exercise restriction for non-athletes until resolution of symptoms and normalization of CRP, ECG and echocardiogram	IIa–C
For athletes, exercise restriction until resolution of symptoms and normalization of CRP, ECG and echocardiogram—at least 3 months	IIa–C
Corticosteroids are not recommended as first-line therapy	III–C

CRP, C-reactive protein; ECG, electrocardiogram; NSAIDs, non-steroidal anti-inflammatory drugs.

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Table 47.5 ECS 2015 GL on pericardial diseases. Treatment of recurrent pericarditis

Aspirin and at full doses, if tolerated, until complete symptom resolution	I–A
Colchicine (0.5 mg twice daily or 0.5 mg daily for patients <70 kg or intolerant to higher doses); use for 6 months as an adjunct to aspirin/NSAIDs	I–A
Colchicine therapy of longer duration (>6 months) in some cases, according to clinical response	IIa–C
CRP to guide the treatment duration and assess the response to therapy	IIa–C
After CRP normalization, a gradual tapering of therapies, tailored to symptoms and CRP, stopping a single class of drugs at a time	IIa–C
Drugs such as IVIG, anakinra and azathioprine in cases of corticosteroid-dependent recurrent pericarditis in patients not responsive to colchicine	IIb–C
Exercise restriction for non-athletes with recurrent pericarditis until symptom resolution and CRP normalization, taking into account the previous history and clinical conditions	IIa–C
Exercise restriction for a minimum of 3 months for athletes with recurrent pericarditis until symptom resolution and normalization of CRP, ECG and echocardiogram	IIa–C
If antiplatelet therapy is required, aspirin should be considered, at medium high doses (1–2.4 g/day)	IIa–C
If symptoms recur during therapy tapering, do not increase the dose of corticosteroids to control symptoms, but increase to the maximum dose of aspirin or NSAIDs, well distributed, generally every 8 hours, and intravenously if necessary, adding colchicine, and adding analgesics for pain control	IIa–C
Corticosteroid therapy is not recommended as a first line-approach	III–B

IVIG: intravenous immunoglobulin.
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Recurrent pericarditis

Definition

Recurrent pericarditis is diagnosed when there is a documented first attack of acute pericarditis, a symptom-free interval of 6 weeks or longer, and evidence of either recurrence or continued activity of pericarditis by means of recurrent pain and one, or more, of the following signs: fever, pericardial friction rub, electrocardiographic changes, echocardiographic evidence of pericardial effusion, and elevations in WBC or ESR or CRP. **Incessant pericarditis** refers to persistent pericarditis lasting more than 4–6 weeks but less than 3 months. **Chronic** is pericarditis lasting more than 3 months.[7]

Presentation

Recurrences occur in up to 25% of patients with acute pericarditis and usually occur less than 6 weeks after discontinuation or reduction of treatment but may also appear as late as 20 months after the initial attack.[4] They are often seen at discontinuation of, or attempts to wean patients from, anti-inflammatory treatment. Prognosis is good in idiopathic cases, and there is no risk of constriction.

Therapy

Aspirin, or a **NSAID**, are given for at least 4 weeks. Doses are as for acute pericarditis with gradual tapering by 50% of the dose every 1–2 weeks (Table 47.6). **Colchicine** is added for up to 6 months.[12] Long-term colchicine is usually well tolerated with rare discontinuation required for diarrhoea. Hepatotoxicity and myelosuppression may occur in patients with chronic renal failure. In truly refractory cases, triple therapy with aspirin or NSAID, colchicine, and corticosteroids, such as prednisone 0.25–0.5 mg/kg/day with rapid tapering to 25 mg/day, and then gradual tapering by 20% of the dose every 1–2 weeks if the patient is asymptomatic and the CRP normal, should be administered. Calcium intake 1,200–1,500 mg/day and vitamin D supplementation 800–1000 IU/day po should be offered to all patients receiving glucocorticoids. Moreover, bisphosphonates are recommended to prevent bone loss in all men ≥50 years and postmenopausal women in whom long-term treatment with glucocorticoids is initiated at a dose ≥5.0–7.5 mg/day of prednisone or equivalent.

Alternatively, azathioprine, 1 mg/kg/day po given once daily or divided twice daily, gradually increased till 2–3 mg/kg/day, intravenous immunoglobulin (IVIG)

Table 47.6 ECS 2015 GL on pericardial diseases. Management of specific aetiologies

Tuberculous pericarditis and effusion	
Diagnostic pericardiocentesis in all patients with suspected tuberculous pericarditis	IIa–C
Intrapericardial urokinase to reduce the risk of constriction	IIb–C
In patients living in non-endemic areas, empiric antituberculosis treatment is not recommended when systematic investigation fails to yield a diagnosis of tuberculous pericarditis	III–C
In patients living in endemic areas, empiric antituberculosis chemotherapy is recommended for exudative pericardial effusion, after excluding other causes	I–C
Adjunctive steroids in HIV-negative cases of TB pericarditis. Avoided in HIV-associated TB pericarditis	IIb–C
Purulent pericarditis	
Urgent pericardiocentesis for diagnosis	I–C
Pericardial fluid should be sent for bacterial, fungal, and TB studies and blood drawn for cultures	I–C
Effective pericardial drainage is for purulent pericarditis	I–C
IV antibiotics	I–C
Subxiphoid pericardiotomy and rinsing of the pericardial cavity	IIa–C
Intrapericardial thrombolysis	IIa–C
Pericardiectomy for dense adhesions, loculated or thick purulent effusion, recurrence of tamponade, persistent infection and progression to constriction	IIa–C
Pericarditis in renal failure	
Dialysis should in uraemic pericarditis	IIa–C
Intensify dialysis if pericarditis develops on dialysis , intensifying dialysis	IIa–C
Pericardial aspiration and/or drainage in non-responsive patients with dialysis	IIb–C
NSAIDs and corticosteroids (systemic or intrapericardial) when intensive dialysis is ineffective	IIb–C
Colchicine is contraindicated in patients with pericarditis and severe renal impairment	III–C
Post-cardiac injury syndromes	
Anti-inflammatory therapy in patients with PCIS to hasten symptom remission and reduce recurrences	I–B
Aspirin[a] as a first choice of post-myocardial infarction pericarditis and those patients already on antiplatelet therapies	I–C
Colchicine added to aspirin or NSAIDs for the therapy of PCIS, as in acute pericarditis	IIa–B
Colchicine after cardiac surgery using weight-adjusted doses (i.e. 0.5 mg od for ≤70 kg and 0.5 mg bd for >70 kg) without a loading dose for the prevention of PPS if there are no contraindications and it is tolerated.	IIa–A
Preventive administration of colchicine is recommended for 1 month	
Careful follow-up after PCIS to exclude possible evolution towards constrictive pericarditis with echocardiography every 6–12 months according to clinical features and symptoms	IIa–C
Traumatic pericardial effusion and haemopericardium in aortic dissection	
Urgent imaging technique (transthoracic echocardiogram or CT) in patients with a history of chest trauma and systemic arterial hypotension	I–B
Immediate thoracotomy in cardiac tamponade due to penetrating trauma to the heart and chest	I–B
In the setting of aortic dissection with haemopericardium, controlled pericardial drainage of very small amounts of the haemopericardium to temporarily stabilize the patient in order to maintain blood pressure at about 90 mmHg	IIa–C
Pericardiocentesis as a bridge to thoracotomy in cardiac tamponade due to penetrating trauma to the heart and chest	IIb–B
Neoplastic involvement of the pericardium	
Pericardiocentesis for cardiac tamponade to relieve symptoms and establish the diagnosis	I–B
Cytological analyses of pericardial fluid for the confirmation of malignant pericardial disease	I–B
Pericardial or epicardial biopsy for the confirmation of malignant pericardial disease	IIa–B
Tumour marker testing for distinguishing malignant from benign effusions in pericardial fluid	IIa–B
Systemic antineoplastic treatment in confirmed cases of neoplastic aetiology	I–B

(*Continued*)

Table 47.6 (continued)

Extended pericardial drainage in patients with suspected or definite neoplastic pericardial effusion in order to prevent effusion recurrence and provide intrapericardial therapy	I–B
Intrapericardial instillation of cytostatic/ sclerosing agents since it may prevent recurrences in patients with malignant pericardial effusion	IIa–B
Intrapericardial cisplatin in pericardial involvement in the course of lung cancer and intrapericardial instillation of thiotepa should be considered in breast cancer pericardial metastases	IIa–B
Radiation therapy to control malignant pericardial effusion in patients with radiosensitive tumours such as lymphomas and leukaemias	IIa–B
Pericardiotomy when pericardiocentesis cannot be performed	IIa–B
Percutaneous balloon pericardiotomy for the prevention of recurrences of neoplastic pericardial effusions	IIb–B
Pericardial window creation via left minithoracotomy in the surgical treatment of malignant cardiac tamponade	IIb–B
Interventional techniques should consider seeding of neoplastic cells, patient prognosis and the overall quality of life of the patients	IIa–C
Radiation pericarditis	
Radiation therapy methods that reduce both the volume and the dose of cardiac irradiation whenever possible	I–C
Pericardiectomy for radiation-induced constrictive pericarditis, but with a worse outcome than when performed for constrictive pericarditis of other causes, because of co-existing myopathy	IIa–B
Chylopericardium	
Chylopericardium is diagnosed in the presence of a milky opalescent pericardial effusion, with a triglyceride level >500 mg/dl, cholesterol:triglyceride ratio <1, negative cultures and lymphocyte predominance (lymphocyte count between a few hundred to several thousand per millilitre)	I–C
Pericardial drainage and parenteral nutrition in symptomatic or large uncontrolled effusion due to chylopericardium	IIa–C
Surgical therapy for chylopericardium if conservative therapy does not reduce pericardial drainage and the course of the thoracic duct is identified	IIa–C
Octreotide 100μg SC x 3/day (reduction in chyle production)	IIb–C

NSAIDs, non-steroidal anti-inflammatory drugs; PCIS, post-cardiac injury syndromes; PPS, post-pericardiotomy syndrome.
[a]Antiplatelet effects of aspirin have been demonstrated for doses up to 1.5 g/day. There are no data for or against the use of higher doses in this setting.
ESC 2015 Guidelines for the diagnosis and management of pericardial diseases. *Eur Heart J*. 2015;**36**:2921–64 with permission from Oxford University Press.

400–500 mg/kg/day for 5 days, or 1 g/kg/day for 2 days, eventually repeated every 4 weeks. Anakinra (a recombinant IL-1β receptor antagonist) 1–2 mg/kg/day up to 100 mg once daily subcutaneously, or intrapericardial triamcinolone, may be empirically tried.[7]

Rarely, a pericardial window, or even pericardiectomy, may be needed.[13]

Specific conditions

Recommendations for pericarditis of specific aetiology are presented in Table 47.6.

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Chapter 48

Pericardial effusion and cardiac tamponade

Pericardial effusion

Definition

Pericardial effusion refers to accumulation of pericardial fluid, blood, or lymph, in excess of the 15 to 50 mL that are normally found in the pericardium. The pericardial fluid, therefore, can be a transudate, typically occurring in patients with congestive heart failure, or an exudate, which contains a high concentration of proteins and fibrin and can occur with any type of pericarditis, severe infections, or malignancy. Classification of pericardial effusion is presented in Table 48.1. Pericardial effusions can occur with or without cardiac tamponade.

Table 48.1 ESC 2015 GL on pericardial diseases
Classification of pericardial effusion

Onset
Acute
Subacute
Chronic (>3 months)
Size
Mild <10 mm
Moderate 10–20mm
Large >20 mm
Distribution
Circumferential
Loculated
Composition
Transudate
Exudate

ESC 2015 Guidelines for the diagnosis and management of pericardial diseases. *Eur Heart J.* 2015;**36**:2921–64 with permission from Oxford University Press.

Pathophysiology

The pressure–volume curve of the normal pericardium is a J-shaped curve. After an initial short shallow portion that allows the pericardium to stretch slightly in response to physiological events, such as changes in posture or volume status, with minimal pressure increase, then the pericardium does not allow further sudden increase of the volume without a marked increase in the intrapericardial pressure. Thus, a slowly accumulating pericardial fluid may allow pericardial distension till the accumulation of 1–2 L of pericardial fluid without the development of cardiac tamponade, whereas a sudden increase of pericardial volume of 100–200 mL, as in haemopericardium, may elevate pericardial pressure to 20–30 mmHg with acute cardiac tamponade.[2]

Clinical settings

Aetiology of pericardial effusion is presented in Table 48.2 (see also Chapter 47).

Idiopathic chronic pericardial effusion is defined as a collection of pericardial fluid that persists for more than 3 months and has no apparent cause. It is well tolerated for long periods in most patients, but severe tamponade can develop unexpectedly at any time.[3] Large idiopathic chronic effusions (>3 months) have a 30–35% risk of progression to cardiac tamponade.[3] Thus, large pericardial effusions (>20 mm) should be drained if they persist for more than a month or if there is right-sided collapse.

Moderate pericardial effusions without tamponade in the setting of **myocardial infarction** may indicate subacute ventricular wall rupture and carry the risk of late true wall rupture[4] (see Chapter 29 on MI).

Neoplasia-associated effusion is seen with lung cancer, breast cancer, melanoma, lymphomas, and leukaemias.[1] Primary tumours, such as mesothelioma, are rare. Intrapericardial instillation of cytostatic/sclerotic agents may be needed. However, approximately 75% of

Table 48.2 ESC 2015 GL on pericardial diseases. Aetiology of pericardial effusion in developed countries

Condition	Reported frequency (%)
Idiopathic	7–48
Neoplasia	9–39
Infection	2–29*
Connective tissue disease	6–12
Metabolic	6–24
Iatrogenic	0–16

*Tuberculosis is the most important cause (up to 70%) in developing countries.
Data sourced from Imazio M, et al. Controversial issues in the management of pericardial diseases. *Circulation*. 2010;**121**:916–28.

Table 48.3 Routine analyses performed on pericardial fluid

Analysis	Test	Aetiology or feature
General chemistry	Specific gravity >1015, protein level >3 g/dL, protein fluid/serum ratio >0.5, LDH >200 mg/dL, fluid/serum ratio >0.6[a] Glucose, blood cell count	Exudate
Cytology	Cytology (higher volumes of fluid, centrifugation, and rapid analysis improve diagnostic yield)	Cancer
Biomarkers	Tumour markers (i.e. CEA >5 ng/mL or CYFRA 21–1 >100 ng/mL) Adenosine deaminase >40 U/L, IFN-gamma	Cancer
Polymerase chain reaction (PCR)	PCR for specific infectious agents (i.e. TBC)	TBC
Microbiology	Acid-fast bacilli staining, Mycobacterium cultures, aerobic, and anaerobic cultures	TBC Other bacteria

LDH, lactate dehydrogenase; TBC, tuberculosis.
[a] These chemical features have been especially validated for pleural fluid and not pericardial fluid, although generally used also for pericardial effusion.
Imazio M, Adler Y. Management of pericardial effusion. *Eur Heart J*. 2013;**34**:1186–97 with permission from Oxford University Press.

pericardial effusions in patients with malignancies are due to other causes, such as radiation or opportunistic infections.
Effusions seen with **heart failure** or in the **last trimester of pregnancy** are transudates that never progress to cardiac tamponade.

Presentation

Symptoms vary according to the rate of pericardial fluid accumulation and aetiology of the effusion. The patients may be asymptomatic or complain of dyspnoea on exertion and fatigue. Nausea (diaphragm), dysphagia (oesophagus), hoarseness (recurrent laryngeal nerve), and hiccups (phrenic nerve) that have been described with large effusions are very rare nowadays.

Physical examination

Usually, physical signs are not specific but quiet heart sounds, and elevated jugular venous pressure may be seen. Pulsus paradoxus is typically a sign of tamponade.

Investigations

Most effusions are detected by transthoracic echocardiography which, together with ECG and assessment of markers of inflammation and myocardial injury, is essential (ESC 2015 GL, I-C). CT and CMR may allow detection of loculated effusions, pericardial thickening, and masses (ESC 2015 GL, IIa-C). In the absence of tamponade, pericardiocentesis is indicated if purulent, tuberculous, or neoplastic pericarditis is suspected. Routine analyses to be performed on pericardial fluid are presented in Table 48.3.

Therapy

An algorithm for management is presented in Figure 48.1. Admission is necessary for high-risk patients as described in Chapter 47. Underlying disease may be detected in up to 60% of cases and therapy is therefore specific.[2] When the diagnosis is unclear or idiopathic and inflammatory markers are elevated, aspirin or a NSAID for 1–2 weeks is given (Table 48.4). Combination of aspirin or a NSAID for 2–4 weeks with colchicine (0.5 mg bd for weight ≥70 kg and od for <70 kg) for 3–6 months is considered for recurrent cases, while corticosteroids at low to moderate doses (prednisone 0.2–0.5 mg/kg/day) for 2–4 weeks may be given for specific indications such as systemic inflammatory diseases and pregnancy.[2] Doses are given in Chapter 47. Intrapericardial triamcinolone has also been tried in resistant cases.[2]

Pericardiocentesis alone frequently results in the resolution of large **idiopathic** effusions, but recurrence is common. Pericardiectomy should be considered only in highly symptomatic recurrences resistant to medical therapy, and in cases of chronic permanent constriction.[1,2] If smaller pericardial effusions recur and the patient remains asymptomatic without haemodynamic compromise, regular follow-up is recommended. **Subcritical uraemic tamponade** often responds to intensified renal dialysis, but if this approach is unsuccessful, drainage is required. When recurrent pericardial effusions are related to **chylopericardium**, the underlying aetiology may be thoracic duct obstruction, requiring surgical treatment.[4] In **neoplastic** pericardial disease, pericardial window by open surgery or thoracoscopy, balloon pericardiotomy, and sclerotic local therapy may be needed.

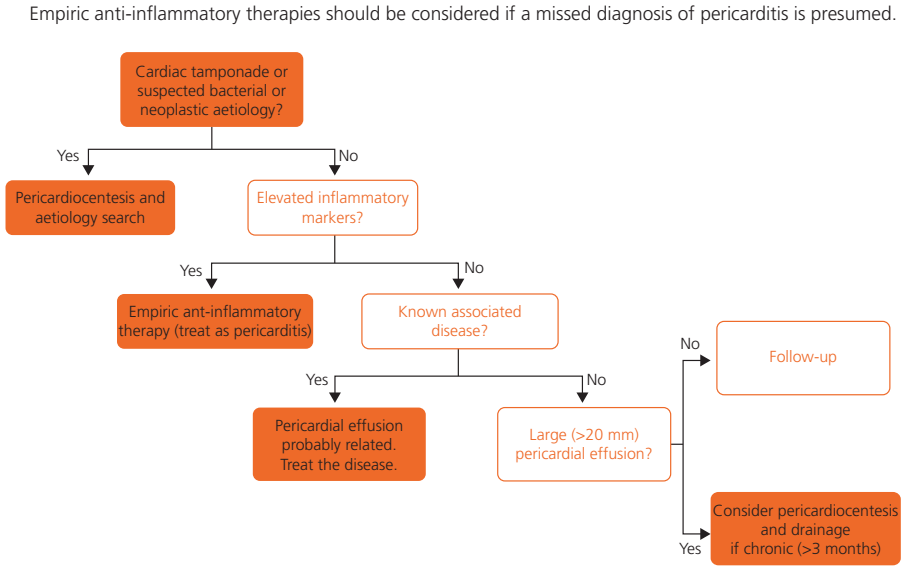

Figure 48.1 ESC 2015 GL on pericardial diseases. A simplified algorithm for pericardial effusion triage and management.

ESC 2015 Guidelines for the diagnosis and management of pericardial diseases. *Eur Heart J.* 2015;**36**:2921–64 with permission from Oxford University Press.

Table 48.4 ESC 2015 GL on pericardial diseases. Therapy of pericardial effusion

Target the therapy at the aetiology	I–C
Aspirin/NSAIDs/colchicine and treatment of pericarditis when pericardial effusion is associated with systemic inflammation	I–C
Pericardiocentesis or cardiac surgery for cardiac tamponade or for symptomatic moderate to large pericardial effusions not responsive to medical therapy, and for suspicion of unknown bacterial or neoplastic aetiology	I–C

ESC 2015 Guidelines for the diagnosis and management of pericardial diseases. *Eur Heart J.* 2015;**36**:2921–64 with permission from Oxford University Press.

Cardiac tamponade

Definition

Cardiac tamponade is a life-threatening, slow or rapid compression of the heart due to the pericardial accumulation of fluid, pus, blood, clots, or gas, as a result of effusion, trauma, or rupture of the heart.[5] Occurrences of tamponade can be acute, subacute, regional, or characterized by low pressure.

Pathophysiology

The true filling pressure is the myocardial transmural pressure, which is intracardiac minus pericardial pressure. The increased intrapericardial pressure equals or exceeds the pressure in the right heart chambers, leading to reduced chamber diastolic compliance and impaired filling, collapse of the right atrium and ventricle during diastole and diminished cardiac output. Expansion of the RV is limited to the interventricular septum, resulting in bulging of the RV into the LV, reduced LV compliance and decreased filling of the LV during inspiration (ventricular interdependence). Maximal pericardial pressure in tamponade occurs during end-diastole, when RA volume is minimal. When fluid collection is slow, the pericardium can stretch to accommodate a large volume with minimum compromise of cardiac function, partly due to systemic neurohumoral responses that compensate for reduced cardiac filling. Thus, intrapericardial haemorrhage from wounds or cardiac rupture occurs in the context of a relatively stiff pericardium and quickly overwhelms the pericardial capacity to stretch before most compensatory mechanisms can be activated, whereas in the case of a slow increase in pericardial volume as a result of inflammation, 2 L or more may accumulate before critical, life-threatening tamponade.[5]

Clinical settings

Pericarditis Tamponade is reported in about 15% of patients with idiopathic pericarditis but in as many as 60% in those with neoplastic, tuberculous, or purulent pericarditis.[6]

Myocardial infarction When pericardial effusion in a parasternal short-axis view exceeds 10 mm in the setting of myocardial infarction, the risk of free wall rupture is high, and pericardial aspiration for measurement of haematocrit in the effusion is useful.[7] Pericardial effusion indicates

Table 48.5 Incidence of iatrogenic tamponade

Procedure	Incidence (%)	Timing
Atrial fibrillation ablation	1–6	During procedure, rarely later
Pacemakers	1.7	Within 7 days of the procedure
ICD	3.8	Within 30 days of the procedure
Percutaneous mitral valvuloplasty	4	During procedure, rarely later
LA appendage occlusion	1.8–3	During procedure
PFO closure	1.5	During procedure
PCI	0.2	During procedure, rarely later

Holmes DR Jr, *et al*. Iatrogenic pericardial effusion and tamponade in the percutaneous intracardiac intervention era. *JACC Cardiovasc Interv*. 2009;**2**:705–17 with permission from Elsevier.

increased mortality in this setting, and early pericardiocentesis may be lifesaving.

Iatrogenic In the current era, invasive cardiac procedures that require anticoagulation and left atrial access using trans-septal puncture have become one of the most common causes of acute tamponade.[8] Its incidence is not exactly known, but it is estimated at 1–6% (Table 48.5). In iatrogenic cardiac perforation, the development and perforation of tamponade depends on the state of anticoagulation, LV and PA pressures, and chamber perforated. RA perforation in the absence of anticoagulation may be well tolerated. LA perforation is more serious because trans-septal access involves anticoagulation, and LA pressure is higher than the RA pressure. RV (RV wall ≥4 mm), and especially LV (LV wall ≥10 mm), perforation may be tolerated, unless severe pulmonary hypertension or aortic stenosis pre-exist, respectively.[8]

Post-operative tamponade is more frequent after valve surgery than CABG and may be seen early or late (5 days to 2 weeks) after the operation. Reported incidence of post-operative pericardial effusions is 1.5% and of tamponade 0.7%.[9] Later, after cardiac surgery, the pericardium may be adherent to the myocardium and thus prevent the development of tamponade; however, posterior localized effusion that may not be accessible to pericardiocentesis may be seen.

Tuberculosis and other infections, neoplasms, collagen vascular disease, radiation, uraemia, aortic dissection, and pneumopericardium are other rare causes of tamponade.[1]

Presentation

Presentation depends on the type and severity of tamponade. Patients are usually weak and faint with tachypnoea and possibly chest pain. The initial symptom may be also one of the complications of tamponade, such as renal failure or right upper quadrant pain due to hepatic congestion. Cardiac tamponade should also be considered in patients in cardiogenic shock, especially if they have increased jugular venous pressure or pulseless electrical activity.

Physical examination

Systemic arterial hypotension, tachycardia, quiet heart sounds, elevated jugular venous pressure, and pulsus paradoxus are the hallmarks of cardiac tamponade. However, most physical signs are not specific.

Systemic arterial hypotension is the rule, but aortic pressure may increase in the early stages of acute tamponade in hypertensive patients due to sympathetic response to pericardial irritation.[5] Patients may also be normotensive, with low pressure tamponade in patients with hypovolaemia or systemic disease.

Tachycardia may not be present in patients with uraemia or hypothyroidism. Bradycardia due to vasovagal reaction may also be initially seen, especially in iatrogenic tamponade.

Heart sounds are quiet, but patients with pre-existing cardiomegaly and anterior or apical pericardial adhesions may have active pulsations.

JVP is usually elevated, with preservation of the x descent but absence of the y descent. However, in acute haemopericardium, there is insufficient time for blood volume to increase, and JVP pulsations may be exaggerated without distension.

Pulsus paradoxus (>10 mmHg fall in systolic pressure during inspiration) may also be seen with pulmonary embolism, chronic obstructive pulmonary disease, constriction, and rarely in pregnancy. Conditions that can impede the detection of pulsus paradoxus in tamponade are: pericardial adhesions, marked left or right ventricular hypertrophy, severe AR, and ASD.

Pericardial rub can be heard in inflammatory effusions.

Kussmaul sign (JVP elevation during inspiration) can be seen but unusually in the absence of pericardial constriction.

Investigations

ECG may show low QRS voltage (<0.5 V in limb leads) and signs of pericarditis. Electrical alternans, defined as the alteration of QRS complex amplitude or axis between beats, are specific for cardiac tamponade, especially when combined with P wave alteration.[5]

Chest X-ray shows cardiomegaly with effusions >250 mL.

Echocardiography reveals diastolic collapse of the RA and early diastolic collapse of the RV when the intrapericardial pressure exceeds intracavitary pressure (Figure 48.2). RA collapse may also be seen in patients

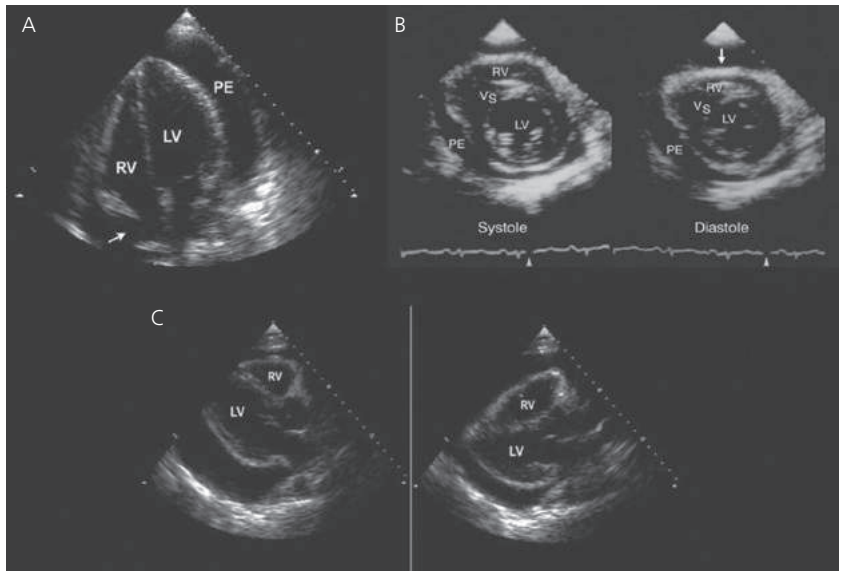

Figure 48.2 Two-dimensional echocardiographic features of cardiac tamponade. A: Apical 4-chamber view showing late diastolic collapse of the right atrium (RA, arrow). Persistence of RA collapse for more than one-third of the cardiac cycle is highly sensitive and specific for tamponade. B: Early diastolic collapse (arrow) of the right ventricle (RV) is specific for tamponade. C: Parasternal long-axis views showing the swinging motion of the heart within the pericardial cavity of a large pericardial effusion; the swinging motion is responsible for the electrocardiographic manifestation termed electrical alternans.

LV, left ventricle; PE, pericardial effusion; VS, ventricular septum.
Khandaker MH, *et al*. Pericardial disease: diagnosis and management. *Mayo Clin Proc*. 2010;**85**:572–93 with permission from Elsevier.

with hypovolaemia, but persistence of RA collapse for more than one-third of the cardiac cycle is highly sensitive and specific for tamponade. During inspiration, the interventricular septum bulges into the LV due to increased systemic venous return to the RV and limited expansion of the RV free wall. With expiration, the transmitral pressure gradient increases, and systemic venous return decreases with reversal of diastolic flow in the hepatic veins.

Left atrial collapse is very specific but not sensitive for tamponade.[4]

The inferior vena cava is dilated, with less than a 50% diameter reduction during inspiration.

When cardiac tamponade is due to aortic dissection or cardiac free wall rupture, a coagulated mass may be seen within the pericardium.

Cardiac CT or **transoesophageal echocardiography** can diagnose loculated pericardial effusions or haematomas, especially after cardiac surgery, not detectable by transthoracic echocardiography.

Cardiac catheterization, if performed, reveals inspiratory increase of the right and concomitant decrease of the left pressure, progressively increasing RA pressure and intracardiac diastolic pressure equilibration (15–30 mmHg) (Table 48.6).

Table 48.6 ESC 2015 GL on pericardial diseases.
Diagnosis and treatment of cardiac tamponade.

In a patient with clinical suspicion of cardiac tamponade, echocardiography is the first imaging technique to evaluate the size, location and degree of haemodynamic impact of the pericardial effusion	I–C
Urgent pericardiocentesis or cardiac surgery	I–C
A judicious clinical evaluation including echocardiographic findings to guide the timing of pericardiocentesis	I–C
A triage system to guide the timing of pericardiocentesis	IIb–C
Vasodilators and diuretics are not recommended in the presence of cardiac tamponade	III–C

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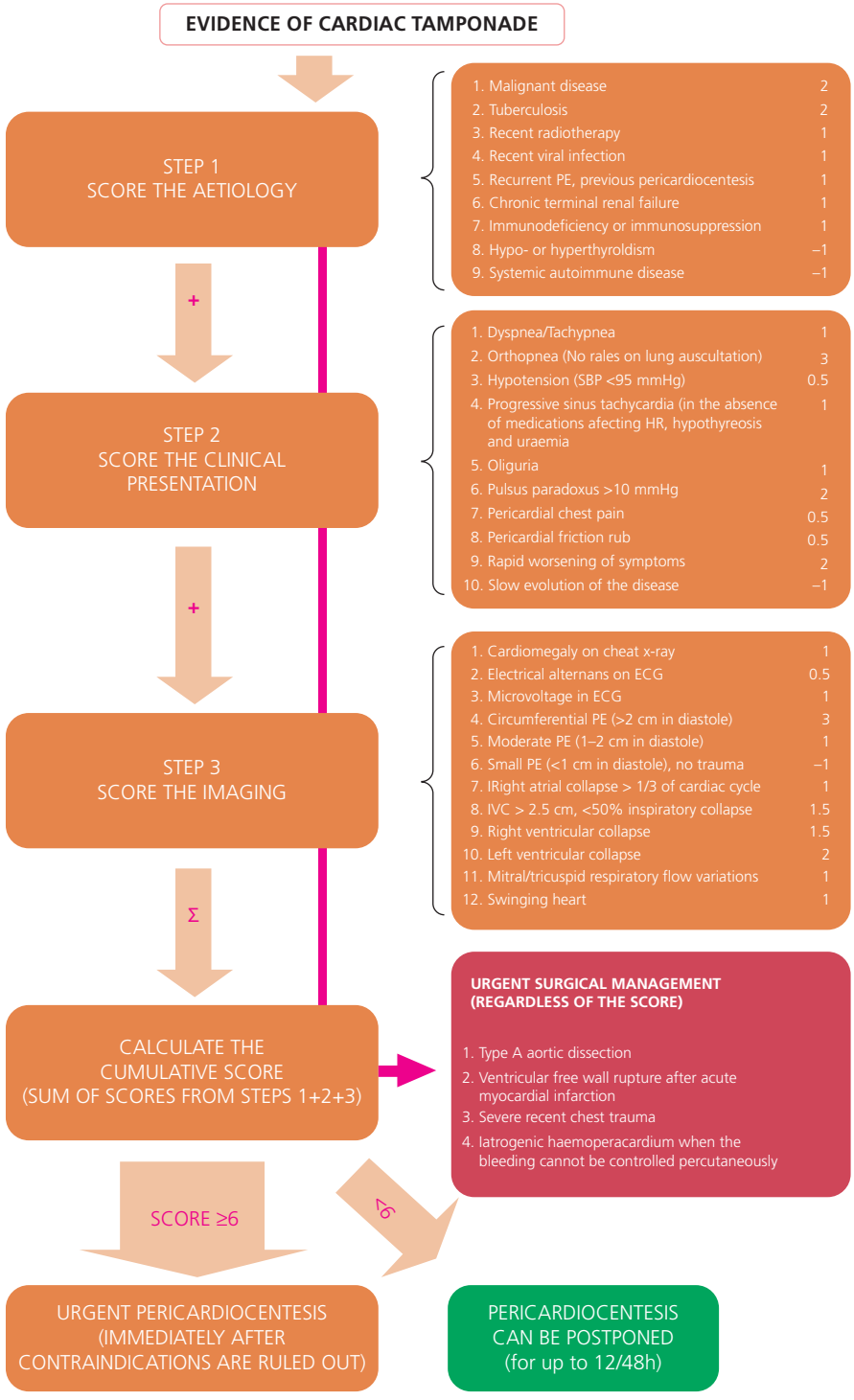
A scoring system for risk stratification of patients has been recently proposed (Figure 48.3).[10]

Therapy

The presence of haemodynamic compromise requires urgent pericardiocentesis or surgical removal of pericardial fluid (Table 48.6). A scoring system for risk stratification of patients has been proposed (Figure 48.3).[10]



PE = pericardial effusion; IVC = inferior vena cava; SBP = systolic blood pressure.

Figure 48.3 Triage for cardiac tamponade.

Ristic AD, *et al*. Triage strategy for urgent management of cardiac tamponade: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2014;**35**:2279–84 with permission from Oxford University Press.

For **pericardiocentesis**, the needle is usually inserted between the xiphoid process and the left costal margin at a 15-degree angle to bypass the costal margin, and then its hub is depressed so that the point is aimed toward the left shoulder and is advanced slowly until fluid is aspirated. Ideally, this should be done in the catheterization laboratory or under echocardiographic guidance and with concomitant administration of IV saline. Attaching an electrode to the needle may provide misleading results. For prolonged drainage, an angiographic pigtail catheter may be left in the pericardium until the amount of fluid drained is <25–50 mL/day. Pericardiocentesis is relatively contraindicated in tamponade due to aortic dissection which represents a surgical emergency. Inadvertent puncture of a cardiac vessel, right ventricle or liver are rare complications.

Surgical drainage is preferable in patients with intrapericardial bleeding or with clotted pericardium.

In hypotensive patients, rapid **volume expansion** with saline or dextran should be provided, especially if the systolic blood pressure is <100 mm Hg.[11] In patients without hypotension and hypovolaemia, fluid infusion may precipitate tamponade.[5]

Inotropic support is controversial since inotropic stimulation of the heart is often already maximal in tamponade.

Mechanical ventilation with positive airway pressure should be avoided because it further decreases cardiac output. In patients with cardiac arrest and a large amount of pericardial fluid, external cardiac compression has little or no value because there is little room for additional filling and because, even if systolic pressure rises, diastolic pressure falls and, in doing so, reduces coronary perfusion pressure.[5]

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Chapter 49

Constrictive pericarditis

Definition

Constrictive pericarditis is due to fibrous thickening and/or calcification of the pericardial sac, with resultant abnormal diastolic filling with raised filling pressures.

Aetiology

Idiopathic, **cardiac surgery**, and **mediastinal radiation therapy** are the main causes in the western world whereas **tuberculosis** is a major cause in immunosuppressed patients and, especially, in developing countries (Table 49.1). More rare causes of constrictive pericarditis include **connective tissue disorders**, **neoplasias**, **asbestosis**, **sarcoidosis**, **trauma**, **drugs**, and **uraemic pericarditis**. Constrictive pericarditis is a relatively rare complication of viral or idiopathic acute pericarditis (<0.5%) but, in contrast, is relatively frequent for specific aetiologies, especially **bacterial**.[1]

Pathophysiology

In constrictive pericarditis, diastolic filling is restricted by a non-compliant, inflamed, scarred, or calcified pericardium after an initial expansion of the myocardium. This results in dissociation of intracardiac and intrathoracic

Table 49.1 ESC 2015 GL on pericardial diseases. Aetiology of constrictive pericarditis in developed countries

Condition	Reported frequency (%)
Idiopathic	33–46
Post-radiation	9–31
Post-surgery	11–37
Post-infectious	4–20*
Connective tissue disease	3–7
Other	1–6

* Tuberculosis is the most important cause in developing countries (up to 90%), where tuberculosis is endemic.
ESC 2015 Guidelines for the diagnosis and management of pericardial diseases. *Eur Heart J.* 2015;**36**:2921–64 with permission from Oxford University Press.

pressures during respiration and interdependence of ventricular filling. On inspiration, intrathoracic pressure decreases but is not transmitted to the left atrium. A reduced pulmonary vein to left atrium pressure gradient produces a fall in flow into the left atrium and left ventricle. Decreased left ventricular filling during diastole allows more room for right ventricular filling, which leads to a septal shift and an increase in right-sided inflow. The exact opposite sequence occurs in expiration.[2] Rapid completion of ventricular filling in early diastole may result in the typical ventricular diastolic waveform of dip and plateau (square root sign) configuration and resembles restrictive cardiomyopathy. Increased ventricular interdependence and discordant changes in LV and RV systolic pressures during respiration are features of pericardial constriction (Figures 49.1 and 49.2).

Presentation

Patients usually present with symptoms and signs of right heart failure, such as increased JVP and peripheral oedema. Symptoms of left ventricular failure, such as dyspnoea on exertion, may also appear. A history of pericarditis, cardiac surgery, or irradiation may be derived within the previous 3–12 months. Rarely, constriction may appear within days after cardiac surgery.

Physical examination

JVP is elevated with a prominent y descent (Friedrich's sign) in sinus rhythm.

Kussmaul sign, i.e. a rise or failure of JVP to decrease with inspiration, may be present and typically occurs in constrictive pericarditis.

Pericardial knock may be present but is difficult to distinguish from an S_3. Both coincide with the nadir of the y descent.

Hepatomegaly (pulsatile liver may be felt), **ascites**, **pleural effusions**, and significant **exercise intolerance** are seen in progressed disease.

Investigations

Transthoracic echocardiography, **chest X-ray in frontal and lateral views, and CT/CMR** are essential (ESC 2015 GL, I-C). Chest X-ray reveals pericardial calcification in 25% of patients with constrictive pericarditis and is not associated with a specific aetiology. However, pericardial thickening and calcification is generally less prominent in non-tuberculous constriction.[3]

ECG shows non-specific ST-T changes and, perhaps, low voltage QRS. Conduction abnormalities are more common in restrictive cardiomyopathy.

Echocardiography Increased ***pericardial thickness*** may be present (not necessarily) and can be better appreciated by transesophageal echocardiography. There is abnormal ***ventricular septal motion***, and dilatation and absent or ***diminished collapse of the IVC*** and hepatic veins may be seen. Preserved or ***increased early diastolic filling*** (peak early velocity of longitudinal expansion (peak Ea) ≥8.0 cm/s) is an important distinction from restrictive cardiomyopathy in which the E is diminished.[4] Doppler and M-mode markers of normal myocardial relaxation indicate constrictive pericarditis rather than restrictivre cardiomyopathy (see Chapter 38). ***Increased hepatic vein***

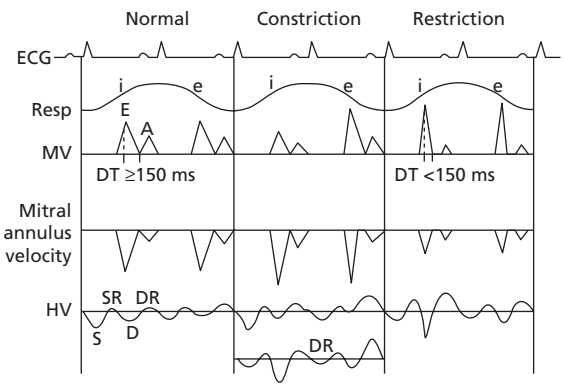

Figure 49.1 Schematic diagram of Doppler echocardiographic features in constrictive pericarditis vs restrictive cardiomyopathy. Schematic illustration of Doppler velocities from mitral inflow (MV), mitral annulus velocity, and hepatic vein (HV). Electrocardiographic (ECG) and respirometer (Resp) recordings indicating inspiration (i) and expiration (e) are also shown.

A, atrial filling; D, diastolic flow; DR, diastolic flow reversal; DT, deceleration time; E, early diastolic filling; S, systolic flow; SR, systolic flow reversal. Stippled areas under the curve represent flow reversal.
Khandaker MH, *et al*. Pericardial disease: diagnosis and management. *Mayo Clin Proc.* 2010;**85**:572–93 with permission from Elsevier.

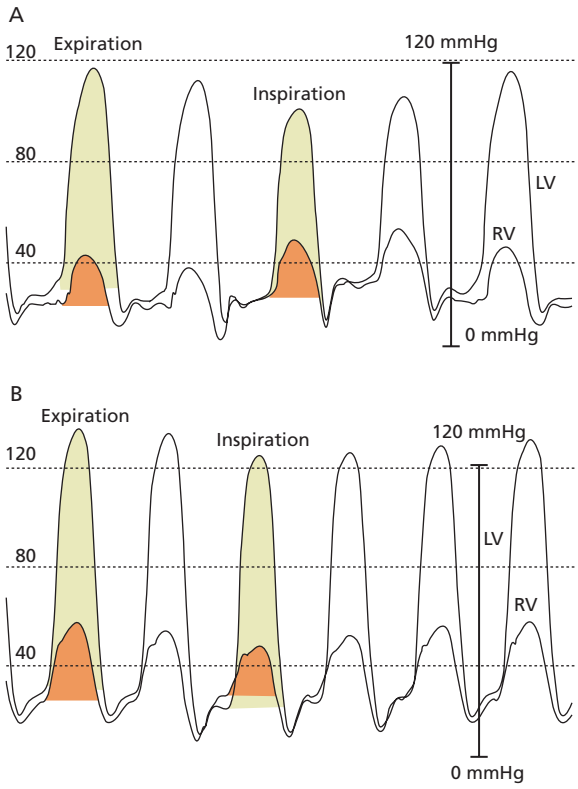

Figure 49.2 Ventricular interdependence and respiratory variation in ventricular filling in constrictive pericarditis and restrictive cardiomyopathy. Both conditions have early rapid filling and elevation and end-equalization of the left ventricular (LV) and right ventricular (RV) pressures at end expiration. A: Discordant pressure change between the LV and RV in constrictive pericarditis. During inspiration, there is an increase in the area of the RV pressure curve (orange shaded area) compared with expiration. The area of the LV pressure curve (yellow shaded area) decreases during inspiration as compared with expiration. Ejection time also varies with respiration in opposite directions in LV and RV. B: Concordant pressure change between the LV and RV in restrictive cardiomyopathy. During inspiration, there is a decrease in the area of the RV pressure curve (orange shaded area) as compared with expiration. The area of the LV pressure curve (yellow shaded area) is unchanged during inspiration as compared with expiration.

Khandaker MH, *et al*. Pericardial disease: diagnosis and management. *Mayo Clin Proc*. 2010;**85**:572–93 with permission from Elsevier.

flow reversal with expiration, reflects the ventricular interaction and the dissociation of the intracardiac and intrathoracic pressures.

Cardiac catheterization It is indicated when non-invasive methods do not provide a definitive diagnosis (ESC 2015 GL, I-C). Volume challenge may be needed for full expression of haemodynamic signs. Prominent x descent (occasionally absent) and y descents on the atrial waveform may produce ***M or W waveforms***. One of the most reliable diagnostic criteria is the ***ratio of RV to LV systolic area*** during inspiration and expiration (Figure 49.2).[5]

Cardiac CT and cardiac MR They can demonstrate increased pericardial thickness (>4 mm) and calcification. Up to 20% of patients do not have thickened pericardium.[6] High sensitivity and specificity have been reported for CMR.[3]

Differential diagnosis

Differentiation from **restrictive cardiomyopathy** is presented in Table 37.4 in Chapter 37 on restrictive cardiomyopathy. Thickened pericardium, significant respiratory variation in transmitral, pulmonary vein, and tricuspid inflows, and preserved indices of myocardial relaxation (velocity of propagation and early mitral annular velocity) are characteristics of pericarditis. In certain cases, endomyocardial biopsy or explorative thoracotomy may still be necessary for a definitive diagnosis. **Tricuspid regurgitation** may result in right heart failure and equalization of diastolic pressures simulating constrictive pericarditis. If echocardiography cannot establish the diagnosis, simultaneous recordings of LV and RV pressures in the catheter laboratory reveals that, on inspiration, the difference between RV and LVEDP becomes more prominent in TR.[7]

Therapy

Medical therapy is palliative by means of reducing fluid by diuretics. In chronic constrictive pericarditis, surgical complete pericardiectomy is necessary (Table 49.2), and should be undertaken before calcification occurs but is associated with an operative mortality of up to 6%.[8,9] Advanced age, NYHA class, and especially a history of radiation are predictors of a poor outcome.[10] In a subset of patients in whom constriction is due to reversible inflammation, it may resolve after 2 or 3 months, either spontaneously or with treatment with anti-inflammatory

Table 49.2 ESC 2015 GL on pericardial diseases. Therapy of constrictive pericarditis

The mainstay of treatment of chronic permanent constriction is pericardiectomy	I–C
Medical therapy of specific pericarditis (i.e. tuberculous pericarditis) to prevent the progression of constriction	I–C
Empiric anti-inflammatory therapy in cases with transient or new diagnosis of constriction with concomitant evidence of pericardial inflammation (i.e. CRP elevation or pericardial enhancement on CT/CMR)	IIb–C

2015 ESC Guidelines for the diagnosis and management of pericardial diseases. *Eur Heart J*. 2015;**36**:2921–64.

agents and/or steroids(**transient constrictive pericarditis**). In patients with effusion in the context of constriction (**effusive-constrictive pericarditis**), evacuation of the pericardium may, in some cases, result in resolution of the restrictive physiology.[11] Patients with systemic inflammation, as detected by cardiac MRI and biomarkers, such as ESR and CRP, may respond to anti-inflammatory medication.[12] Standard antituberculosis drugs for 6 months are recommended for the prevention of pericardial constriction in patients with tuberculous pericarditis (ESC 2015 GL, I-C). If the patient is not improving or is deteriorating after 4–8 weeks of antituberculosis therapy, pericardiectomy is recommended (ESC 2015 GL, I-C).

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Part IX

Tachyarrhythmias

Relevant guidelines

SVT

ACC/AHA/ESC 2003 Guidelines on SVT

ACC/AHA/ESC Guidelines for the management of patients with supraventricular arrhythmias. *Eur Heart J*. 2003;**24**:1857–97.

ACC/AHA/HRS 2015 Guideline on SVT

2015 ACC/AHA/HRS Guideline for the management of adult patients with supraventricular tachycardia. *J Am Coll Cardiol*. Published online September 23, 2015. doi:10.1016/j.jacc.2015.08.856.

PACES/HRS 2014 Consensus statement on arrhythmias in GUCH

PACES/HRS Expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease. *Heart Rhythm*. 2014;**11**:e102–65.

HRS 2015 Statement on postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope

2015 Heart Rhythm Society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *HeartRhythm*. 2015;**12**:e41–63.

ESC 2011 Guidelines on pregnancy

ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**:3147–97.

AF

ESC 2010 Guidelines on AF

ESC Guidelines for the management of atrial fibrillation. *Eur Heart J*. 2010;**31**:2369–429.

ESC 2012 Guidelines on AF update

2012 Focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. *Europace*. 2012;**14**:1385–413.

AHA/ACC/HRS 2014 Guideline on AF

2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation. *J Am Coll Cardiol*. 2014;**64**:e1–76.

ESC 2015 Guidelines on NSTE-ACS

2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2015;**37**:267–315.

HRS/EHRA/ECAS Expert consensus statement on catheter and surgical ablation of AF

HRS/EHRA/ECAS Expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace*. 2012;**14**:528–606.

AHA/ACC 2014 Guidelines on valve disease

2014 AHA/ACC Guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:2438–88.

ESC 2012 Guidelines on valve disease

Guidelines on the management of valvular heart disease. *Eur Heart J*. 2012;**33**:2451–96.

PACES/HRS 2014 Consensus statement on arrhythmias in GUCH

PACES/HRS Expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease. *Heart Rhythm*. 2014;**11**:e102–e165.

EHRA 2015 Practical guide on new oral anticoagulants

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace*. 2015;**17**:1467–507.

EHRA/EAPCI 2014 Consensus statement on left atrial appendage occlusion

EHRA/EAPCI Expert consensus statement on catheter-based left atrial appendage occlusion. *Europace*. 2014;**16**:1397–416.

ACC/HRS/SCAI 2015 Left atrial appendage occlusion device overview

2015 ACC/HRS/SCAI Left atrial appendage occlusion device societal overview. *JACC*. 2015;**66**:1497–513.

AHA/ASA 2014 Guidelines for the prevention of stroke

Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack. *Stroke*. 2014;**45**:2160–236.

AHA/ASA 2013 Guidelines for acute ischemic stroke

Guidelines for the early management of patients with acute ischemic stroke. *Stroke*. 2013;**44**:870–947.

ESC 2011 Guidelines on pregnancy

ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**:3147–97.

VT

ACC/AHA/ESC 2006 Guidelines on ventricular arrhythmias

ACC/AHA ESC 2006 Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Circulation*. 2006;**114**:e385–484.

2015 ESC 2015 Guidelines on ventricular arrhythmias and prevention of sudden cardiac death

2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015;**36**:2793–867.

ACCF/AHA/HRS 2012 Guidelines for device-based therapy of cardiac rhythm abnormalities

2012 ACCF/AHA/HRS Focused update incorporated into the ACCF/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2013;**61**:e6–75.

EHRA/HRS/APHRS 2014 Expert consensus on ventricular arrhythmias

EHRA/HRS/APHRS Expert consensus on ventricular arrhythmias. *Europace*. 2014;**16**:1257–83.

EHRA/HRS 2009 Expert consensus on catheter ablation of ventricular arrhythmias

EHRA/HRS Expert consensus on catheter ablation of ventricular arrhythmias. *Europace*. 2009;**11**:771–817.

PACES/HRS 2014 Consensus statement on arrhythmias in GUCH

PACES/HRS Expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease. *Heart Rhythm*. 2014;**11**:e102–e165.

HRS/ACC/AHA Expert consensus statement on the use of ICD in patients not represented in clinical trials

HRS/ACC/AHA Expert consensus statement on the use of implantable cardioverter-defibrillator therapy in patients who are not included or not well represented in clinical trials. *J Am Coll Cardiol*. 2014;**64**:1143–77.

AHA 2015 Scientific Statement on ACHD

American Heart Association Council on Clinical Cardiology. Congenital heart disease in the older adult: a scientific statement from the American Heart Association. *Circulation*. 2015;131:1884–931.

AHA 2010 Guidelines for cardiopulmonary resuscitation

2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and emergency cardiovascular care. *Circulation* 2015;**132**[suppl 2]:S315–S367.

ESC 2011 Guidelines on pregnancy

ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**:3147–97.

Chapter 50

Classification of tachyarrhythmias, mechanisms of arrhythmogenesis, and acute management

Definitions and classification

Definitions

The term **tachyarrhythmia** (Greek *tachy* = fast, and *arrhythmia* = rhythm disturbance) is used to describe conditions in which the heart rate exceeds the conventional number of 100 bpm, either in response to metabolic demand or other stimuli or due to disease. The term **tachycardia** requires more than 3 (or 5) consecutive beats, otherwise, we are talking about premature beats or extrasystoles. A tachycardia is called **sustained** when lasting more than 30 s, **paroxysmal** when it starts and stops abruptly, and **incessant** or **permanent** when it occurs most of the time with annoying perseverance. The term **chronic** refers to incessant tachycardias which occur on a long-term basis and may result in cardiac dilatation and impairment of ventricular contractility.

Classification of arrhythmias

Traditionally, tachyarrhythmias have been classified as **ventricular** or **supraventricular**. The term supraventricular (SVT) describes tachycardias (atrial and/or ventricular rates > 100 bpm at rest), the mechanism of which involves tissue from the His bundle or above.[1] Traditionally, SVT includes all kinds of tachycardias, apart from ventricular tachycardias and atrial fibrillation (Table 50.1). From a clinical point of view, tachyarrhythmias can also be classified as narrow or wide QRS tachycardias, depending on the QRS duration during the arrhythmia (Table 50.2). Although a detailed electrophysiological study is usually necessary for a definite diagnosis and localization of the focus of the tachycardia, the 12-lead ECG can provide information for the differential diagnosis of most of these rhythms.

Classification of antiarrhythmic drugs

The Vaughan Williams classification, as modified by Singh and Harrison (Table 50.3), of the antiarrhythmic agents is outdated and oversimplistic but more practical than that proposed by the Sicilian Gambit.[2] Most drugs have additional modes of action.

Table 50.1 Classification of tachyarrhythmias

ATRIAL ARRHYTHMIAS
Sinus tachycardia
Physiological sinus tachycardia
Inappropriate sinus tachycardia
Sinus reentrant tachycardia
Atrial tachycardia
Focal atrial tachycardia
Multifocal atrial tachycardia
Macro-reentrant tachycardia
Cavotricuspid isthmus-dependent, counter-clockwise or clockwise (typical atrial flutter)
Non cavotricuspid isthmus–dependent, mitral isthmus-dependent, and other atypical left or right atrial flutters
Atrial fibrillation
ATRIOVENTRICULAR JUNCTIONAL ARRHYTHMIAS
Atrioventricular nodal reentrant tachycardia (typical or atypical)
Non-reentrant junctional tachycardias
Non-paroxysmal junctional tachycardia
Focal junctional tachycardia
Other non-reentrant variants
ATRIOVENTRICULAR ARRHYTHMIAS
Atrioventricular reentrant tachycardia
Orthodromic
Antidromic
VENTRICULAR ARRHYTHMIAS
Monomorphic ventricular tachycardia
Accelerated idioventricular rhythm
Polymorphic ventricular tachycardia
Pleomorphic ventricular tachycardia
Bidirectional ventricular tachycardia
Torsade de pointes
Ventricular flutter
Ventricular fibrillation

Table 50.2 Differential diagnosis of tachyarrhythmias

Narrow QRS (<120 ms) tachycardias
Regular
Physiological sinus tachycardia
Inappropriate sinus tachycardia
Sinus reentrant tachycardia
Focal atrial tachycardia
Atrial flutter
Atrial fibrillation with very fast ventricular rate
Atrioventricular nodal reentrant tachycardia
Non-paroxysmal or focal junctional tachycardia
Orthodromic atrioventricular reentrant tachycardia
Idiopathic ventricular tachycardia (especially high septal VT)
Irregular
Atrial fibrillation
Atrial focal tachycardia or flutter with varying block
Multifocal atrial tachycardia
Wide QRS (>120 ms) tachycardias
Regular
Antidromic atrioventricular reentrant tachycardia
Any regular atrial or junctional reentrant tachycardias with:
aberration/bundle branch block
preexcitation/bystander accessory pathway
Ventricular tachycardia/flutter
Irregular
Atrial fibrillation or atrial tachycardia with varying block conducted with aberration
Antidromic atrioventricular reentrant tachycardia with a variable VA conduction
Preexcited AF
Polymorphic VT
Torsade de pointes
Ventricular fibrillation

Table 50.3 Vaughan Williams classification

Class I	Fast Na^+ channel blockers (slowing of conduction)
	IA (quinidine, procainamide)
	IB (lidocaine)
	IC (propafenone, flecainide)
Class II	Beta-blockers
Class III	Repolarization K+ channel blockers (prolongation of repolarization) (amiodarone,* ibutilide, dofetilide, vernakalant, sotalol)
Class IV	Calcium channel blockers (non-dihydropyridine: verapamil, diltiazem)

*Amiodarone exhibits effects of all classes.

Electrophysiological mechanisms of arrhythmogenesis

The action potential

Cardiac electrical activity starts by the spontaneous excitation of 'pacemaker cells' in the sinoatrial node in the right atrium and spreads through sinoatrial exit pathways (see Chapter 62 on bradyarrhythmias). By travelling through intercellular gap junctions (cell-to-cell connections), the excitation wave depolarizes adjacent atrial myocytes, ultimately resulting in excitation of the atria. The excitation wave then propagates via the atrioventricular node and the Purkinje fibres to the ventricles where ventricular myocytes are depolarized, resulting in excitation of the ventricles. Depolarization of each atrial or ventricular myocyte is represented by the initial action potential (AP) upstroke where the negative resting membrane potential depolarizes to positive voltages (Figures 50.1 and 50.2).[3] The action potential is produced by transmembrane flow of ions (**inward depolarizing currents, mainly through $Na^+$and Ca^{2+} channels**, and **outward repolarizing currents, mainly through K^+ channels)**. The resting potential of atrial and ventricular myocytes during AP **phase 4** (resting phase) is stable and negative (–85 mV) due to the high conductance of the potassium channels. Excitation by electrical impulses from adjacent cells activates the inward Na^+ current that depolarizes myocytes rapidly (**phase 0**). Transient outward K^+ current (**phase 1**) creates a notch during the early phase of repolarization (I_{to}). Balance of the inward depolarizing L-type Ca^{2+} current ($I_{Ca\text{-}L}$) and outward rectifier K^+ currents (slow-I_{Ks}, rapid-I_{Kr}, and ultra-rapid-I_{Kur}) forms a plateau phase (**phase 2**). Deactivation (closing) of the inward current $I_{Ca\text{-}L}$ and increase of the outward currents creates **phase 3**, with final repolarization mainly due to potassium efflux through the inward rectifier I_{K1} channels, and the membrane potential returns to its resting potential (**phase 4**). The pacemaker current (I_f) contributes to action potential generation in the sinus node and significantly determines heart rate.[4] It is called the funny current because it displays unusual gating properties. I_f is a mixed Na^+/K^+ current, which conducts an inward current during phases 3 and 4 and may underlie slow membrane depolarization in cells with pacemaker activity (i.e. cells with I_f and little, or no, I_{K1}). I_f activation is accelerated by intracellular cyclic adenosine monophosphate (cAMP) levels, thus regulated by sympathetic and parasympathetic activities, which control synthesis and degradation of intracellular cAMP, respectively.

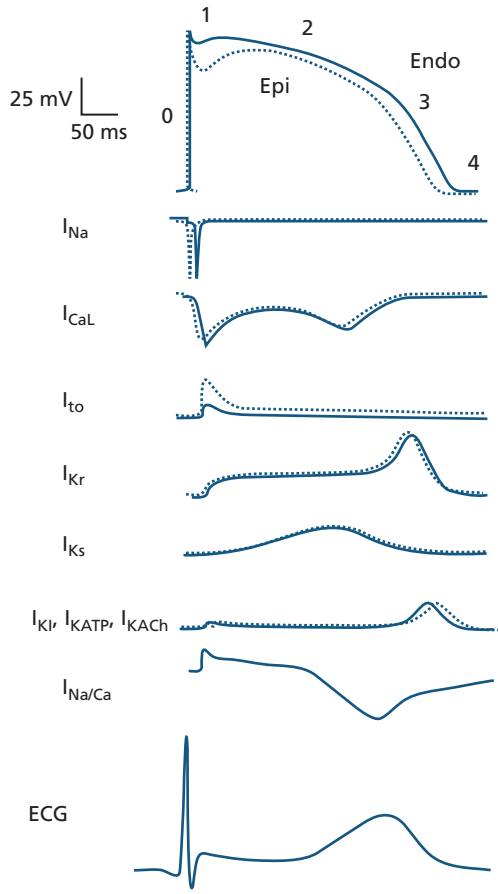

Figure 50.1 The ionic currents of the action potential (AP). Epicardial (Epi) AP and current are shown by dotted lines and endocardial (Endo) by solid lines. Depolarizing inward currents are depicted downward and repolarizing outward currents upward. The Epi AP has a characteristic notch caused by larger phase 1 I_{to} compared with Endo.

ECG indicates electrocardiogram; I_{CaL}, inward calcium currents; I_{K1}, inward rectifier current; I_{KACh}, acetylcholine-activated current; I_{KATP}, adenosine triphosphate–sensitive current; I_{Kr}, rapid delayed rectifier current; I_{Ks}, slow delayed rectifier current; I_{Na}, inward sodium current; $I_{Na/Ca}$, sodium calcium exchange; and Ito, transient outward current.

Obeyesekere MN, *et al*. Management of ventricular arrhythmias in suspected channelopathies. *Circ Arrhythm Electrophysiol*. 2015;**8**:221–31 with permission from Wolters Kluwer.

Opening and closing (gating) of ion channels enable transmembrane ion currents that consist of proteins called pore-forming alpha (±)-subunits and accessory beta (β)-subunits. Terminology of genes encoding these proteins describes their function. For example, the gene encoding the alpha-subunit of the cardiac sodium channel is called SCN5A: sodium channel, type 5, alpha-subunit. The alpha-subunit is termed Nav 1.5: Na^+ channel family, subfamily 1, member 5, and V means that channel gating is regulated by transmembrane voltage changes (voltage-dependent).[1] Polymorphisms and mutations in genes encoding ion channels are associated with slow conduction and QRS duration prolongation and, consequently, future development of cardiac arrhythmias.[5,6] For a detailed description of acquired diseases due to mutations of these genes affecting the action potential, see Part X on genetic channelopathies and Part XI on bradyarrhythmias.

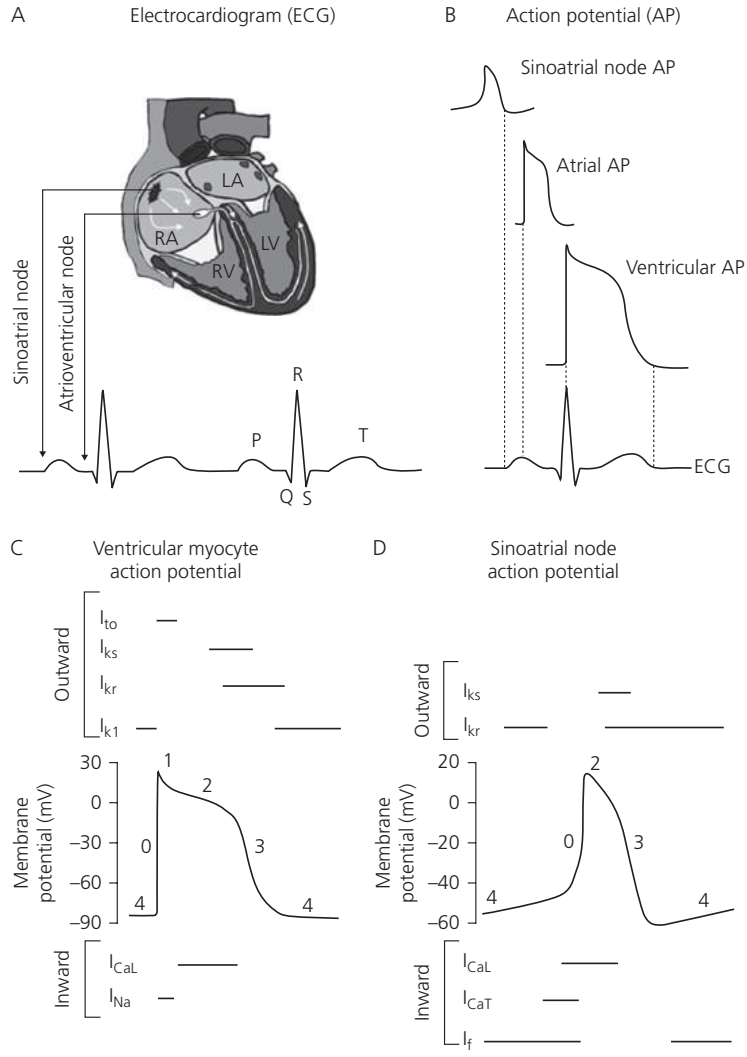

Figure 50.2 Cardiac electrical activity. A: Schematic representation of the electrical conduction system and its corresponding signal on the surface electrocardiogram (ECG). B: Relationship between ECG and action potentials (APs) of myocytes from different cardiac regions. C, D: Schematic representation of inward and outward currents that contribute to action potential formation in the sinoatrial node and ventricular myocytes. The QT interval indicates the duration of ventricular depolarization and repolarization, which is caused by transmembrane flow of ions (e.g. inward depolarizing currents, mainly through Na^+ and Ca^{2+} channels, and outward repolarizing currents, mainly through K^+ channels). Initial depolarization of cardiac myocytes through gap junctions (cell-to-cell connections) activates the inward Na^+ current that depolarizes myocytes rapidly (phase 0). Transient outward K^+ current (phase 1) creates a notch during the early phase of repolarization (Ito). Balance of the inward depolarizing Ca^{2+} current (ICa-L) and outward rectifier K^+ currents (IKs and IKr) forms a plateau phase (phase 2). Deactivation of the inward current and increase of the outward current (IKs, IKr, IK1) complete repolarization (phase 3), and the membrane potential returns to its resting potential (phase 4).

Amin AS, *et al*. Cardiac ion channels in health and disease. *Heart Rhythm*. 2010;**7**:117–26 with permission from Elsevier.

Mechanisms of arrhythmias

Although the initiation of tachycardias is a complex process depending on the interaction of several factors, the main mechanisms responsible for the initiation of tachycardias are thought to be cell membrane hyperexcitability, i.e. enhanced automaticity or triggered activity and reduction in cell-to-cell electrical coupling, resulting in conduction block and reentry.[7] **Abnormal automaticity** is due to the maximum diastolic potential spontaneously becoming less negative (–40 to –60 mV; phase 4 of the AP). This is usually secondary to infarction, tissue stretch, and drugs. **Triggered activity** is caused by early after-depolarizations or delayed after-depolarizations, i.e. depolarizing oscillations in membrane voltage introduced by one or more preceding action potentials. ***Early after-depolarizations*** (i.e. occurring during phase 3 of the action potential) may be due to electrolyte disturbances, such as hypokalaemia, hypomagnesaemia, antiarrhythmic drugs (class Ia and class III), sympathetic stimulation, hypoxia, and hypercapnia. Typically, they occur in the long QT syndrome. ***Delayed after-depolarizations*** (i.e. after complete repolarization of the action potential) may be due to calcium overload, digoxin, catecholamines, and artificial pacing. Automatic and triggered arrhythmias depend on cell membrane hyperexcitability which is driven primarily by L-type calcium channels and/or adrenergic receptor stimulation.[8] A key molecule in membrane depolarizations (and in the generation of a delayed after-depolarization) is the electrogenic sodium-calcium exchanger, which allows diastolic calcium leak from the sarcoplasmic reticulum (Figure 50.3).[9]

Reentry denotes circulation of a wave of depolarization which is initiated when:

- Two functionally distinct pathways are present.
- Unidirectional block is induced in one pathway, for example, by a premature stimulus or by a physiological tachycardia.
- Sufficient slow conduction exists to allow recovery of excitability in the blocked pathway and permit retrograde conduction over that pathway and completion of the circuit.

Reentrant mechanisms can be conventionally classified as:

Anatomical due to defined loop. There is a large excitable gap between the crest and tail of impulse, i.e. properly timed stimuli can capture the circuit and reset the tachycardia. Typical examples are the atrioventricular reentrant tachycardias due to accessory atrioventricular connections.

Functional due to altered cellular electrophysiological properties of myocardial tissue, such as functional barriers of conduction block or decremental conduction, leading to propagation failure. Functional reentry is exemplified by the 'leading circle' hypothesis which may be important in atrial fibrillation. In this model, the reentrant pathway is the shortest possible one and is determined on an instantaneous basis by refractoriness ahead of the activation wavefront. The cycle length, therefore, is determined only by refractoriness, and the excitable gap is as short as possible, independent of the cycle length. Functional circuits can also result in patterns, such as spirals or scrolls, that have been implicated in both atrial and ventricular fibrillation.[8]

Anisotropic due to changes in microanatomical structures, such as cellular coupling and fibre orientation heterogeneity, which lead to anisotropic conduction or spatial inhomogeneity of refractoriness. The length of the circular pathway is determined by electrophysiological-anatomical changes, and there may be an excitable gap. This kind of reentry can be seen after myocardial infarctions.

There is evidence that more than 90% of the clinical tachycardias are due to reentrant mechanisms. Typical examples of reentry are tachycardias associated with the Wolff–Parkinson–White syndrome, the AV junctional reentry tachycardias, atrial flutter, and, most probably, atrial fibrillation. In addition, certain forms of sustained monomorphic ventricular tachycardia, such as VT in patients with coronary artery disease and bundle branch reentry in cases of dilated cardiomyopathy, demonstrate reentrant circuit with fully excitable gap. Anisotropic reentry appears to play an important role in ventricular tachycardias occurring in the setting of chronic healed myocardial infarcts. Torsades de pointes and some forms of ventricular tachycardia complicating coronary artery disease are due to after-depolarization-induced triggered activity.

Reentrant mechanisms are postulated when programmed stimulation demonstrates that the tachycardia behaves in a manner similar to that of reentry. Thus, easy induction and termination by programmed stimulation, as well as entrainment of the tachycardia, usually indicate a reentrant mechanism. Tachycardias due to triggered activity may also be initiated and terminated by pacing and may be distinguished from reentrant ones because more premature stimulation may cause progressively faster triggered activity. Usually, distinction from reentry is difficult. Arrhythmias due to abnormal automaticity occur spontaneously or in response to isoprenaline and are not induced by programmed stimulation.

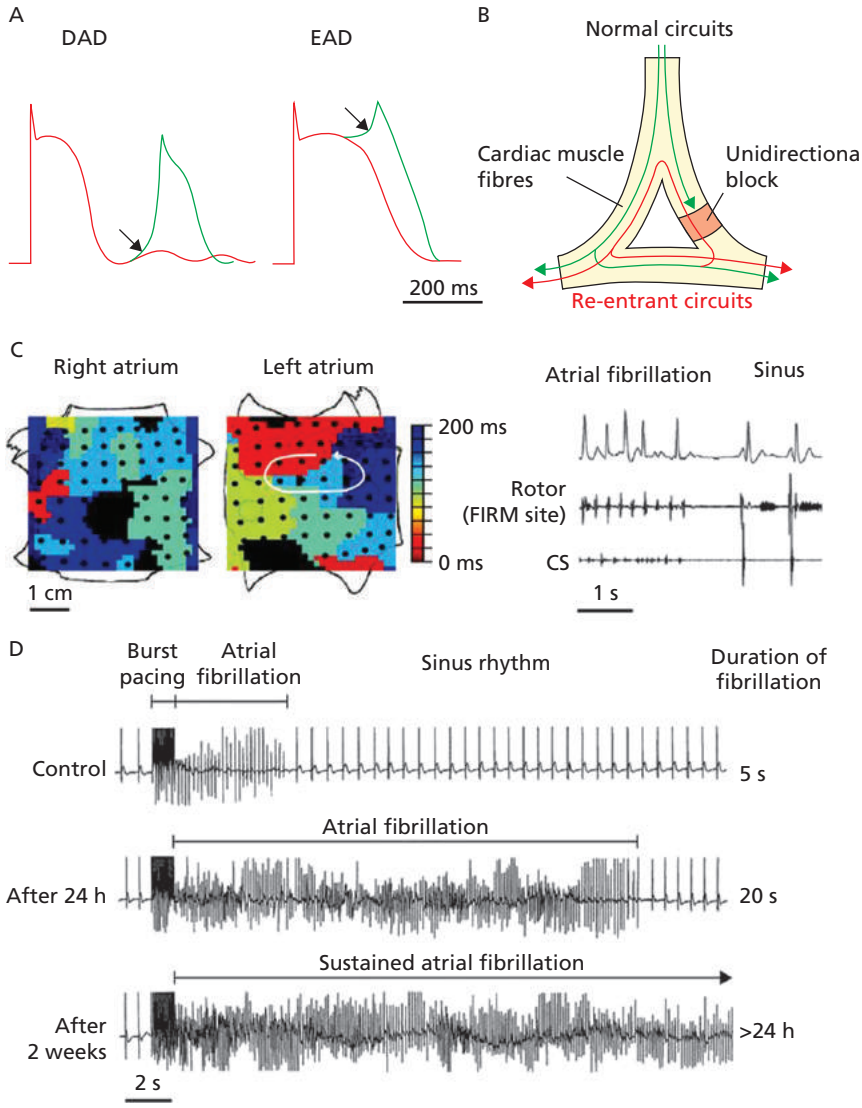

Figure 50.3 Conventional physiological mechanisms of arrhythmia. After-depolarizations are membrane depolarizations that occur late in or after the completion of the action potential. Delayed after-depolarizations (DADs) occur after full repolarization and early after-depolarizations (EADs) during late repolarization. (B) Circus movement reentry is characterized by an activation pattern that travels along a preferred anatomical structure to reactivate previously excited tissue. Such reentry is dependent on unidirectional block and is supported by slow conduction and short refractory periods. (C) Acute termination of atrial fibrillation (AF) to sinus rhythm by FIRM (focal impulse and rotor modulation) ablation. Left: left atrial rotor with counterclockwise activation (red to blue) and disorganized right atrium during AF in a 60-year-old man. Right: FIRM ablation at left atrial rotor terminated AF to sinus rhythm in less than 1 min, with ablation artefact recorded at the centre of the rotor. The patient is AF-free on implanted cardiac monitor after more than 1 year. The demonstration of spiral waves and their functional importance in human AF potentially provides a widely applicable rational approach to AF ablation. (D) AF-induced changes (remodelling) that promote AF. Work done in paced goats provides strong evidence for an evolution of the substrate. In control goats, high-frequency burst pacing induced only 5 s of AF whereas, after 24 h of artificially maintained AF, the duration increased to 20 s. After 2 weeks, episodes of fibrillation lasted more than 24 h.

Grace AA, Roden DM. Systems biology and cardiac arrhythmias. *Lancet*. 2012;**380**:1498–1508 with permission from Elsevier.

Differential diagnosis of tachyarrhythmias

Physical examination is unremarkable in the absence of tachycardia. The presence of irregular cannon A waves and/or irregular variation in S_1 intensity during tachycardia suggest a ventricular origin of the tachycardia.

Regular arrhythmia suggests AVRT, AVNRT or other junctional tachycardia, AT, atrial flutter, or VT.

Irregular arrhythmia suggests AF, multifocal AT, or atrial flutter with variable AV conduction.

ECG In the absence of tachycardia, the presence of pre-excitation establishes the diagnosis of Wolff–Parkinson–White syndrome. Patients with atrial flutter, AVNRT, or AVRT due to a concealed accessory pathway have normal resting ECG.

Narrow QRS (<120 ms) tachycardia Differential diagnosis should address conditions described in Table 50.2 and Figures 50.4 and 50.5. Apart from SVT, VT of high septal origin and fascicular tachycardias may also have a narrow QRS.

Wide QRS (>120 ms) tachycardia Differential diagnosis between SVT and VT is presented in Table 50.2 and Figure 50.6 and in Chapter 56 on VT.

Wearable or **implantable loop recorders** are more useful in detecting tachycardia episodes than Holter monitoring.[10]

Electrophysiologic evaluation is usually required for a definitive diagnosis.

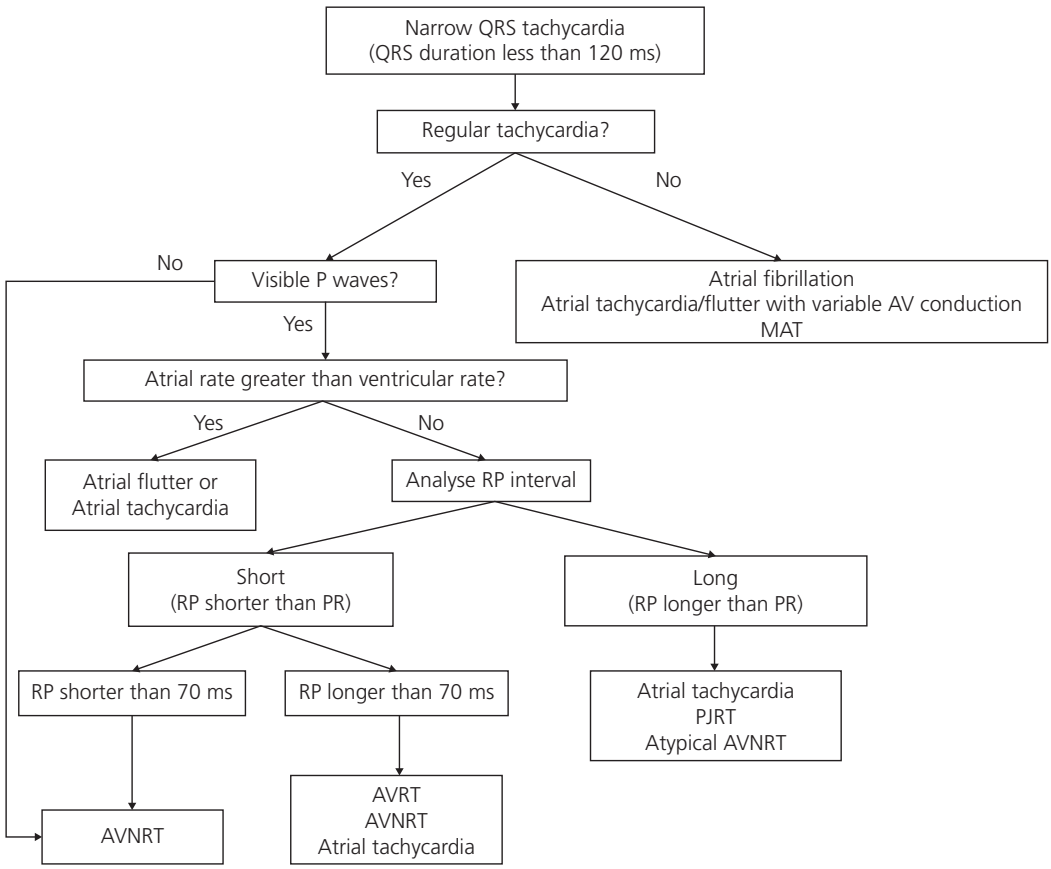

Figure 50.4 ACC/AHA/ESC 2003 GL on SVT. Differential diagnosis for narrow QRS tachycardia. Patients with focal junctional tachycardia may mimic the pattern of slow-fast AVNRT and may show AV dissociation and/or marked irregularity in the junctional rate.

AV indicates atrioventricular; AVNRT, atrioventricular nodal reciprocating tachycardia; AVRT, atrioventricular reciprocating tachycardia; MAT, multifocal atrial tachycardia; ms, milliseconds; PJRT, permanent form of junctional reciprocating tachycardia due to slowly conducting accessory pathway; QRS, ventricular activation on ECG.

ACC/AHA /ESC 2003 guidelines for the management of patients with supraventricular arrhythmias. *Eur Heart J.* 2003;**24**:1857–97, with permission from Oxford University Press.

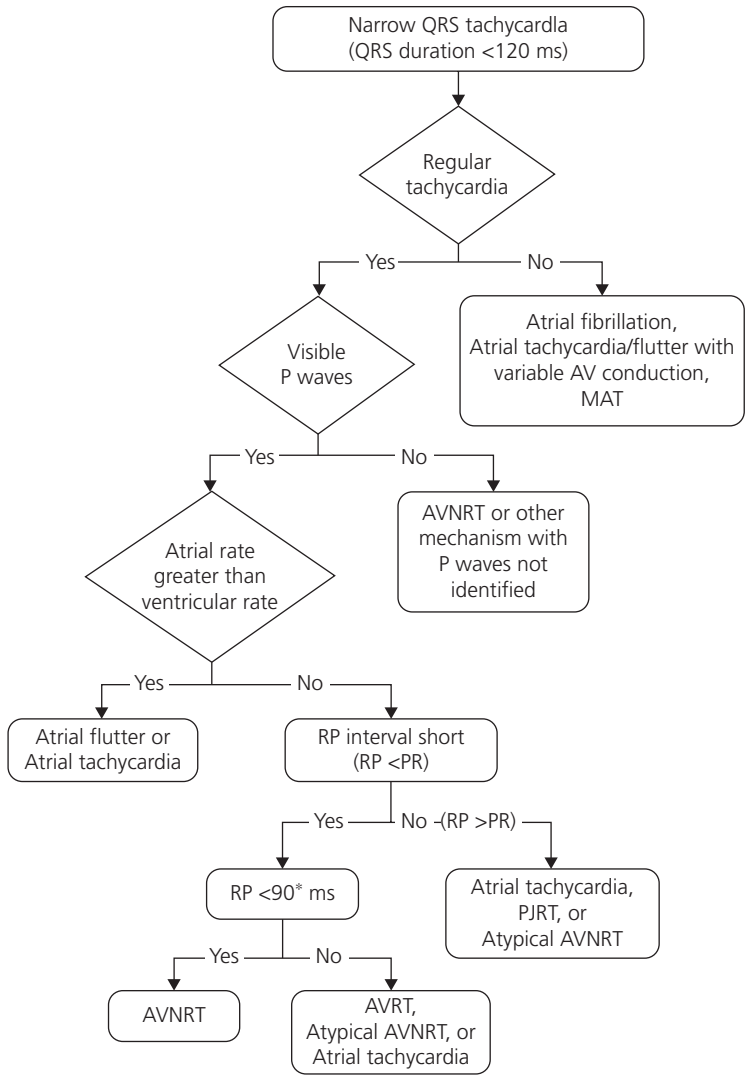

Figure 50.5 ACC/AHA/HRS 2015 GL on SVT. Differential diagnosis for adult narrow QRS tachycardia.

Patients with junctional tachycardia may mimic the pattern of slow-fast AVNRT and may show AV dissociation and/or marked irregularity in the junctional rate.
*RP refers to the interval from the onset of surface QRS to the onset of visible P wave (note that the 90-ms interval is defined from the surface ECG , as opposed to the 70-ms ventriculoatrial interval that is used for intracardiac diagnosis).
ACC/AHA/HRS 2015 Guideline for the management of adult patients with supraventricular tachycardia. *J Am Coll Cardiol*. 2015;doi:10.1016/j.jacc.2015.08.856 with permission from Elsevier.

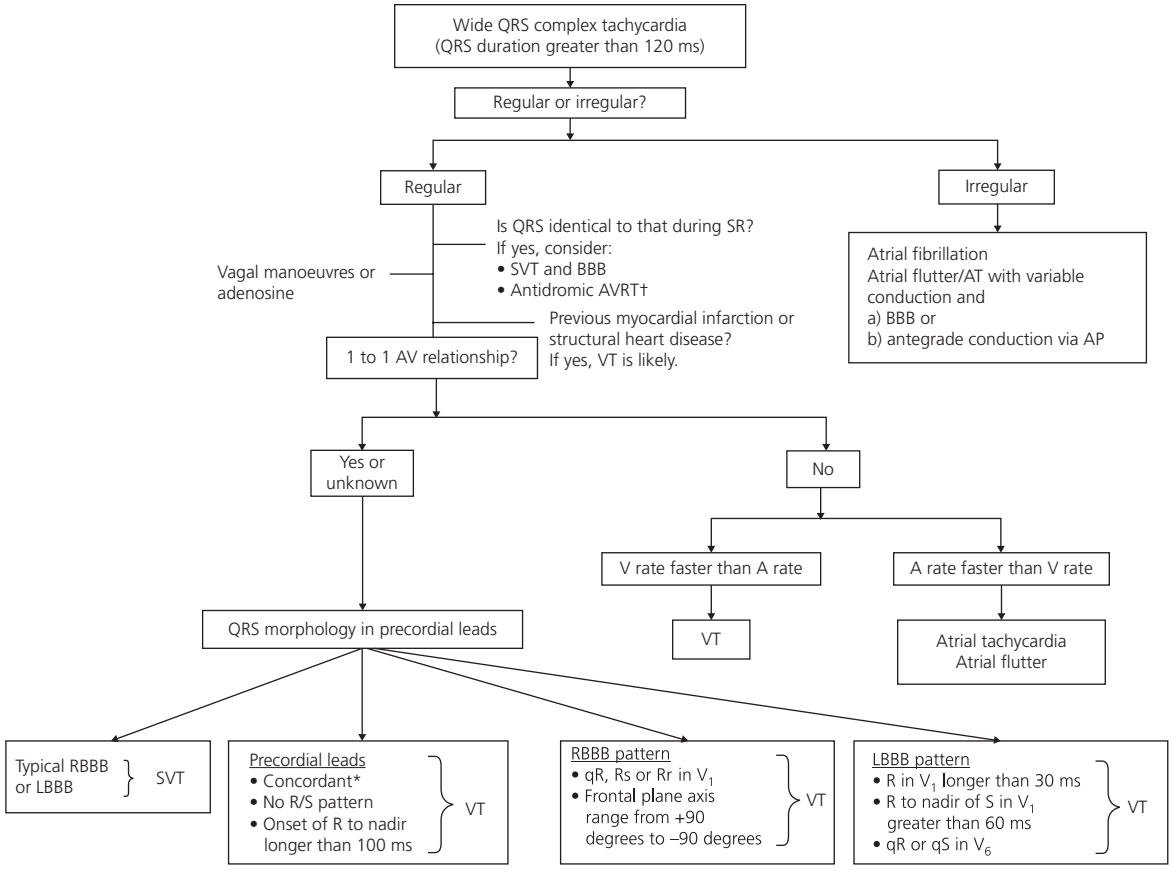

Figure 50.6 ACC/AHA/ESC 2003 GL on SVT. Differential diagnosis for wide QRS complex tachycardia (more than 120 ms). A QRS conduction delay during sinus rhythm, when available for comparison, reduces the value of QRS morphology analysis. Adenosine should be used with caution when the diagnosis is unclear because it may produce VF in patients with coronary artery disease and AF with a rapid ventricular rate in pre-excited tachycardias.

*Concordant indicates that all precordial leads show either positive or negative deflections. Fusion complexes are diagnostic of VT. †In pre-excited tachycardias, the QRS is generally wider (i.e. more pre-excited) compared with sinus rhythm.

A indicates atrial; AP, accessory pathway; AT, atrial tachycardia; AV, atrioventricular; AVRT, atrioventricular reciprocating tachycardia; BBB, bundle branch block; LBBB, left bundle branch block; ms, milliseconds; QRS, ventricular activation on ECG; RBBB, right bundle branch block; SR, sinus rhythm; SVT, supraventricular tachycardias; V, ventricular; VF, ventricular fibrillation; VT, ventricular tachycardia.

ACC/AHA /ESC 2003 guidelines for the management of patients with supraventricular arrhythmias. *Eur Heart J.* 2003;**24**:1857–97, with permission from Oxford University Press.

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Chapter 51

Epidemiology, presentation, and therapy of supraventricular tachycardias

Definitions and classification

Usually, paroxysmal supraventricular tachycardia (SVT) denotes arrhythmias other than atrial fibrillation and ventricular tachycardias. This definition is inaccurate as discussed in Chapter 50 on the classification of tachyarrhythmias but traditionally used. Figure 51.1 presents the mechanisms of supraventricular tachycardias.

Epidemiology of SVT

The prevalence of SVT is 2.25/1000 persons and the incidence 35/100000 person-years (MESA study).[1] Thus, there are approximately 89 000 new cases/year and 570 000 persons with SVT in the United States. Mean age at presentation is 37 to 45 years,[1,2] and the incidence and prevalence of SVTs increase with age, with a risk of arrhythmia more than five times greater in persons >65 years than in those <65 years old.[1] Age of tachycardia onset is lower for atrioventricular reentrant tachycardia (AVRT) due to accessory pathway than atrioventricular nodal reentrant tachycardia (AVNRT). In a recent study on 1754 patients undergoing catheter ablation, AVNRT was the main aetiology (56%), followed by AVRT (27%) and atrial tachycardia (AT, 17%).[2] The proportion of AVRT in both sexes decreased with age, whereas AVNRT and AT increased. The majority of patients with AVRT were men (55%), whereas the majority of patients with AVNRT and AT were women (70% and 62%, respectively). Atrial flutter has an incidence of 0.09%, and 58% of the patients have AF (MESA study).[3] Its incidence increases with age, from 5/100 000 for those less than 50 years to 587/100 000 over 80 years of age, and is 2.5 times more common in men than in women. The risk of developing atrial flutter increases 3.5 times in subjects with heart failure and 1.9 times ($p < 0.001$) in subjects with chronic obstructive pulmonary disease. Atrial flutter is usually associated with heart disease, such as heart failure (16%) or chronic obstructive lung disease (12%) whereas an apparently normal heart is found in <2% of patients.[3]

Presentation of SVT

Patients present due to paroxysms of regular or irregular palpitations with a characteristically sudden onset and offset that occur mostly in daylight, and may be associated with fatigue, light-headedness, dyspnoea, chest discomfort, and presyncope. Syncope and cardiac arrest are rare (<15%), usually denote underlying structural heart disease or AF in the presence of a conducting accessory pathway,

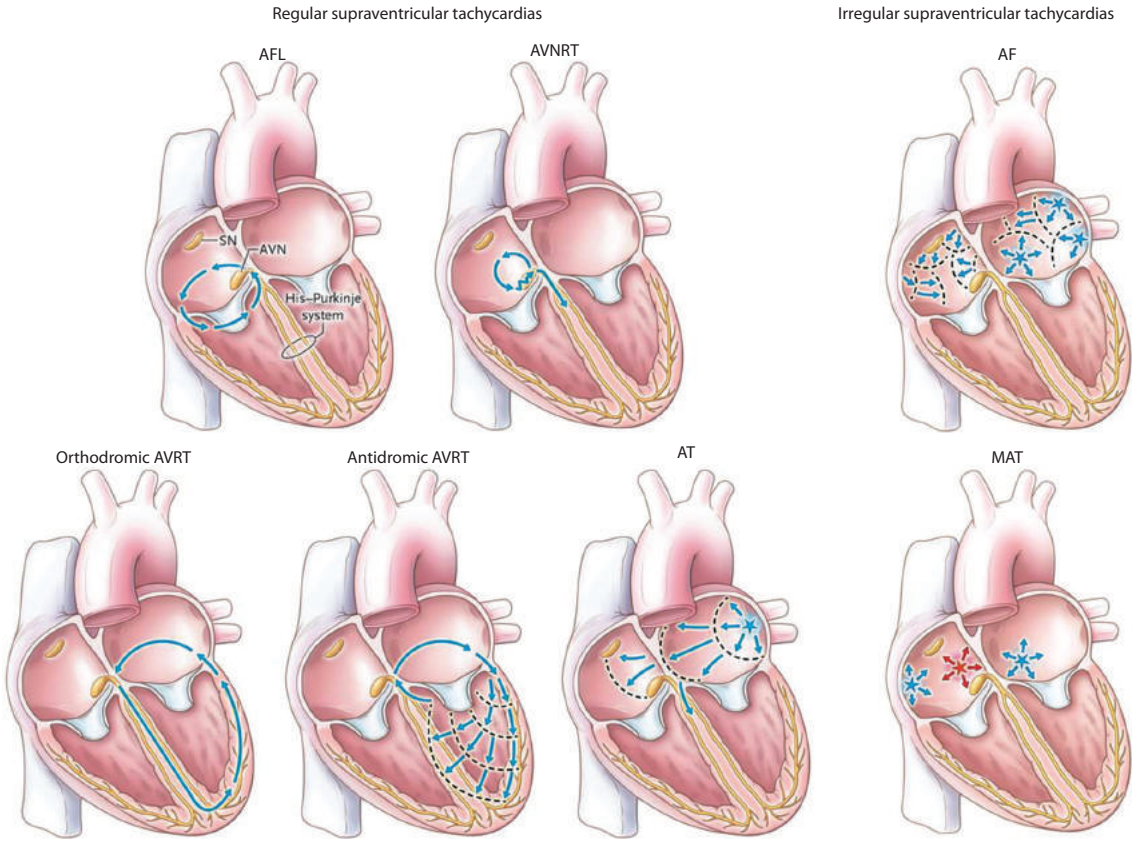

Figure 51.1 Mechanisms of supraventricular tachycardia.

AFL, atrial flutter; AVNRT, atrioventricular nodal reentrant tachycardia; AVRT, atrioventricular reentrant tachycardia; AT, atrial tachycardia; MAT, multifocal AT. Link MS. Evaluation and Initial Treatment of Supraventricular Tachycardia. *N Engl J Med*. **367**:1438–48 with permission from Massachusetts Medical Society.

and may be due to rapid heart rate or vasomotor factors.[4,5] Polyuria is due to release of atrial natriuretic peptide in response to increased atrial pressure, and vagal manoeuvres usually interrupt the tachycardia. Patients may also present with AF that has been initiated by the SVT and which usually,[6,7] but not invariably,[8] is eliminated by ablation of the SVT itself.

Therapy of SVT

Acute management depends on the haemodynamic condition of the patient (Figures 51.2 to 51.5 and Tables 51.1 to 51.3).

In ***narrow QRS tachycardia, vagal manoeuvres*** such as Valsalva, unilateral carotid massage, and facial immersion in cold water, may be tried to terminate the tachycardia. A modified Valsalva manoeuvre with leg elevation and supine positioning at the end of the strain is more effective and safe, and can be taught to patients.[9]

Adenosine, a naturally occurring nucleoside with a short-lived negative dromotropic effect on the AV node, given in rapid IV doses up to 0.25mg/kg will terminate or reveal most supraventricular tachycardias (Figure 51.3). Adenosine does not affect most ventricular tachycardias, with the exception of some forms associated with apparently normal hearts, and can therefore be used as a diagnostic agent.[10] AF may be caused (1–5%) but is usually transient. Adenosine is contraindicated in severe bronchial asthma. Its action is antagonized by theophylline and potentiated by dypiridamole and carbamazepine. Verapamil should not be used in this way because of the considerable incidence of life-threatening hypotension which is associated with its administration in ventricular tachycardia.Chronic therapy is also discussed in individual chapters. ***Catheter ablation*** offers now a means of permanent therapy for most kinds of SVT. Permanent pacing for SVT is now obsolete. It might be considered only for symptomatic recurrent SVT that is reproducibly terminated by pacing when catheter ablation and/or drugs fail to control it, provided no rapid accessory pathway is present (see Chapter 65).[11] Diagnostic and therapeutic approaches to SVT should be individualized in patients >75 years by means of considering comorbidities, physical and cognitive functions, patient preferences, and severity of symptoms (ACC/AHA/HRS 2015 GL on SVT, I-B-NR), since advanced age is not a contraindication for catheter ablation.

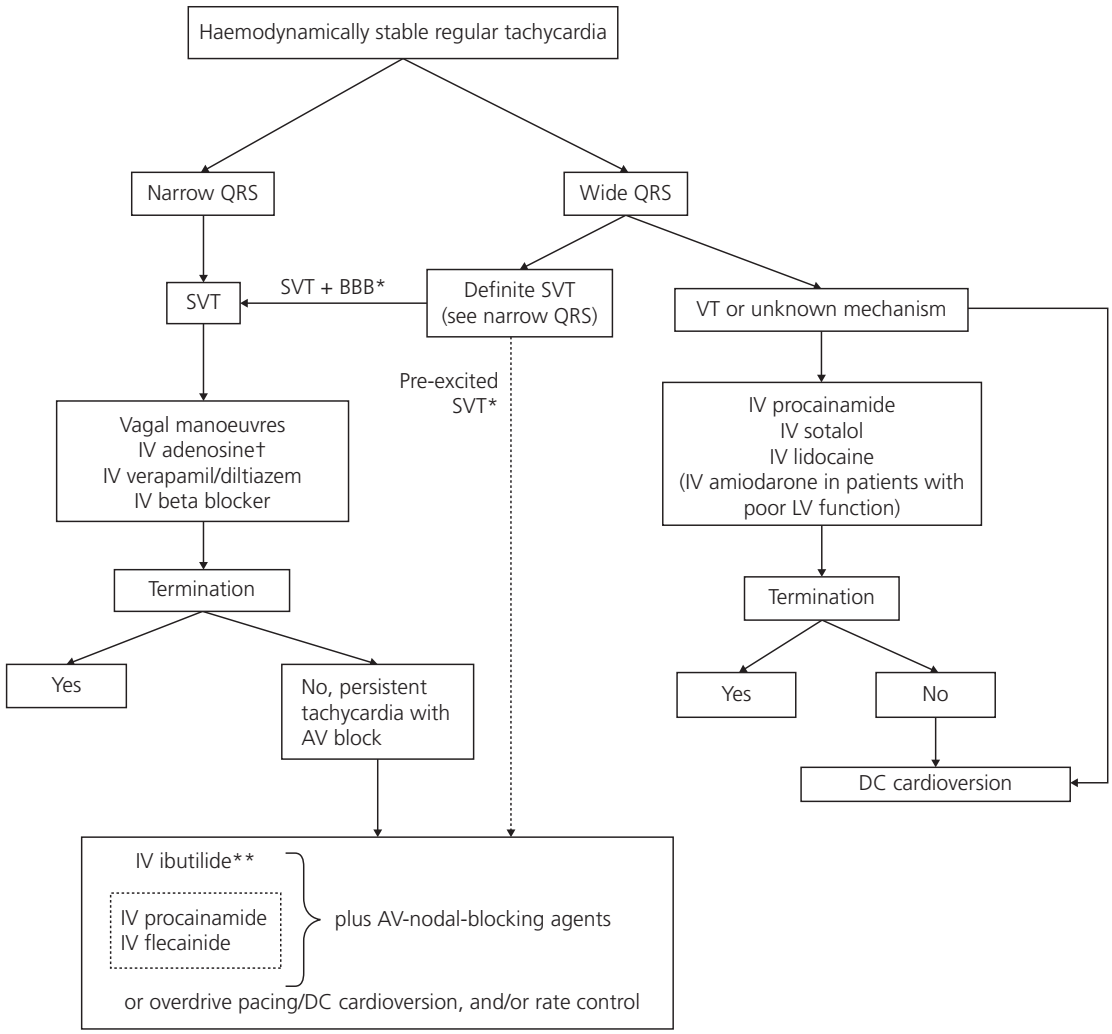

Figure 51.2 ACC/AHA/ESC 2003 GL on SVT. Acute management of patients with haemodynamically stable and regular tachycardia.

*A 12-lead ECG during sinus rhythm must be available for diagnosis. †Adenosine should be used with caution in patients with severe coronary artery disease and may produce AF, which may result in rapid ventricular rates for patients with pre-excitation. **Ibutilide is especially effective for patients with atrial flutter but should not be used in patients with EF less than 30% due to increased risk of polymorphic VT.

AF indicates atrial fibrillation; AV, atrioventricular; BBB, bundle branch block; DC, direct current; IV, intravenous; LV, left ventricle; QRS, ventricular activation on ECG; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

ACC/AHA /ESC 2003 guidelines for the management of patients with supraventricular arrhythmias. *Eur Heart J*. 2003;**24**:1857–97, with permission from Oxford University Press.

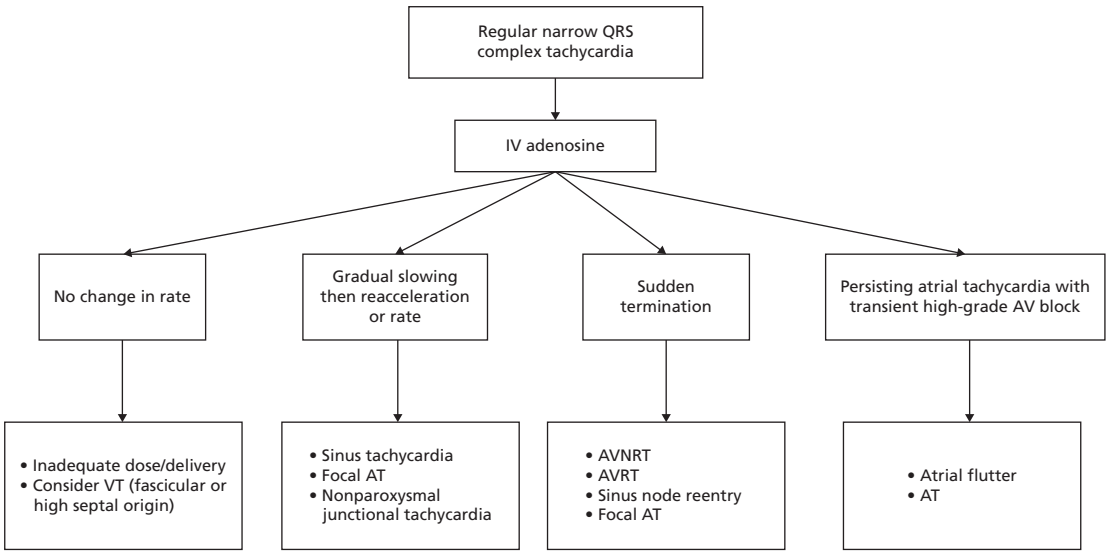

Figure 51.3 ACC/AHA/ESC 2003 GL on SVT. Responses of narrow complex tachycardias to adenosine.

AT indicates atrial tachycardia; AV, atrioventricular; AVNRT, atrioventricular nodal reciprocating tachycardia; AVRT, atrioventricular reciprocating tachycardia; IV, intravenous; QRS, ventricular activation on ECG; VT, ventricular tachycardia.
ACC/AHA /ESC 2003 guidelines for the management of patients with supraventricular arrhythmias. *Eur Heart J*. 2003;**24**:1857–97, with permission from Oxford University Press.

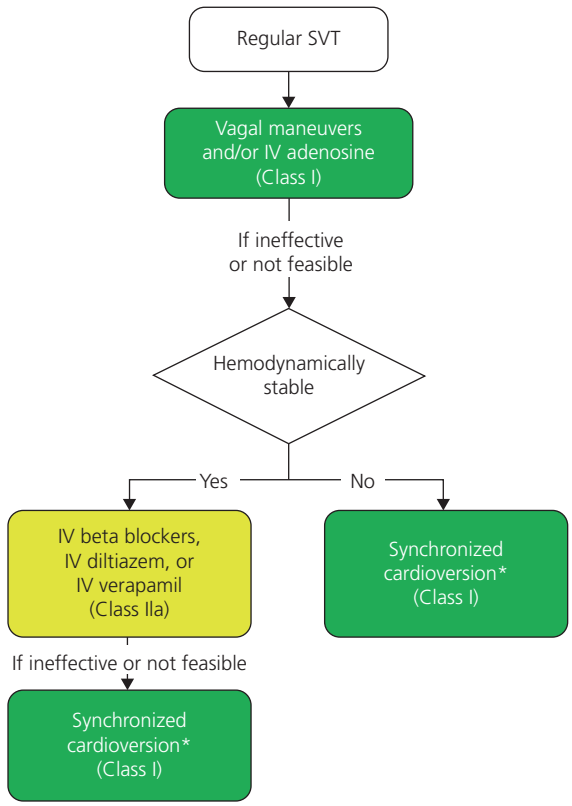

Figure 51.4 ACC/AHA/HRS 2015 GL on SVT. Acute treatment of regular SVT of unknown mechanism.

Drugs listed alphabetically.
*For rhythms that break or recur spontaneously, synchronized cardioversion is not appropriate.
ACC/AHA/HRS 2015 Guideline for the Management of Adult Patients With Supraventricular Tachycardia. *J Am Coll Cardiol*. 2015; doi:10.1016/j.jacc.2015.08.856 with permission from Elsevier.

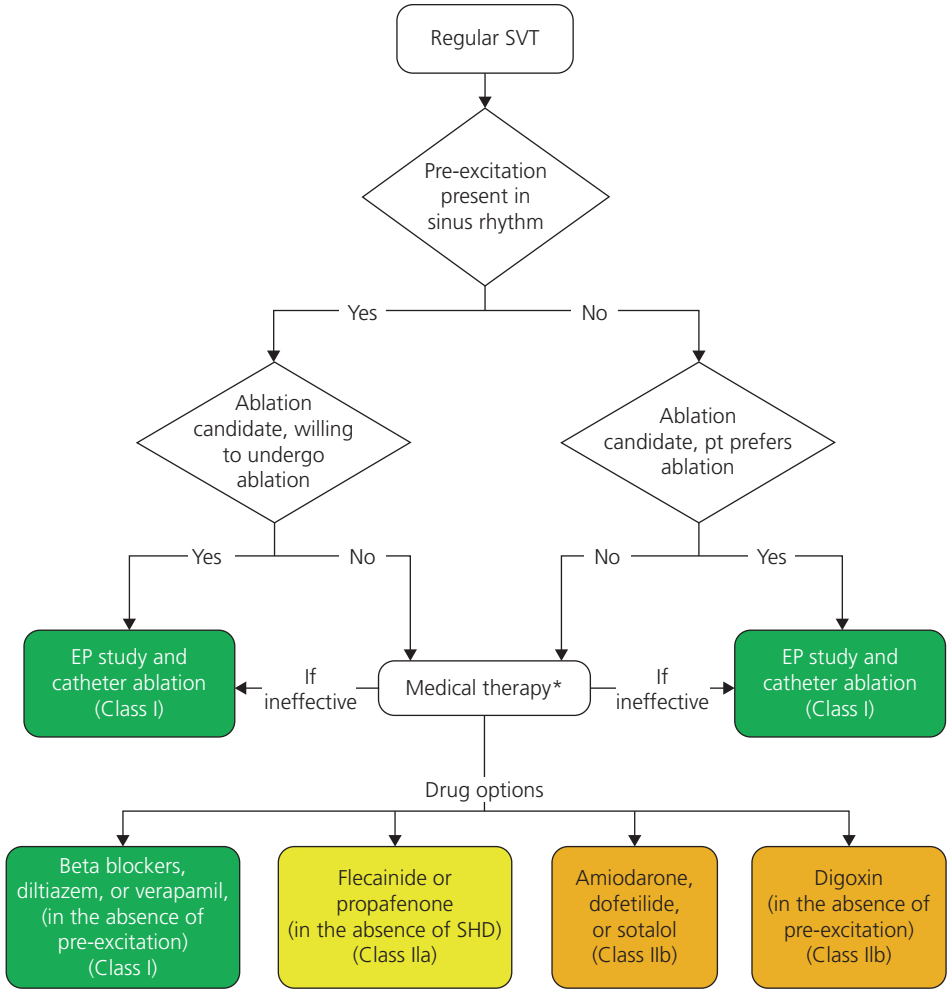

Figure 51.5 ACC/AHA/HRS 2015 GL on SVT. Ongoing management of SVT of unknown mechanism.

Drugs listed alphabetically.
*Clinical follow-up without treatment is also an option.
EP indicated electrophysiological; pt, patient; SHD, structural heart disease (including ischemic heart disease); SVT, supraventricular tachycardia; and VT, ventricular tachycardia.
ACC/AHA/HRS 2015 Guideline for the Management of Adult Patients With Supraventricular Tachycardia. *J Am Coll Cardiol*. 2015; doi:10.1016/j.jacc.2015.08.856 with permission from Elsevier.

Table 51.1 ACC/AHA/ESC GL on SVT 2003. Recommendations for acute management of haemodynamically stable and regular tachycardia

Narrow QRS-complex tachycardia (SVT)		
Vagal manoeuvres		I-B
Adenosine		I-A
Verapamil, diltiazem		I-A
Beta blockers		IIb-C
Amiodarone		IIb-C
Digoxin		IIb-C
Wide QRS-complex tachycardia		
• SVT + BBB	See above	
• Pre-excited SVT/AF		
Flecainide (not in reduced LVEF)		I-B
Ibutilide (not in reduced LVEF)		I-B
Procainamide (not in reduced LVEF)		I-B
DC cardioversion		I-C
• Wide QRS-complex tachycardia of unknown origin	Procainamide (not in reduced LVEF)	I-B
Sotalol (not in reduced LVEF)		I-B
Amiodarone		I-B
DC cardioversion		I-B
Lidocaine		IIb-B
Adenosine (caution in severe coronary artery disease)		IIb-C
Beta blockers (first line therapy in RVOT VT)		III-C
Verapamil (first line therapy in fascicular VT)		III-B
Wide QRS-complex tachycardia of unknown origin in patients with poor LV function	Amiodarone DC cardioversion, lidocaine	I-B

(All drugs are given IV).
ACC/AHA /ESC 2003 guidelines for the management of patients with supraventricular arrhythmias. *Eur Heart J.* 2003;**24**:1857–97, with permission from Oxford University Press.

Table 51.2 ACC/AHA/ESC 2003 GL on SVT. Acute treatment of SVT

Vagal manoeuvres for regular SVT	I-B-R
Adenosine for regular SVT	I-B-R
Synchronized cardioversion for haemodynamically unstable SVT when vagal manoeuvres or adenosine or other pharmacological therapy are ineffective or not feasible	I-B-NR
IV diltiazem or verapamil for haemodynamically stable SVT	IIa-B-R
IV beta blockers for haemodynamically stable SVT	IIa-C-LD

ACC/AHA /ESC 2003 guidelines for the management of patients with supraventricular arrhythmias. *Eur Heart J.* 2003;**24**:1857–97, with permission from Oxford University Press.

Table 51.3 ACC/AHA/ESC 2003 GL on SVT. Ongoing management of symptomatic SVT

Oral beta blockers, diltiazem, or verapamil in the absence of pre-excitation	I-B-R
Electrophysiological study with the option of ablation	I-B-NR
Educate patients how to perform vagal manoeuvres	I-C-LD
Flecainide or propafenone in patients without structural heart disease or ischaemic heart disease and who are not candidates for, or prefer not to undergo, catheter ablation	IIa-B-R
Sotalol for patients who are not candidates for, or prefer not to undergo, catheter ablation	IIb-B-R
Dofetilide for patients who are not candidates for, or prefer not to undergo, catheter ablation	IIb-B-R
Oral amiodarone for who are not candidates for, or prefer not to undergo, catheter ablation and in whom beta blockers, diltiazem, dofetilide, flecainide, propafenone, sotalol, or verapamil are ineffective or contraindicated	IIb-C-LD
Oral digoxin for patients with symptomatic SVT without pre-excitation who are not candidates for, or prefer not to undergo, catheter ablation	IIb-C-LD

ACC/AHA /ESC 2003 guidelines for the management of patients with supraventricular arrhythmias. *Eur Heart J.* 2003;**24**:1857–97, with permission from Oxford University Press.

SVT in congenital heart disease

The most frequently encountered SVTs in ACHD are atrial arrhythmias in ASD, incisional flutter in operated patients with Fallot and Fontan, and atrioventricular reentry in Ebstein's anomaly (see also Part I). Post-surgical flutters require electroanatomic mapping to define the isthmus, since they can be cavotricuspid isthmus- or non-cavotricuspid isthmus-dependent, or both, and catheter ablation in experienced centres is recommended. Evaluation for baffle pathway abnormalities (ie, in D-TGA atrial switch and Fontan circulations), ventricular dysfunction, and atrial thrombus should be performed in patients with new incident intra-atrial reentrant tachycardia (IART) (AHA 2015 statement, I-C).[12] Tables 51.4 to 51.6 and Figures 51.6 and 51.7 present recommendations for adults with congenital heart disease and SVT.

Table 51.4 Therapy of SVT in ACHD

ACC/AHA/ESC GL on SVT 2003. Treatment of SVTs in adults with congenital heart disease		
Failed antiarrhythmic drugs and symptomatic:		
Repaired ASD	Catheter ablation in an experienced centre	I-C
Mustard or Senning repair of transposition of the great vessels	Catheter ablation in an experienced centre	I-C
Unrepaired asymptomatic ASD not haemodynamically significant	Closure of the ASD for treatment of the arrhythmia	III-C
Unrepaired haemodynamically significant ASD with atrial flutter	Closure of the ASD combined with ablation of the flutter isthmus	I-C
PSVT and Ebstein's anomaly with haemodynamic indications for surgical repair	Surgical ablation of accessory pathways at the time of operative repair of the malformation at an experienced centre	I-C

ACC/AHA /ESC 2003 guidelines for the management of patients with supraventricular arrhythmias. *Eur Heart J*. 2003;**24**: 1857–97 with permission from Oxford University Press.

Table 51.5 ACC/AHA/HRS 2015 GL on SVT. SVT in patients with adult congenital heart disease

Acute treatment	
Acute antithrombotic therapy in AT or atrial flutter as for AF	I-C-LD
Synchronized cardioversion for hemodynamically unstable SVT	I-B-NR
IV diltiazem or esmolol (observing for the development of hypotension) for hemodynamically stable SVT	I-C-LD
IV adenosine	I-B-NR
IV ibutilide or procainamide for hemodynamically stable atrial flutter	IIa-B-NR
Atrial pacing for termination of hemodynamically stable SVT in patients anticoagulated as per AF	IIa-B-NR
Elective synchronized cardioversion for AT or atrial flutter when acute pharmacological therapy is ineffective or contraindicated	IIa-B-NR
Oral dofetilide or sotalol for hemodynamically stable AT and/or atrial flutter	IIb-B-NR
Ongoing management	
Antithrombotic therapy in AT or atrial flutter as for AF	I-C-LD
Assessment of associated hemodynamic abnormalities for potential repair of structural defects	I-C-LD
Preoperative catheter ablation or intraoperative surgical ablation of accessory pathways or AT in patients undergoing surgical repair of Ebstein anomaly	IIa-B-NR
Oral beta blockers or sotalol for prevention of recurrent AT or atrial flutter	IIa-B-NR
Catheter ablation for recurrent symptomatic SVT	IIa-B-NR
Surgical ablation of AT or atrial flutter in patients undergoing planned surgical repair	IIa-B-NR
Atrial pacing to decrease recurrences of AT or atrial flutter in patients with sinus node dysfunction	IIb-B-NR
Oral dofetilide for prevention of recurrent AT or atrial flutter	IIb-B-NR
Amiodarone for prevention of recurrent AT or atrial flutter when other medications and ablation are ineffective or contraindicated	IIb-B-NR
Flecainide should not be used in patients with significant ventricular dysfunction	III-B-NR

ACC/AHA/HRS 2015 Guideline for the management of adult patients with supraventricular tachycardia. *J Am Coll Cardiol*. 2015; doi:10.1016/j.jacc.2015.08.856 with permission from Elsevier.

Table 51.6 PACES/HRS 2014 consensus statement on arrhythmias in ACHD. Arrhythmia surgery in adults with congenital heart disease undergoing open cardiac surgery

Concomitant atrial arrhythmia surgery	
Modified right atrial Maze in Fontan conversion with symptomatic right atrial IART.	I-B
Modified right atrial Maze in addition to left atrial Cox Maze III in Fontan conversion with documented AF.	I-B
Left atrial Cox Maze III with right cavotricuspid isthmus ablation in AF.	IIa-B
Modified right atrial Maze for typical or atypical right atrial flutter.	IIa-B
Modified right atrial Maze for inducible typical or atypical right atrial flutter without documented clinical sustained atrial tachycardia.	IIb-B
Prophylactic atrial arrhythmia surgery	
Modified right atrial Maze in Fontan conversion or revision surgery without documented atrial arrhythmias.	IIa-B
Concomitant atrial arrhythmia surgery for Ebstein anomaly.	IIa-B
Prophylactic atrial arrhythmia surgery in structural defects associated with atrial dilatation.	IIb-C
Left atrial Maze surgery in the absence of documented or inducible atrial tachycardia in left-sided valvular heart disease with severe left atrial dilatation or limitations of venous access.	IIb-C
Closure of left atrial appendage.	IIb-C
Prophylactic arrhythmia surgery not indicated in increased risk of surgical mortality from ventricular dysfunction or major co-morbidities, when prolongation of cardiopulmonary bypass or cross-clamp times due to arrhythmia surgery might negatively impact outcomes.	III-C

PACES/HRS expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease. *Heart Rhythm*. 2014;**11**:e102–65.

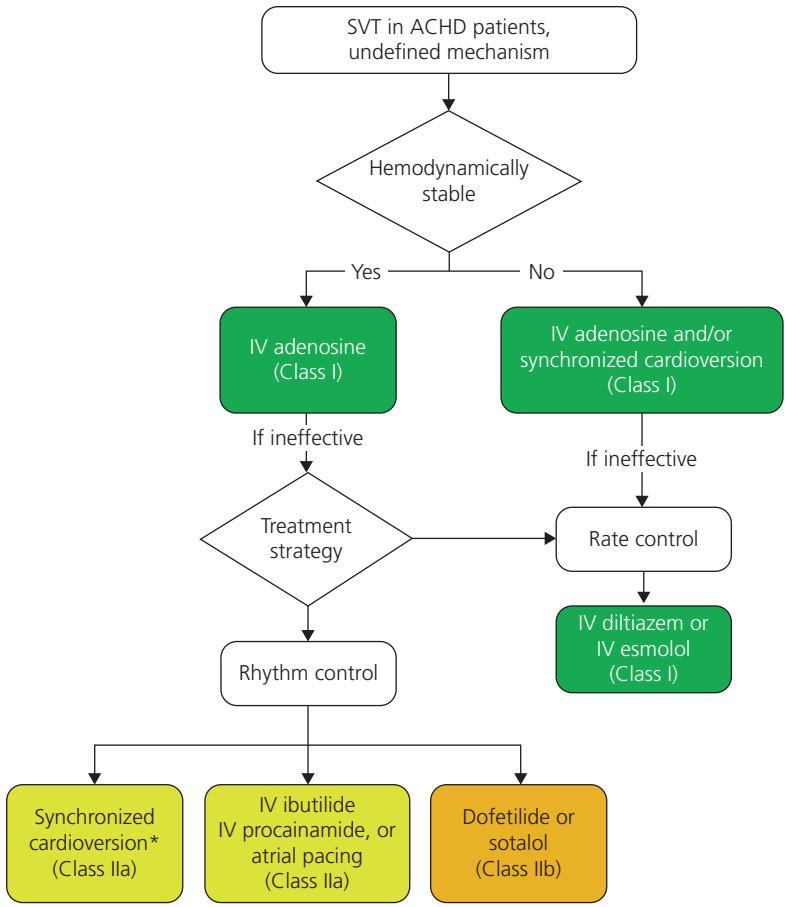

Figure 51.6 ACC/AHA/HRS 2015 GL on SVT Acute treatment of SVT in ACHD Patients.

Drugs listed alphabetically.
*For rhythms that break or recur spontaneously, synchronized cardioversion is not appropriate.
ACHD indicates adult congenital heart disease; IV, intravenous; and SVT, supraventricular tachycardia.
ACC/AHA/HRS 2015 Guideline for the Management of Adult Patients With Supraventricular Tachycardia. *J Am Coll Cardiol*. 2015; doi:10.1016/j. jacc.2015.08.856 with permission from Elsevier.

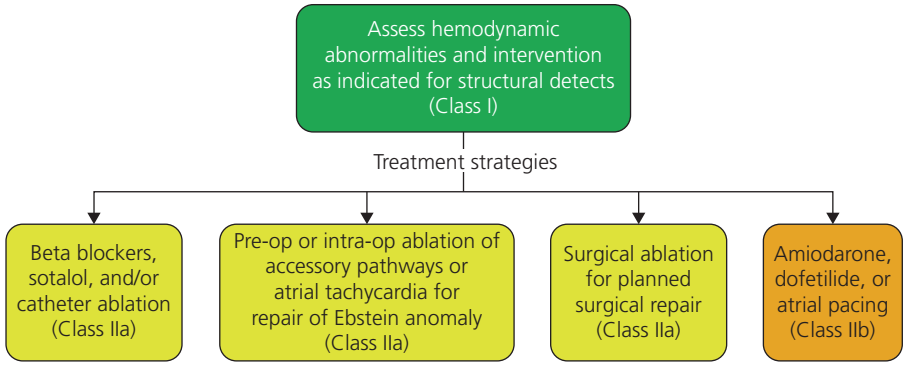

Figure 51.7 ACC/AHA/HRS 2015 GL on SVT Ongoing management of SVT in ACHD Patients.

Drugs listed alphabetically.
ACHD indicates adult congenital heart disease; intra-op, intraoperative; pre-op, preoperative; and SVT, supraventricular tachycardia.
ACC/AHA/HRS 2015 Guideline for the Management of Adult Patients With Supraventricular Tachycardia. *J Am Coll Cardiol*. 2015; doi:10.1016/j. jacc.2015.08.856 with permission from Elsevier.

SVT in pregnancy

Premature atrial beats are observed in up to 50% of pregnant women and are benign. Exacerbations of SVT occur in 20–40% of them.[13] Adenosine and electrical cardioversion are not contraindicated (Tables 51.7 and 51.8). Digoxin is safe but of limited value. Catheter ablation may be performed during the second trimester, ideally with the aid of electroanatomic mapping that reduces exposure to radiation. Treatment of cases of atrial tachycardia during pregnancy is generally more challenging with respect to their drug-resistant nature, tendency to be persistent, and their association with structural heart disease. Rate control, using beta-blocking agents and/or digoxin, should be used to avoid tachycardia-induced cardiomyopathy. Prophylactic antiarrhythmic drug therapy includes flecainide, propafenone, or sotalol for patients with definite symptoms. Detailed comments on the drug use in pregnancy are presented in Appendix 3.

Table 51.7 ESC 2011 GL on pregnancy

Management of supraventricular tachycardia (SVT)	
For acute conversion of paroxysmal SVT, vagal manoeuvre followed by IV adenosine.	I-C
Immediate electrical cardioversion for acute treatment of any tachycardia with haemodynamic instability.	I-C
For long-term management of SVT, oral digoxin[1] or metoprolol/propranolol.[2]	I-C
For acute conversion of paroxysmal SVT, IV metoprolol or propranolol.	IIa-C
For long-term management of SVT, oral sotalol[3] or encainide[4] if digoxin or a beta-blocking agent fails.	IIa-C
For acute conversion of paroxysmal SVT, IV verapamil.	IIb-C
For long-term management of SVT, oral propafenone or procainamide as a last option if other suggested agents fail and before amiodarone[3] is used.	IIb-C
For long-term management of SVT, oral verapamil for rate regulation if the other AV nodal blocking agents fail.	IIb-C
Atenolol[2] should not be used for any arrhythmia.	III-C

1: AV nodal blocking agents should not be used in patients with pre-excitation on resting ECG.
2: Beta-blocking agents should be used with caution in the first trimester.
3: Class III drugs should not be used in cases with prolonged QTc.
4: Consider AV nodal blocking agents in conjunction with flecainide and propafenone for certain atrial tachycardias.
ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**:3147–97 with permission from Oxford University Press.

Table 51.8 ACC/AHA/HRS 2015 GL on SVT. SVT in pregnancy

Acute treatment	
Vagal manoeuvres	I-C-LD
Adenosine	I-C-LD
Synchronized cardioversion for haemodynamically unstable SVT when other pharmaocological therapyis ineffective or contraindicated	I-C-LD
IV metoprolol or propranolol when adenosnie is ineffective or contraindicated	IIa-C-LD
IV verapamil when adenosnie and beta blockers are ineffective or contraindicated	IIb-C-LD
IV procainamide	IIb-C-LD
IV amiodarone for potentially life-threatening SVT when other therapies are ineffective or contraindicated	IIb-C-LD
Ongoing management	
The following drugs, alone or in combination, for highly symptomatic SVT:	IIa-C-LD
a. Digoxin	
b. Flecainide	
c. Metoprolol	
d. Propafenone	
e. Propranolol	
f. Sotalol	
g. Verapamil	
Catheter ablation for highly symptomatic, recurrent, drug-refractory SVT with efforts toward minimizing radiation exposure	IIb-C-LD
Oral amiodarone for highly symptomatic, recurrent SVT when other therapies are ineffective or contraindicated	IIb-C-LD

ACC/AHA/HRS 2015 Guideline for the management of adult patients with supraventricular tachycardia. *J Am Coll Cardiol*. 2015; doi:10.1016/j.jacc.2015.08.856 with permission from Elsevier.

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Chapter 52

Atrial tachycardias

Atrial and junctional premature beats

Atrial premature beats

Atrial premature beats (APBs) are common in the healthy population, and their prevalence increases with age, history of cardiovascular disease, physical activity, and BNP levels.[1] Their prognostic significance is rather controversial. In the ARIC study, APBs were not associated with sudden cardiac death. However, ventricular premature activity was associated with sudden death, and this effect was additive when APCs occurred concurrently.[2] In the NHANES III data APBs, but not VPBs, were associated with total and cardiovascular mortality.[3] Frequent APBs (≥30 per hour or runs of ≥30 beats) may trigger AF, with a median count of more than 2 APBs per hour,[4] and thus may be associated with a poor prognosis in terms of death or stroke.[3,5] They may also trigger SVT in the presence of a suitable background. Non-conducted APBs are a common cause of unexpected pauses. They can arise anywhere in the atria, including the sinus node. An APB is characterized by an abnormally shaped atrial depolarization wave which occurs prior to the next anticipated sinus beat. Several electrocardiographic leads may be needed to distinguish the different P wave shape, and, in the rare case of sinus node premature beats, the P wave will be identical. The post-extrasystolic cycle is typically less than compensatory due to penetration and resetting of the sinus node by the premature depolarization, but suppression of the sinus node automaticity may also occur and result in pauses equal to, or longer than, the sinus cycle. Intraventricular conduction may be normal or aberrant, whereas the PR interval is marginally longer than that of normal sinus rhythm due to atrioventricular nodal delay. This especially occurs in the rare case of interpolated APBs which do not depolarize the sinus node and do not affect the sinus rate. Blocked premature beats may masquerade as pauses or bradycardias when P waves are not seen. The T wave of those beats that precede a pause should be carefully inspected to detect any 'hidden' premature P wave. Apart from age and cardiovascular disease, other potential causes of APBs are hypertension, pulmonary disease, such as bronchial carcinoma and pneumonia, hyperthyroidism, alcohol abuse, illicit drugs, and anxiety states. **Therapy** is directed towards avoidance or correction of the offending cause. Caffeine in moderate doses is well tolerated.[6] In symptomatic patients, beta-blockers are useful.

Junctional premature beats

Premature beats probably arise from the AV junction and conduct antegradely to the ventricles and retrogradely to the atria. There are, therefore, inverted retrograde P (negative in inferior leads and positive in aVR), the timing of which, relative to the QRS complex, depends on the exact origin of the beat and the conduction times to the atria and the ventricles. The retrograde P may occur immediately before, during, or following the QRS complex, which itself may display various degrees of aberration. Concealed His bundle extrasystoles may simulate first- or second-degree AV block, but they can also be associated with conduction disease.[7]

Physiological sinus tachycardia

Definition

Sinus tachycardia is defined as a non-paroxysmal increase in sinus rate to more than 100 bpm, in keeping with the level of physical, emotional, pathological, or pharmacologic stress.[8]

Aetiology and pathophysiology

Common causes are presented in Table 52.1. Sinus tachycardia is due to physiological influences on individual pacemaker cells or from an anatomical shift in the site of origin of atrial depolarization superiorly within the sinus node.

Table 52.1 Causes of physiological sinus tachycardia

Anxiety-emotional stress
Pyrexia
Anaemia
Acidosis
Hypoxia
Hypovolaemia
Infection
Hyperthyroidism
Phaeochromocytoma
Stimulants: Alcohol, caffeine, nicotine
Drugs: Salbutamol, aminophylline, thyroxine, atropine, catecholamines, doxorubicin, daunorubicin
Recreational/illicit drugs: Amphetamines, cocaine, cannabis, ecstasy

Diagnosis

In normal sinus rhythm, the P wave on a 12-lead ECG in adults is positive in leads I, II, and aVF and V_3 to V_6. It is negative in aVR and V_1 and V_2. In sinus tachycardia, P waves have a normal contour, but a larger amplitude may develop and the wave may become peaked.

Therapy

Elimination of the offending cause is mandatory. If additional symptomatic treatment is required, beta-blockers are the agents of choice, and, when contraindicated, verapamil or diltiazem may be used.

Inappropriate sinus tachycardia

Definition

Inappropriate sinus tachycardia is a fast sinus rhythm (>100 bpm) at rest or minimal activity that is out of proportion with the level of physical, emotional, pathological, or pharmacologic stress. The syndrome of inappropriate sinus tachycardia is also defined as a sinus heart rate >100 bpm at rest (with a mean 24-hour heart rate >90 bpm not due to primary causes) and is associated with distressing symptoms of palpitations.[9]

Pathophysiology

Enhanced automaticity of the sinus node or increased sympathetic drive is the postulated mechanisms.

Presentation

Mean age of presentation is 38 years, and women are mainly affected. Symptoms may vary from palpitations (or even no symptoms at all) to presyncope.

Diagnosis

It is based on:

The presence of a **persistent sinus tachycardia** (heart rate >100 bpm) during the day, with excessive rate increase in response to activity, and nocturnal normalization of rate as confirmed by a 24-hour Holter recording.

The tachycardia (and symptoms) is usually **nonparoxysmal**, with P wave morphology and endocardial activation identical to sinus rhythm.

Exclusion of a secondary systemic cause (e.g. **hyperthyroidism, physical deconditioning**) and postural orthostatic tachycardia syndrome (**POTS**). In POTS, there is an increase in heart rate of ≥30 bpm when moving from a recumbent to a standing position held for more than 30 sec (or ≥40 bpm in individuals 12–19 years), in the absence of orthostatic hypotension (>20 mmHg drop in systolic blood pressure).[9]

Table 52.2 Inappropriate sinus tachycardia

ACC/AHA/ESC 2003 GL on SVT. Recommendations for treatment of inappropriate sinus tachycardia		
Medical	Beta blockers	I-C
	Verapamil, diltiazem	IIa-C
Interventional	Catheter ablation sinus node modification/ elimination*	IIb-C
ACC/AHA/HRS 2015 GL on SVT. Treatment of Inappropriate Sinus Tachycardia		
Evaluation for and treatment of reversible causes		I-C-LD
Ivabradine in symptomatic SVT		IIa-B-R
Beta blockers in symptomatic SVT		IIb-C-LD
Combination of beta blockers and ivabradine		IIb-C-LD

*Used as a last resort.
ACC/AHA /ESC 2003 guidelines for the management of patients with supraventricular arrhythmias. *Eur Heart J*. 2003;24:1857-97, with permission from Oxford University Press.
ACC/AHA/HRS 2015 Guideline for the management of adult patients with supraventricular tachycardia. *J Am Coll Cardiol*. 2015; doi:10.1016/j.jacc.2015.08.856 with permission from Elsevier.

A complete history, physical examination, and 12-lead ECG as well as complete blood counts and thyroid function studies are mandatory, whereas ECG ambulatory monitoring, further biochemistry, treadmill exercise and autonomic testing are optional.

Therapy

Beta-blockers, verapamil, and diltiazem, with or without benzodiazepines, are usually effective (Table 52.2). Catheter modification of the sinus node is moderately effective (60%), but the benefits may be short-term and can be complicated by the need of permanent pacing in 10% of the patients.[9,10] Narrowing of the SVC and phrenic nerve palsy may also occur. Sinus node modification is not recommended any more.[9] Ivabradine, a specific sinus node I_f current inhibitor, may also be useful.[11] It is contraindicated in hypotension and its use should be avoided with strong CYP3A4 inhibitors and inducers (see Table 53.19).

Sinus reentrant tachycardia

Definition

Sinus nodal reentrant tachycardia is due to reentry within the sinus node, with or without involvement of the perisinus atrial tissue. Up to 27% of focal AT are actually due to sinus nodal reentry. Usually, underlying cardiac disease exists.[8]

Diagnosis

It is based on:

The tachycardia is **paroxysmal**.

P wave morphology is almost identical to sinus rhythm.

Endocardial atrial activation is similar to that of sinus rhythm.

Induction and/or termination of the arrhythmia occurs with premature atrial stimuli.

Termination occurs with **vagal manoeuvres or adenosine**.

Induction of the arrhythmia is independent of atrial or AV nodal conduction time.

Therapy

Vagal manoeuvres or adenosine may be used for acute therapy. Beta-blockers, verapamil, and diltiazem may be tried for long-term control. In non-responders, catheter ablation is usually successful.[12]

Focal atrial tachycardia

Definition

Focal atrial tachycardia (AT) is characterized by a P wave rate of >250/min, although it can be <200/min, and an isoelectric interval between P waves (Figures 52.1 and 52.2).

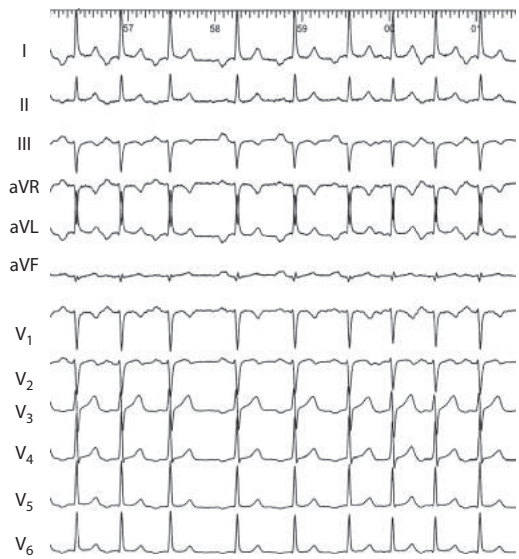

Figure 52.1 Left atrial tachycardia. Morphology of P waves in V_1 suggests a left PV origin.

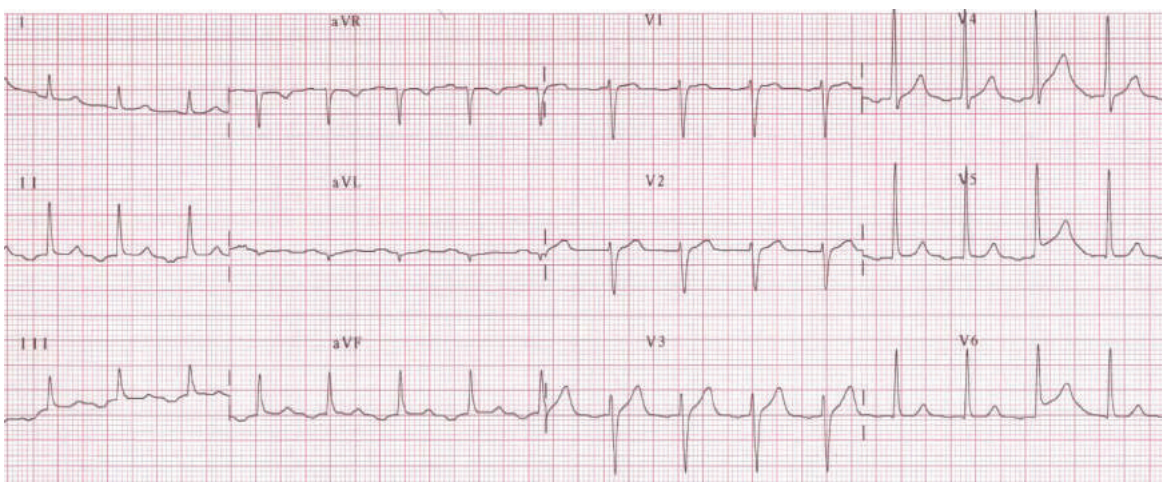

Figure 52.2 Atrial tachycardia originating at the coronary sinus ostium. Note negative P waves in inferior leads.

Pathophysiology

Atrial activation originates from a discrete focus (<2 cm in diameter) with centrifugal spread.[13] Focal AT accounts for up to 10% of SVT referred for ablation.[14] Micro-reentry, abnormal automaticity, and triggered activity are the postulated mechanisms, although electroanatomic abnormalities that may be detected in patients with focal AT are in support of micro-reentry, particularly in the elderly.[15] In childhood, the lack of effectiveness of DC cardioversion suggests abnormal automaticity as the underlying mechanism. Focal AT, as opposed to multifocal AT, is usually not associated with underlying heart disease, and the prognosis is benign, unless tachycardia-induced cardiomyopathy develops.

Presentation

Onset of episodes may occur at any age, from birth to old age. Palpitations are of substantial variation in duration, with **sudden increases and decreases in rate**. There is usually an **abrupt onset and termination** with bursts of activity. The clinical course is variable, and spontaneous remission is common.[16]

Diagnosis

Classically, the P wave for focal AT is described as distinct with an intervening **isoelectric interval**, in contrast to a continuous undulation typical of macro-reentry tachycardia. However, an isoelectric interval may not be identifiable during accelerated heart rates and/or in the presence of atrial disease, resulting in slowing of conduction.

Focal AT is characterized by a **change in P wave morphology** and dissociation between the atrium and ventricular response. The foci mainly occur along the crista terminalis (>30%), tricuspid annulus and coronary sinus ostium, mitral annulus, perinodal or para-Hisian region, ostia of the pulmonary veins, left-sided septum, and near the aortic coronary cusps. The morphology of the P wave may assist in identifying the tachycardia origin.[17,18] Foci arising from the superior crista terminalis display a negative or positive-negative P wave in lead V_1 or the P wave may be indistinguishable from that during the sinus rhythm. A positive or negative-positive biphasic P wave in V_1 and negative in lead I indicates a left atrial focus. P waves from right PV foci are narrow and uniphasic whereas, from the left PV, broad and notched in lead V_1. CS ostium foci produce P waves negative in the inferior leads and positive in aVL and aVR.

The distinction between focal AT and AVNRT or AVRT can be made by analysing the R-P relationship on the surface ECG. Typically, focal AT is associated with **a long and variable R-P relationship**. However, focal AT can show a short R-P relationship at higher rates and increased AV node conduction. Atypical AVNRT and a concealed accessory pathway with slow retrograde conduction may demonstrate a long R-P interval, but the R-P interval is typically constant.

The diagnosis of focal AT can only be established with certainty at the electrophysiology laboratory.

Therapy

Antiarrhythmic therapy (flecainide, sotalol, amiodarone) are partially effective in controlling symptoms (Table 52.3, and Figures 52.3 and 52.4). Catheter ablation is the treatment of choice for patients with success rates ranging from 40 to 90%.[19]

Table 52.3 Therapy of focal atrial tachycardia

ACC/AHA/ESC GL on SVT 2003. Recommendations for treatment of focal atrial tachycardia*		
Acute treatment**		
A. Conversion		
Haemodynamically unstable patient	DC cardioversion	I-B
Haemodynamically stable patient	Adenosine	IIa-C
	Beta-blockers	IIa-C
	Verapamil, diltiazem	IIa-C
	Procainamide	IIa-C
	Flecainide/propafenone	IIa-C
	Amiodarone, sotalol	IIa-C

(*Continued*)

Table 52.3 Continued

B. Rate regulation (in absence of digitalis therapy)		
	Beta-blockers	I-C
	Verapamil, diltiazem	I-C
	Digoxin	IIb-C
Prophylactic therapy		
Recurrent symptomatic AT	Catheter ablation	I-B
	Beta blockers, calcium channel blockers	I-C
	Disopyramide*** Flecainide/propafenone (all combined with beta-blockers)	IIa-C
	Sotalol, amiodarone	IIa-C
Asymptomatic or symptomatic incessant AT	Catheter ablation	I-B
Non-sustained and asymptomatic	No therapy	I-C
	Catheter ablation	III-C
ACC/AHA/HRS 2015 GL on SVT. Focal AT		
Acute treatment		
	IV beta blockers, diltiazem, or verapamil for haemodynamically stable patients	I-C-LD
	Synchronized cardioversion for haemodynamically unstable patients	I-C-LD
	Adenosine to restore sinus rhythm or diagnose the tachycardia mechanism	IIa-B-NR
	IV amiodarone to restore sinus rhythm or slow the ventricular rate in haemodynamically stable patients	IIb-C-LD
	Ibutilide to restore sinus rhythm in haemodynamically stable patients	IIb-C-LD
Ongoing management of symptomatic focal AT		
	Catheter ablation	I-B-NR
	Oral beta blockers, diltiazem or verapamil	IIa-C-LD
	Flecainide or propafenone for patients without structural heart disease or ischemic heart disease	IIa-C-LD
	Sotalol or amiodarone	IIb-C-LD

* Excluded are patients with multifocal atrial tachycardia in whom beta-blockers and sotalol are often contraindicated due to pulmonary disease.
** All listed drugs for acute treatment are administered intravenously.
*** Flecainide, propafenone, and disopyramide should not be used, unless they are combined with an AV nodal blocking agent.
AT indicates atrial tachycardia; DC, direct current.
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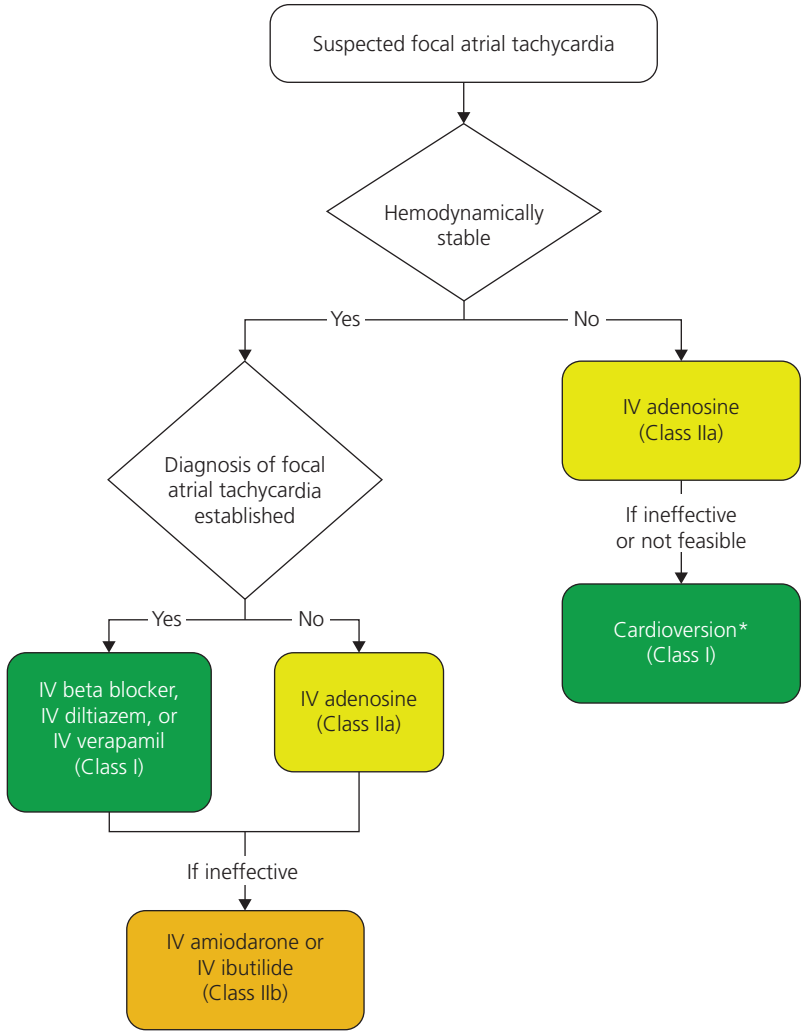

Figure 52.3 ACC/AHA/HRS 2015 GL on SVT. Acute treatment of suspected focal atrial tachycardia.

Drugs listed alphabetically.

*For rhythms that break or recur spontaneously, synchronized cardioversion is not appropriate.

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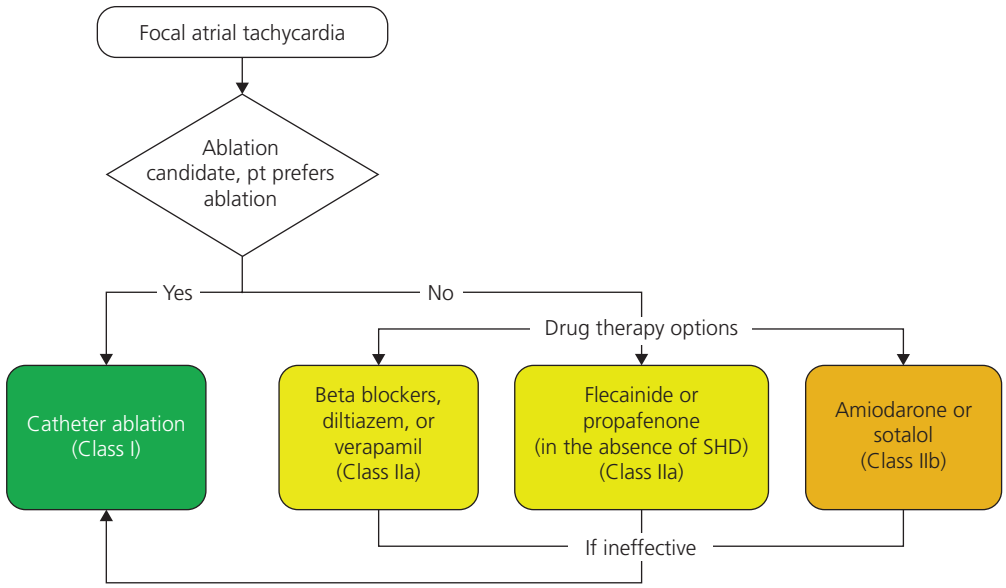

Figure 52.4 ACC/AHA/HRS 2015 GL on SVT. Ongoing management of suspected focal atrial tachycardia.

Drugs listed alphabetically.

SHD, structural heart disease (including ischaemic heart disease).

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Multifocal atrial tachycardia

Multifocal atrial tachycardia is an irregular tachycardia characterized by three or more different P wave morphologies at different rates. The arrhythmia is most commonly associated with underlying **pulmonary disease** but may result from **metabolic or electrolyte derangements** or, rarely now, by **digitalis toxicity**. Calcium channel blockers and correction of the underlying disorder are the main therapeutic means (Table 52.4). There is no role for DC cardioversion, antiarrhythmic drugs, or ablation.

Table 52.4 ACC/AHA/HRS 2015 GL on SVT. Multifocal AT

Acute treatment	
IV metoprolol or verapamil	IIa-C-LD
Ongoing management of recurrent symptomatic multifocal AT	
Verapamil	IIa-B-NR
Diltiazem	IIa-C-LD
Metoprolol	IIa-C-LD

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Macro-reentrant atrial tachycardias (atrial flutters)

The mechanism of macro-reentrant atrial tachycardia is reentrant activation around a large central obstacle, generally several centimetres in diameter, at least in one of its dimensions. The central obstacle may consist of normal (i.e. cavotricuspid isthmus, CTI) or abnormal (i.e. post-operative or post-ablation scar) structures. The obstacle can be fixed, functional, or a combination of each. There is no single point of origin of activation, and atrial tissues outside the circuit are activated from various parts of the circuit.[13] Entrainment mapping is used to delineate the localization of the reentrant circuit. The postpacing interval (PPI) measured after entrainment overdrive pacing describes the distance from the pacing catheter's location to the reentrant circuit, and a difference between the PPI and the tachycardia cycle length (TCL) ≤20 ms indicates that the pacing site is part of the reentrant circuit. The number of pacing stimuli needed to entrain (NNE) may also be useful; at sites within the reentrant circuit NNE is small (median 2), whereas at remote sites it is large (>3).[20]

Cavotricuspid isthmus-dependent atrial flutter

Cavotricuspid isthmus-dependent flutter refers to circuits involving the CTI. The circuit is around the tricuspid annulus and contains a propagating wavefront and an excitable gap. The crista terminalis and Eustachian ridge are the functional posterior barriers, and the tricuspid annulus the anterior barrier. In approximately 60% of patients, there is underlying disease, such as COPD, pneumonia, myocardial ischaemia, or cardiac or pulmonary surgery. In the majority of patients there is underlying disease such as heart failure, COPD, pneumonia, myocardial ischaemia, or cardiac or pulmonary surgery.[21]

Definitions and classification

The most common patterns of CTI-dependent atrial flutter include a tachycardia showing a **counterclockwise** rotation in the left anterior oblique view around the tricuspid valve (**typical atrial flutter**) (Figure 52.5). A less common pattern (10%) involves **clockwise** rotation around the tricuspid annulus (i.e. **reverse typical flutter**).[13] **Counterclockwise CTI-dependent atrial flutter** is characterized electrocardiographically by dominant negative flutter waves in the inferior leads and a positive flutter deflection in lead V_1, with transition to a negative deflection in lead V_6 at rates of 250 to 350 bpm. **Clockwise CTI-dependent flutter** shows the opposite pattern (i.e. positive flutter waves in the inferior leads and wide, negative flutter waves in lead V_1, transitioning to positive waves in lead V_6).

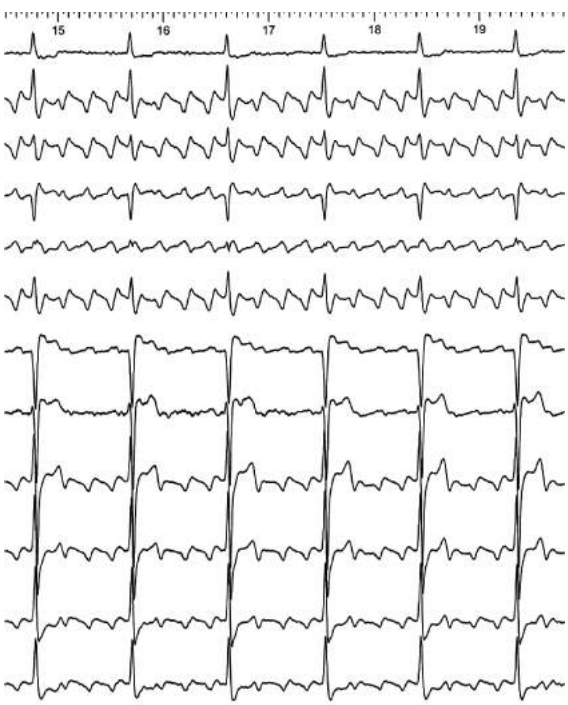

Figure 52.5 Typical atrial flutter with sawtooth P waves in inferior leads.

Double-wave reentry is defined as a circuit in which two flutter waves simultaneously occupy the usual flutter pathway. This arrhythmia is transient, usually terminating within three to six complexes but may, on rare occasions, deteriorates into AF.

Lower-loop reentry is defined as a flutter circuit in which the reentry wavefront circulates around the inferior vena cava due to conduction across the crista terminalis.

Atrial flutter may present with unusual ECG patterns, and confirmation of isthmus involvement can be made only by entrainment pacing of the CTI during electrophysiological study. It should be noted, however, that a long post-pacing interval may be due to delayed conduction and does not exclude isthmus-dependent flutter.[22] Regardless of the circuit, arrhythmias dependent on CTI conduction are amenable to isthmus ablation.

Presentation

Patients present with **sudden-onset palpitations, dyspnoea**, or **chest pain**. More insidious symptoms, such as fatigue and worsening of heart failure, may also occur. The typical sawtooth ECG patterns described in Definitions and classification may or may not be present. Usually, there is a **2:1 AV conduction**, with a resultant ventricular rate of approximately 150 beats/min. **Varying block** produces an irregular rhythm whereas 1:1 conduction may lead to haemodynamic instability.

Therapy

In emergencies, DC cardioversion (<50 J) is indicated (Table 52.5 and Figure 52.6). Otherwise, ibutilide IV or overdrive pacing are used. For acute rate control, diltiazem IV is as effective as verapamil, but with a lower incidence of hypotension.[8] Atrial flutter lasting >48 h requires anticoagulation. No antiarrhythmic therapy is of proven efficacy for long-term rhythm control, and catheter ablation is the current treatment of choice, offering a >90% success rate and 10% recurrence (Table 52.6 and Figure 52.7).[23,24] There is no procedure-related mortality.[24,25]

Non-cavotricuspid isthmus-dependent atrial flutter

Lesion-related macro-reentry may be right or left atrial and is following repair of a congenital defect (usually ASD), mitral valve surgery, maze procedures, or left atrial ablation for AF (Figure 52.8).

Atrial tachycardias following PV isolation for AF are usually macroreentrant (mitral isthmus or LA roof-dependent) and rarely focal. Perimitral macroreentry can be diagnosed and differentiated by cavotricuspid isthmus or LA roof-dependent or focal AT, by entrainment of the tachycardia (ie PPI-TCL <40 ms) from the proximal CS electrode and demonstrating a S-Au >75% of tachycardia CL, ie activation

using the tachycardia circuit.[26] The S-Au (stimulus to upstream atrial electrogram) interval is the time between the last pacing stimulus of the entrainment sequence to the first atrial electrogram at the pair of electrodes with atrial activation immediately preceding the pacing stimulus. In the case of cavotricuspid isthmus or LA roof-dependent macroreentry or focal AT, the S-Au is <25% of TCL indicating direct activation. In a similar way pacing from the PVs can diagnose roof-dependent macroreentry.[26]

Conduction delays within the circuit can prolong the atrial tachycardia cycle length, making it overlap with the classical focal atrial tachycardia range (>400 ms cycle length). Incisional macro-reentrant AT may also coexist with isthmus-dependent flutter or incorporate the CTI, thus resulting in multiple reentry circuits, and may respond to isthmus ablation.[27] Electroanatomic mapping and catheter ablation of the circuit are usually required for long-term therapy.[28] Atrial tachycardias in GUCH are also discussed in Chapter 51.

Right atrial free wall macro-reentry without atriotomy may also occur.[13]

Table 52.5 Acute management of atrial flutter

ACC/AHA/ESC GL on SVT 2003. Recommendations for acute management of atrial flutter		
Poorly tolerated flutter		
Conversion	DC cardioversion	I-C
Rate control	Beta-blockers Verapamil or diltiazem	IIa-C
	Digoxin (especially in HF), amiodarone	IIb-C
Stable flutter		
Conversion	Atrial or transoesophageal pacing	I-A
	DC cardioversion	I-C
	Ibutilide (not in low LVEF)	IIa-A
	Flecainide, propafenone, procainamide (all with beta blockers)	IIb-A
	Sotalol	IIb-C
	Amiodarone	IIb-C
Rate control	Diltiazem or verapamil	I-A
	Beta-blockers	I-C
	Digoxin (especially in HF)	IIb-C
	Amiodarone	IIb-C
ACC/AHA/HRS 2015 GL on SVT. Acute treatment of atrial flutter		
	Oral dofetilide or IV ibutilide for acute pharmacological cardioversion	I-A
	IV or oral beta blockers, diltiazem, or verapamil for acute rate control in hemodynamically stable patients	I-B-R
	Elective synchronized cardioversion in stable patients with welltolerated atrial flutter when a rhythm control strategy is being pursued	I-B-NR
	Synchronized cardioversion of atrial flutter in hemodynamically unstable patients who do not respond to pharmacological therapies	I-B-NR
	Rapid atrial pacing for acute conversion in patients who have pacing wires in place as part of a permanent pacemaker or implantable cardioverter-defibrillator or for temporary atrial pacing after cardiac surgery	I-C-LD
	Acute antithrombotic therapy as for AF	I-B-NR
	IV amiodarone for acute control of the ventricular rate (in the absence of pre-excitation) in patients with systolic heart failure when beta blockers are contraindicated or ineffective	IIa-B-R

Cardioversion should be considered only if the patient is anticoagulated (INR = 2–3), the arrhythmia is less than 48 hours in duration, or the TOE shows no atrial clots.

ACC/AHA /ESC 2003 guidelines for the management of patients with supraventricular arrhythmias. *Eur Heart J*. 2003;**24**:1857–97, with permission from Oxford University Press.

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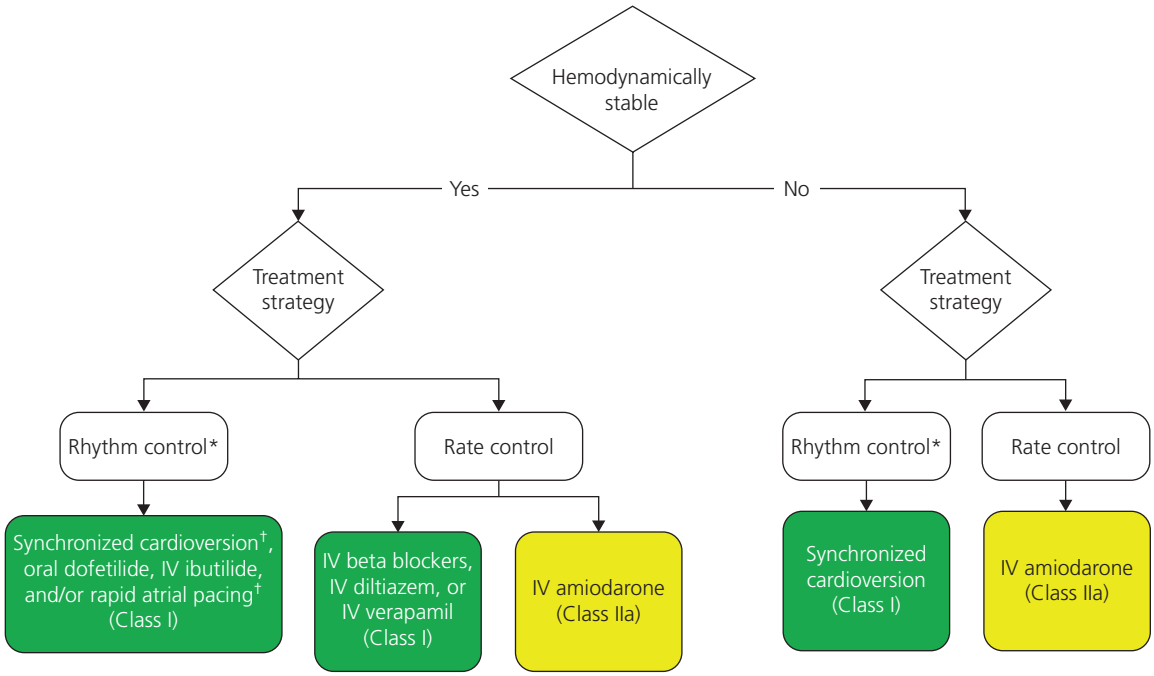

Figure 52.6 ACC/AHA/HRS 2015 GL on SVT. Acute Treatment of atrial flutter.

Drugs listed alphabetically.
* Anticoagulation as per guideline is mandatory.
† For rhythms that break or recur spontaneously, synchronized cardioversion or rapid atrial pacing is not appropriate.
IV indicates intravenous.
ACC/AHA/HRS 2015 Guideline for the management of adult patients with supraventricular tachycardia. *J Am Coll Cardiol*. 2015; doi:10.1016/j.jacc.2015.08.856 with permission from Elsevier.

Table 52.6 Long term management of atrial flutter

ACC/AHA/ESC 2003 GL on SVT. Recommendations for long-term management of atrial flutter		
First episode and well-tolerated atrial flutter	Cardioversion alone	I-B
	Catheter ablation	IIa-B
Recurrent and well-tolerated atrial flutter	Catheter ablation	I-B
	Dofetilide	IIa-C
	Amiodarone, sotalol	IIb-C
	Flecainide, propafenone, quinidine, procainamide, disopyramide (all with beta-blockers and not in structural heart disease)	IIb-C
Poorly tolerated atrial flutter	Catheter ablation	I-B
Atrial flutter appearing after use of class IC agents or amiodarone for treatment of AF	Catheter ablation	I-B
	Stop current drug and use another	IIa-C
Symptomatic, non-CTI-dependent flutter after failed antiarrhythmic drug therapy	Catheter ablation	IIa-B
ACC/AHA/HRS 2015 GL on SVT. Ongoing management of atrial flutter		
Catheter ablation of the CTI is useful in patients either symptomatic or refractory to pharmacological rate control		I-B-R
Beta blockers, diltiazem, or verapamil to control the ventricular rate in hemodynamically tolerated atrial flutter		I-C-LD

(*Continued*)

Table 52.6 Continued

Catheter ablation for recurrent symptomatic non-CTI-dependent flutter after failure of at least 1 antiarrhythmic agent	I-C-LD
Antithrombotic therapy as for AF	I-B-NR
Drugs to maintain sinus rhythm in patients with symptomatic, recurrent atrial flutter, with the drug choice depending on underlying heart disease and comorbidities:	IIa-B-R
a. Amiodarone	
b. Dofetilide	
c. Sotalol	
Catheter ablation for CTI-dependent atrial flutter that occurs as the result of flecainide, propafenone, or amiodarone used for treatment of AF	IIa-B-NR
Catheter ablation of the CTI in patients undergoing catheter ablation of AF who also have a history of documented clinical or induced CTI-dependent atrial flutter	IIa-C-LD
Catheter ablation for recurrent symptomatic non-CTI-dependent flutter as primary therapy, before therapeutic trials of antiarrhythmic drugs	IIa-C-LD
Flecainide or propafenone to maintain sinus rhythm in patients without structural heart disease or ischemic heart disease and symptomatic recurrent atrial flutter	IIb-B-R
Cather ablation for asymptomatic patients with recurrent atrial flutter	IIb-C-LD

Catheter ablation of the AV junction and insertion of a pacemaker should be considered if catheter-ablative cure is not possible and the patient fails drug therapy.
ACC/AHA /ESC 2003 guidelines for the management of patients with supraventricular arrhythmias. *Eur Heart J*. 2003;**24**:1857–97, with permission from Oxford University Press.
ACC/AHA/HRS 2015 Guideline for the management of adult patients with supraventricular tachycardia. *J Am Coll* Cardiol. 2015; doi:10.1016/j.jacc.2015.08.856 with permission from Elsevier.

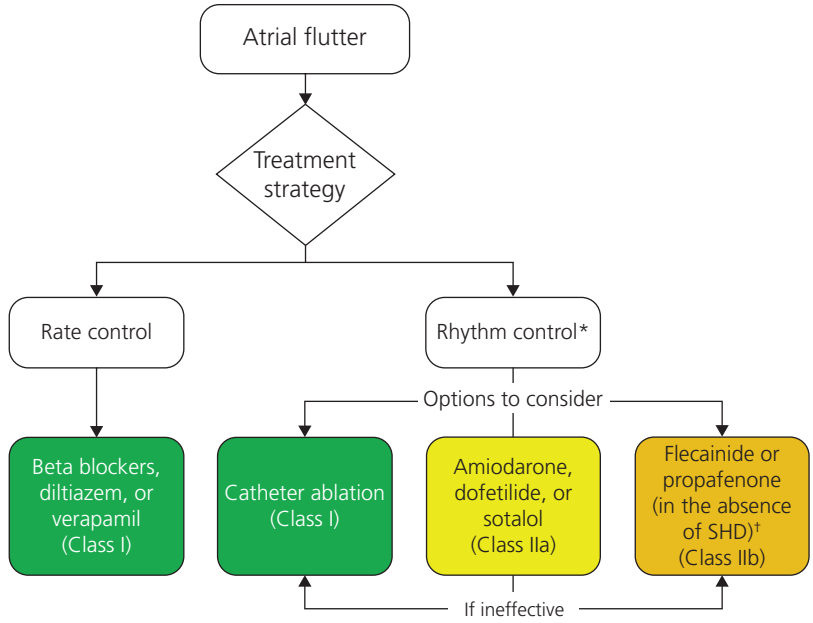

Figure 52.7 ACC/AHA/HRS 2015 GL on SVT. Ongoing management of atrial flutter.

Drugs listed alphabetically.
* After assuring adequate anticoagulation or excluding left atrial thrombus by transoesophageal echocardiography before conversion.
† Should be combined with AV nodal–blocking agents to reduce risk of 1:1 conduction during atrial flutter.
AV indicates atrioventricular; SHD, structural heart disease (including ischaemic heart disease).
ACC/AHA/HRS 2015 Guideline for the management of adult patients with supraventricular tachycardia. *J Am Coll Cardiol*. 2015; doi:10.1016/j.jacc.2015.08.856 with permission from Elsevier.

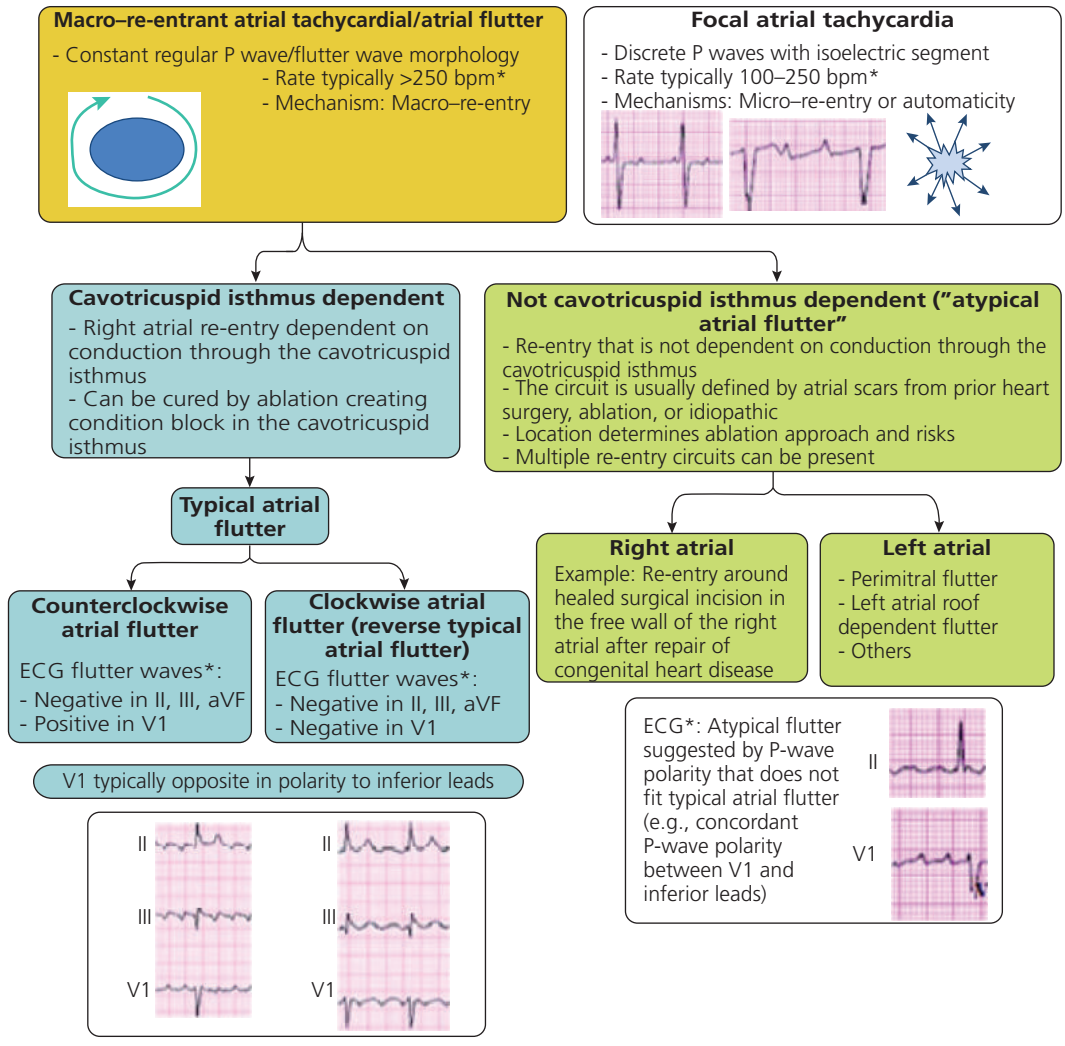

Figure 52.8 Types of atrial tachycardias often encountered in patients with a history of AF, including those seen after catheter or surgical ablation procedures. P-wave morphologies are shown for common types of atrial flutter; however, the P-wave morphology is not always a reliable guide to the re-entry circuit location or to the distinction between common atrial flutter and other macro–re-entrant atrial tachycardias.

* Exceptions to P-wave morphology and rate are common in scarred atria. AF indicates atrial fibrillation and ECG, electrocardiogram.
AHA/ACC/HRS 2014 Guideline or the management of patients with atrial fibrillation. *J Am Coll Cardiol*. 2014;**64**:2246–80 with permission from Elsevier.

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Chapter 53

Atrial fibrillation

Definitions and classification

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation without effective atrial contraction.[1–3] On the ECG, there is replacement of consistent P waves by rapid oscillations or fibrillatory waves that vary in amplitude, shape, and timing (when visible, usually in lead V_1, the atrial length is variable and <200 ms, i.e. >300 bpm), associated with an irregular ventricular response.[2] QRS complexes may also be of variable amplitude. Regular R-R intervals are possible in the presence of AV block or coexistent AV junctional or ventricular tachycardia.

Paroxysmal AF is defined as recurrent AF (≥2 episodes) self-terminating within 7 days. Usually, self-termination occurs within 48 h. After this, the likelihood of spontaneous conversion is low. Up to 15% of patients with paroxysmal AF progress to persistent forms annually.[4]

Persistent AF is present when an AF episode either lasts longer than 7 days or requires termination by cardioversion, either with drugs or by direct current cardioversion.

Long-standing persistent AF is AF that has lasted for ≥1 year.

Permanent AF refers to the situation when the presence of the arrhythmia is accepted by the patient and physician. Hence, rhythm control interventions are, by definition, not pursued in patients with permanent AF. Should a rhythm control strategy be adopted, the arrhythmia is redesignated as 'long-standing persistent AF'.

Silent AF, i.e. asymptomatic AF, is discovered at a routine medical evaluation or following a complication and may present as any of the temporal forms of AF.

Lone (idiopathic) AF has been variously defined but generally applies to young individuals (under 60 years of age) without clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension. Its prevalence is not exactly known, with reports varying from 10 to 30% among patients with AF.[5]

Non-valvular AF The AHA/ACC/HRS 2014 guidelines define nonvalvular AF as AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.[1] The ESC 2012 GL update defines nonvalvular AF only when it is not related to rheumatic valvular disease (predominantly mitral stenosis) or prosthetic heart valves.[3]

Although, in certain cases, AF is vagally mediated (i.e. after meals or habitual aerobic training) whereas, in others, it follows sympathetic overactivity, the terms **vagal** and **adrenergic** AF are oversimplifications since the balance between sympathetic and parasympathetic influence is as important as absolute tone.

Epidemiology

AF is the most common sustained arrhythmia in humans and affects 1–3% of the general population worldwide. It affects 3–6 million people in the United States,[5,6] while in Asian countries its incidence is slightly lower.[7,8] In the European Union, 8.8 million adults over 55 years were estimated to have AF in 2010, and this number is expected to double by 2060 to 17.9 million.[9] According to the first global assessment of AF, conducted within the framework of the recently published Global Burden of Diseases, Injuries, and Risk Factors Study (the GBD 2010 Study), the estimated global prevalence of AF in 2010 was 33.5 million (20.9 million men and 12.6 million women), with almost 5 million new cases occurring each year.[10] The prevalence of AF increases with age, from approximately 2% in the general population to 5–15% at 80 years.[5,11,12] The lifetime risk of developing AF has been calculated as 20–25% in those who have reached the age of 50,[12,13] and appears higher in recent studies,[12] although this may be partly due to enhanced surveillance.[13] The incidence of early-onset AF in persons <50 years is 0.62 cases per 1000 person-years for men and 0.19 cases per 1000 person-years for women.[5] Whites have an increased risk of AF compared to blacks, Asians or Hispanics.[14]

The presence of AF accounts for a 50% (men) to 90% (women) increased risk for overall mortality over 40 years follow-up in the Framingham Heart Study, thus diminishing the female advantage in survival.[15] AF is also associated with a 5-fold increased risk for stroke, a 2-fold increased risk for dementia, and a tripling of risk for heart failure.[16,17,18] Individuals with AF associated with a potentially reversible cause have a lower risk of heart failure but similar risks of stroke and mortality over follow-up as compared to individuals without such precipitants.[19] AF is the main cause of coronary embolism, being independently associated with an increased risk of myocardial infarction, especially NSTEMI in women.[20,21]

AF and its associated morbidity represent a significant socio-economic burden on the healthcare system. Direct cost estimates range from $2000 to 14 200 per patient-year in the USA and from €450 to 3000 in Europe. This is comparable with other chronic conditions, such as diabetes. In the USA, the total cost of nonvalvular AF was

approximately $6.65 billion in 2005, and despite a static mean length of stay, the cost of inpatient care has increased from $2.15 billion in 2001 to $3.46 billion in 2010.[22]

Patients with AF or heart failure have a significantly higher risk of post-operative mortality following noncardiac surgery, than patients with coronary artery disease, and even minor procedures carry a risk.[23]

Aetiology

Causes of AF are presented in Table 53.1. **Hypertension** is the most common cause of AF encountered in clinical practice, followed by **ischaemic heart disease**.[1] Approximately 30% of patients with **heart failure** or **valve disease** have AF. Patients with coronary artery disease, **diabetes**, or **COPD** are at higher risk for AF (15–20%). **Diastolic dysfunction** presents a potentially important link between many common risk factors, such as hypertension, age, obesity, and diabetes, and the development of AF.[24] Postulated mechanisms of risk are increased atrial afterload, atrial myocyte stretching, and atrial wall stress. **Frequent atrial ectopy** (more than 2 APBs per hour) have been associated with increased risk of AF.[25] **Chronic kidney disease and albuminuria**,[26] **obesity**,[27] **metabolic syndrome**,[28] and **alcohol** consumption (>2 drinks a day)[29] are associated with an increased prevalence of AF in adults. A U-shaped association between consumption of **marine n-3 PUFA** and risk of incident AF has been reported; moderate fish consumption (0.63 g of marine n-3 PUFA—two servings) has a protective effect.[30] Consumption of extra virgin **olive oil** (at least 50 mg or 4 tablespoons) in the context of a Mediterranean dietary pattern may also reduce the risk of atrial fibrillation.[31] **Thyroid** disease is less common than previously thought. **ASDs** are associated with increased incidence of AF, regardless of treatment, and persistent AF is unlikely to be affected by ASD closure. Paroxysmal AF may improve, but transcatheter ASD closure may also trigger atrial arrhythmias (see Chapter 4). **Chemotherapy agents**, such as anthracylines (at a rate of 2–10%), melphalan (7–12%), and cisplatin (12–32%), particularly with intrapericardial use, may cause AF.[32] Moderate to severe **sleep apnoea** is associated with a fourfold increase in the risk of AF.[33] **Psoriasis** is associated with increased risk of AF and ischaemic stroke.[34] **Exercise** intensity has a U-shaped relationship with AF.[35] Long-term vigorous exercise may predispose to AF (2–10 times more prevalent in active athletes),[36] but light to moderate physical activities, particularly leisure time activity and walking, are associated with significantly lower AF incidence in older adults,[35] and there is an inverse relationship between cardiorespiratory fitness and incident AF, especially among obese patients.[37] Low serum **magnesium** is associated with the development of AF, even in persons without cardiovascular disease.[38] Recently, a J-shaped association was found between **QTc interval** duration and risk of AF. This association was strongest with respect to the development of lone AF.[39]

Parental AF increases the future risk for offspring AF,[40] and a family history of AF is associated with substantial risk of lone AF,[41] thus supporting a genetic susceptibility to developing the arrhythmia. **Mutations** associated with AF are presented in Table 57.1 of the chapter on genetic channelopathies. Mutations that cause loss of function of the sodium channel (such as in SCN5A and 10A genes), gain

Table 53.1 Causes of AF

Systemic hypertension
Ageing
Heart failure
Coronary artery disease
Valve disease
Diabetes mellitus
Obesity
Chronic obstructive pulmonary disease
Chronic renal disease
Cardiomyopathies
Congenital heart disease (mainly ASD)
Post-operative (cardiac, pulmonary, or oesophageal)
Pulmonary hypertension (pulmonary embolism)
Pericarditis
Myocarditis
Intracardiac tumours or thrombi
Primary or metastatic disease in, or adjacent to, the atrial wall
Phaeochromocytoma
Chemotherapy agents
Hyperthyroidism
Subarachnoid haemorrhage
Non-haemorrhagic, major stroke
Metabolic syndrome
Sleep apnoea
Alcohol abuse
Hypomagnesaemia
Familial
Psoriasis
Long-term vigorous exercise
Sick sinus syndrome
AF as a result of ventricular pacing
Lone AF

of function of the potassium channels (KCN genes), or affect connexins and transcription factors, as well as others, are mainly responsible. Approximately 20% of patients with AF carry a common single nucleotide polymorphism on chromosome 4q25 that is associated with a lack of response to antiarrhythmic therapy for rhythm control,[42] and novel genetic loci for AF are continually discovered by genome-wide association studies.[43–45] However, although the heritability of AF has been estimated to be as high as 60%,[46] the known genetic variants appear to explain only a fraction of the heritability.[47]

Pathophysiology

Structural remodelling of the atria due to heart disease (Figure 53.1), atrial wall stretch, genetic causes, or other non-identified mechanisms result in electrical dissociation between muscle bundles and local conduction heterogeneities that facilitate the initiation and perpetuation of AF through multiple mechanisms.[48] Structural atrial abnormalities consist of areas of patchy fibrosis, enhanced connective tissue deposits juxtaposed with normal atrial fibres, inflammatory changes, intracellular substrate accumulation, and disruption of cell coupling at gap junctions with remodelling of connexins (i.e. transmembrane ion channel proteins in the gap junctions).[49] Connexin gene variants are associated with AF, and connexin gene transfer in animal studies has prevented AF.[50] Fibrosis and inflammatory changes, identified by biopsy and delayed enhancement magnetic resonance, have also been documented in patients with lone AF.[51,52]

After the onset of AF, changes of atrial electrophysiological properties and mechanical function occur within days (>24 h). Shortening of the atrial effective refractory period results from abbreviation of the atrial action potential duration, which is caused by a decrease in the calcium channel current (I_{Ca}) and an increase in the potassium channel current (I_{K1}) and the constitutively active acetylcholine-sensitive current (I_{KACh}).[49] Increased diastolic sarcoplasmic reticulum $Ca2^{+}$ leak and related delayed after-depolarizations/triggered activity promote cellular arrhythmogenesis.[53] Ryanodine receptor type 2-mediated sarcoplasmic reticulum calcium leak also drives AF progression.[54] Downregulation of the Ca^{2+} inward current and impaired release of Ca^{2+} from intracellular Ca^{2+} stores cause loss of contractility and increased compliance with subsequent atrial dilation. Electrical remodelling of the

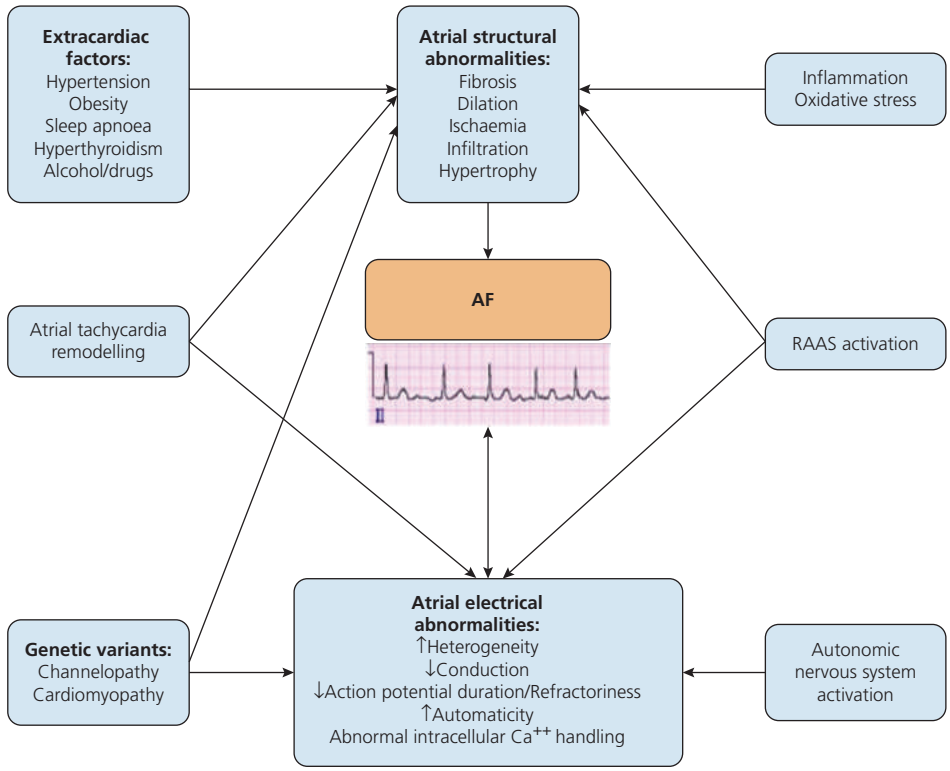


Figure 53.1 Mechanisms of AF.

AF indicates atrial fibrillation; Ca^{++}, ionized calcium; and RAAS, renin-angiotensin-aldosterone system.
AHA/ACC/HRS 2014 Guideline or the management of patients with atrial fibrillation. *J Am Coll Cardiol*. 2014;**64**:2246–80 with permission from Elsevier.

atria is, therefore, perpetuated by AF itself in a way that 'AF begets AF'.[55] Restoration of sinus rhythm results in recovery of normal atrial refractoriness within a few days. LA structure and function are increasingly abnormal with a greater electrical burden of AF, and LA dysfunction may be present despite normal LA size and sinus rhythm.[56] A fast fibrillatory rate is associated with worse prognosis in patients without structural heart disease due to adverse atrial remodelling and prolonged episodes, but, in patients with heart failure, a low fibrillatory rate indicates poor prognosis probably due to adverse remodelling and atrial fibrosis.[57] Data from the Framingham Heart Study indicate that AF recurs in most individuals, including those diagnosed with secondary precipitants.[19]

Electrophysiologic mechanisms

The initiation and perpetuation of AF require both triggers for its onset and a substrate for its maintenance.

Focal electrical activity, contributing to the initiation and perhaps perpetuation of AF, has been identified at pulmonary vein (PV) ostia.[58] Due to shorter refractory periods, as well as abrupt changes in myocyte fibre orientation, the PV left atrial junctions have a stronger potential to initiate and perpetuate atrial tachyarrhythmias.[59] Mechanisms of focal activity might involve increased local automaticity, triggered activity, and micro-reentry (Figures 53.1 and 53.2). Apart from the PVs, other cardiac veins and certain areas of the posterior left atrial wall may have a profibrillatory role.[60] Localized anisotropic reentry,

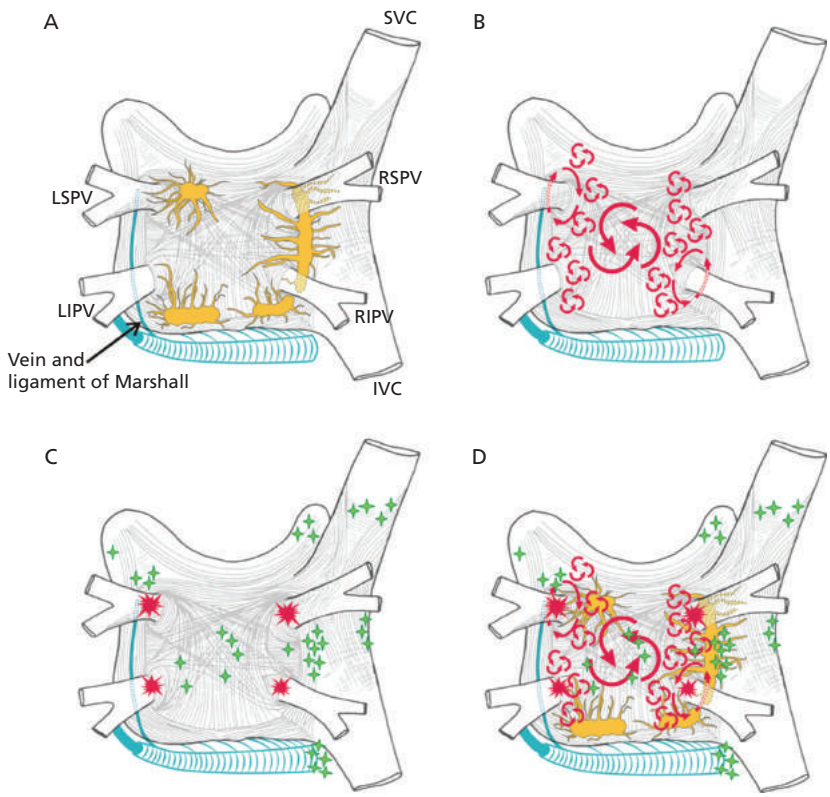


Figure 53.2 Structure and mechanisms of atrial fibrillation. (A) Schematic drawing of the left and right atria as viewed from the posterior. The extension of muscular fibres onto the PVs can be appreciated. Shown in yellow are the four major LA autonomic ganglionic plexi and axons (superior left, inferior left, anterior right, and inferior right). Shown in blue is the coronary sinus which is enveloped by muscular fibres which have connections to the atria. Also shown in blue is the vein and ligament of Marshall which travels from the coronary sinus to the region between the left superior PV and the LA appendage. (B) Large and small reentrant wavelets that play a role in initiating and sustaining AF. (C) Common locations of PV (red) and also the common sites of origin of non-PV triggers (shown in green). (D) Composite of the anatomical and arrhythmic mechanisms of AF.

HRS/EHRA/ECAS 2012 expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *Heart Rhythm*. 2012;**9**:632–96 with permission from Elsevier.

leading to rotors with a high dominant frequency, and fibrillatory conduction may also play a role in maintaining AF.[61] Elimination of these rotors and AF nests may be one of the mechanisms for the efficacy of real-time frequency analysis or complex fractionated electrogram-guided ablation.[62]

According to the **multiple wavelet hypothesis**, proposed by Moe and colleagues, AF is perpetuated by continuous conduction of several independent wavelets propagating through the atrial musculature in a seemingly chaotic manner. Fibrillation wavefronts continuously undergo wavefront-waveback interactions, resulting in wavebreak and the generation of new wavefronts, while block, collision, and fusion of wavefronts tend to reduce their number. As long as the number of wavefronts does not decline below a critical level, the multiple wavelets will sustain the arrhythmia.

Areas rich in **autonomic innervation** may be the source of activity that triggers AF.[63] Ganglionated plexi that can be identified around the circumference of the left atrial PV junction may also contribute to induction and perpetuation of AF.[60] These plexi are usually located 1–2 cm outside the PV ostia; they mediate both sympathetic and parasympathetic activity, and their ablation (autonomic denervation) has been found efficacious when added to antral PV isolation.[64]

These mechanisms are not mutually exclusive and may coexist at various times. While, in most patients with paroxysmal AF, localized sources of the arrhythmia can be identified, such attempts are often not successful in patients with persistent or permanent AF. This can be interpreted within the context of the multifactorial aetiology of AF.

Haemodynamic consequences

Loss of atrial contraction and atrioventricular synchrony, irregular ventricular response, rapid heart rate, and impaired coronary arterial blood flow affect the haemodynamic function during AF. Loss of atrial contraction, especially when diastolic filling is impaired, may reduce cardiac output by up to 15%. Irregular ventricular response affects both myocardial contractility and coronary flow. Rapid ventricular rates may compromise coronary flow and exacerbate MR. A persistently elevated ventricular rate (>130 bpm) is also a known cause of tachycardia-induced cardiomyopathy (see Chapter 41).[65] Ventricular response is limited by the intrinsic refractoriness of the AV node and its atrial inputs and is being affected by concealed conduction to the node and autonomic tone. AF is also a cause of functional MR due to atrial dilatation.[66]

Thromboembolism

Thrombotic material in AF usually arises in the left atrial appendage due to decreased flow and stasis, possible endothelial dysfunction, and a hypercoagulable state, as indicated by increased fibrinogen, D-dimer, thromboglobulin, and platelet factor 4 levels. In the Framingham study, the percentage of strokes attributable to AF increases steeply from 1.5% at 50–59 years of age to 23.5% at 80–89 years of age.[67] Approximately 24% of all strokes are due to AF.[68] Undiagnosed silent AF is a probable cause of cryptogenic strokes,[69,70] and subclinical episodes of AF are associated with silent cerebral infarcts, particularly in diabetics.[71,72] Numbers of AF-related incident ischaemic strokes at age ≥80 years have trebled over the last 25 years, despite the introduction of anticoagulants, and are projected to treble again by 2050.[73] Among patients with AF at moderate-to-high risk of stroke receiving anticoagulation, those with persistent AF have a higher risk of thromboembolic events and worse survival compared with paroxysmal AF.[74] The risk of stroke is similar in patients with or without valvular disease.[75] Serial ECGs, Holter monitoring, mobile outpatient telemetry, external loop recorders, and implantable loop recorders detect post-stroke AF in 23.7% of patients.[18] However, AF early after stroke can be caused by a transient neurogenic mechanism, and AF several months post-stroke can be an incidental finding; therefore, it cannot be concluded that the cause of cryptogenic stroke has been identified in all patients found to have post-stroke AF.[18]

Prior embolic events, intracranial haemorrhage, myocardial infarction, vascular disease, hypertension, diabetes, female gender, and advancing age, but not thyroid disease, are independent risk factors for stroke.[76,77] Renal impairment (CrCl <60 mL/min) doubles the risk of stroke and increases the risk of major bleeding by almost 60% in anticoagulated patients with AF.[78] The morphology of the left atrial appendage on MRI may affect the risk of stroke.[79] High-sensitivity troponin, N-terminal pro-brain natriuretic peptide, and growth differentiation factor 15 (GDF-15) are predictive of stroke and death in AF.[80]

Extracranial systemic embolic events constitute 11.5% of clinically recognized thromboembolic events in patients with AF and are associated with a high morbidity and mortality, comparable to that of ischaemic stroke.[81]

Mortality

In a recent European registry (EORP-AF), 1-year mortality was 5.7% despite good adherence to anticoagulation.[82] In a recent report on a large Swedish registry, AF was an independent risk factor of all-cause mortality. The highest relative risk of mortality was seen in women and in the youngest patients compared with controls.[83] Interestingly, in the RE-LY trial, <10% of deaths were attributed to stroke; main causes of death were sudden cardiac death (22%) and heart failure (15%).[84] Data from the ARIC study indicate that incident AF is associated with an increased

risk of sudden and non-sudden cardiac death in the general population.[85] AF is independently associated with a 3-fold increased risk of VF.[86]

Diagnosis

Patients may present with palpitations or the arrhythmia may be an incidental finding. The 2012 ESC GL on AF recommend opportunistic screening for AF in patients ≥65 years of age using pulse taking, followed by an ECG (I-B). Frequent atrial ectopy, atrial tachycardia, and atrial flutter may present with rapid irregular R-R intervals and mimic AF or detected in patients with AF. Most atrial tachycardias and flutters show longer atrial cycle lengths ≥200 ms, but patients on antiarrhythmic drugs may have slower atrial cycle lengths during AF. When the ventricular rate is fast, atrioventricular nodal blockade during the Valsalva manoeuvre, carotid massage, or intravenous adenosine administration can help to unmask atrial activity. Extremely rapid ventricular rates (>200 bpm) suggest the presence of an accessory pathway or ventricular tachycardia.

Investigations

Complete **history** (including family and social history), **physical examination**, **12-lead ECG**, **blood pressure measurement**, **echocardiography**, and basic laboratory investigations (**full blood count; renal, liver, and thyroid function; electrolytes, including calcium and magnesium, glucose, and lipid profile**) are mandatory in every patient who presents with first detected AF. The quality of life of the patient should be also assessed, using either the EHRA[2] or the Canadian Cardiovascular Society[87] scales (EHRA I, asymptomatic; EHRA II, mild symptoms; EHRA III, severe symptoms; EHRA IV, disabling symptoms).

Additional tests in selected cases are:

Chest radiography to exclude lung disease or before starting amiodarone.

Ambulatory ECG monitoring to document AF episodes and detect other initiating arrhythmia. Implantable or wireless loop recorders[88] increase detection rate and are useful in the investigation of cryptogenic stroke.[69,70]

Six-minute walk test or **treadmill exercise test** to assess rate control.

Ischaemia testing if coronary artery disease is suspected.

Ambulatory blood pressure monitoring in case of borderline hypertension.

Transoesophageal echocardiography to exclude left atrial appendage thrombus or mobile aortic plaques when cardioversion is planned.

Electrophysiology study when other supraventricular arrhythmia that initiates AF is suspected or when presumed AF presents as a wide-QRS tachycardia.

Sleep study when sleep apnoea is suspected.

Genetic testing is not indicated (Table 53.2). However, patients with AF and multigenerational family members with AF may be considered for referral to a tertiary care centre for genetic counselling and testing (AHA/ACC/HRS 2014 GL on AF, IIb-C).

Risk stratification

The main complications of AF are thromboembolism and impairment of LV function. Reduced LV function predisposes to thromboembolism and may evolve into tachycardiopathy. Baseline echocardiography, therefore, is essential for initial assessment of LA size and LVEF and follow-up. Arrhythmia-induced impairment of LV function should be considered with fast and persistently elevated ventricular rate (>130 bpm).[65]

Absolute stroke rates for non-anticoagulated patients vary between 1.5% and 10%, depending on the presence of risk factors. Prior stroke/TIA is the most powerful risk factor and reliably confers a stroke risk averaging 10% per year.[77] Patients <60 years with lone AF have a very low cumulative stroke risk estimated to be 1.3% over 15 years.[2] The probability of stroke in young patients with lone AF appears to increase with advancing age or development of hypertension.

Risk stratification schemes are based on the predisposing factors that have been discussed. The simplest thromboembolic risk assessment scheme is the $CHADS_2$ score (cardiac failure, hypertension, age, diabetes, stroke (doubled)) risk index.[89] It has been recently revised as the CHA_2DS_2-VASc score (Table 53.3).[90] These schemes apply to patients with any form of AF (paroxysmal, persistent, or permanent). N-terminal proBNP is often elevated in AF and independently associated with an increased risk for stroke and mortality, thus improving risk stratification beyond the CHA_2DS_2-VASc score.[91]

Table 53.2 HRS/EHRA 2011 statement on genetic testing

State of genetic testing for atrial fibrillation	
Genetic testing is not indicated for atrial fibrillation at this time.	III
SNP genotyping, in general, and SNP rs2200733 genotyping at the 4q25 locus, in particular, for AF is not indicated at this time, based on the limited outcome data currently available	III

HRS/EHRA 2011 Expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Europace*. 2011;**13**:1077–109 with permission from Oxford University Press.

Table 53.3 Risk of thromboembolism

$CHADS_2$ score	
Risk factor	**Score**
Heart failure	1
Hypertension	1
Age >75	1
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2

CHA_2DS_2-VASc score	
Risk factor	**Score**
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age >75	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease (MI, peripheral artery disease, aortic plaque)	1
Age 65–74	1
Sex category (i.e. female sex)	1

Adjusted stroke rate according to CHA_2DS_2-VASc score	
Score	**Adjusted stroke rate (% per year)**
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

Previous stroke, TIA, systemic embolism, and age ≥75 years are considered major risk factors.

Therapy

Acute therapy

Direct current cardioversion is indicated in haemodynamic instability (Table 53.4) or when pharmacologic cardioversion has failed. Biphasic R wave synchronized shock (at least 150–200 J to avoid repeated shocks and occurrence of shock-induced VF) with anteroposterior electrode placement (at least 8 cm from a pacemaker battery, if present) is recommended.[92] To avoid thromboembolism (risk of 1–2%), a TOE should be performed to rule out atrial thrombi, unless AF is <48 h from a definite onset or adequate anticoagulation with warfarin or rivaroxaban (X-VeRT study)[93] has been documented for 3 weeks (Figures 53.3 and 53.4). UFH (60 U/kg IV) or LMWH (1 mg/kg IV) are given before cardioversion. A pacing catheter or external pacing pads may be needed in patients with sick sinus syndrome or in elderly patients with structural heart disease. Ventricular arrhythmias (in digitalis intoxication or hypokalaemia) are rare. Pre-treatment with drugs, such as amiodarone, ibutilide, sotalol, flecainide, and propafenone, increases success rates.

Factors that predispose to AF recurrence are age, AF duration before cardioversion, number of previous recurrences, an increased LA size or reduced LA function, and the presence of coronary heart disease or pulmonary or mitral valve disease. Atrial ectopic beats with a long-short sequence, faster heart rates, and variations in atrial conduction also increase the risk of AF recurrence.

Pharmacological cardioversion is less effective than DC cardioversion. The same precautions for anticoagulation and thromboembolic risk prevention apply as in DC cardioversion. Drugs used are (Tables 53.5 and 53.6):

Flecainide (1.5–3 mg/kg IV over 10–20 min) or **propafenone** (2 mg/kg IV over 10 min) achieve SR in 67–92% and 41–91% of patients, respectively, within the next 6 h. They are both contraindicated in patients with coronary artery disease or impaired LV function, and are not effective in atrial flutter or persistent AF. They may prolong QRS duration with resultant ventricular tachycardia (and flecainide, also the QT), and inadvertently increase the ventricular rate due to conversion to atrial flutter and 1:1 conduction to the ventricles.

The **'pill-in-the pocket'** approach refers to oral flecainide (200–300 mg po) or propafenone (450–600 mg po) that may achieve SR in up to 45% of patients who present with <7 days AF.[94] They can also be used outside the hospital once treatment has proved safe in hospital for selected patients without sinus or AV node dysfunction, bundle branch block, QT interval prolongation, Brugada syndrome, or structural heart disease, and especially previous MI. Before antiarrhythmic medication is initiated, a beta blocker or non-dihydropyridine calcium channel antagonist should be given to prevent rapid AV conduction in the event atrial flutter occurs (<0.2%).[2]

Ibutilide is a class III agent blocking the rapid component of the rectifier potassium channel (I_{Kr}) and also activates the slow inward sodium current.[95] It is a moderately potent drug for acute conversion of AF (45–75%). In one or two doses (Table 53.6), it achieves conversion within 90 min in 50% of patients. It prolongs the QTc by approximately 60 ms, and there is a 3.6% to 8.3% risk of torsades de pointes (watch for abnormal T-U waves or prominent QT prolongation). Co-administration of beta blockade may increase efficacy

and diminish the proarrhythmic risk.[96] It is more effective in atrial flutter.

Amiodarone achieves cardioversion in 40–60% of patients (80–90% with pre-treatment) but later than the other drugs. Hypotension and slow ventricular rate may be seen.

Dofetilide is also a pure class III agent (selective I_{kr} blocking agent), that is moderately effective in cardioverting AF or atrial flutter to SR (30%) and significantly effective in maintaining SR for 1 year (60%).[97] It is also effective, even in AF of >7 days in duration, but the response may be delayed (Table 53.6). QTc prolongation also occurs and there is a small but not negligible risk of torsade de points that may translate into increased mortality.[98] Inpatient monitoring is recommended (FDA) when initiating dofetilide therapy to avoid torsade de pointes ventricular tachycardia, especially in patients with heart failure, hypertrophy, bradycardia, and female gender.

Vernakalant blocks early activating potassium channels (IKur) and frequency-dependent sodium channels. It is relatively atrial-selective because the density of IKur channels is higher in the atria, and the effects on sodium channels are rate-dependent. In a dose of 3 mg/kg IV over 10 min, a second infusion of 2 mg/kg IV over 10 min after 15 min rest may convert AF (of duration ≤7 days or ≤3 days after surgery) in up to 51% of patients within 90 min.[99] Vernakalant is contraindicated in patients with systolic blood pressure <100 mmHg, severe aortic stenosis, heart failure (class NYHA III and IV), ACS within the previous 30 days, or QT interval prolongation (uncorrected QT >440 ms). Before its use, the patients should be adequately hydrated. The drug is not contraindicated in patients with stable coronary artery disease, hypertensive heart disease, or mild heart failure.[3] Vernakalant is not approved in the USA.

Peri-cardioversion anticoagulation In patients with AF <48 h from a definite onset, a bolus of UFH (5000 U IV) or LMWH (1 mg/kg IV) is given, especially if the patient is >65 years old. If AF has occurred for more than 48 h, trans-oesophageal echocardiography is necessary to exclude left atrial thrombus. Patients who have been on oral anticoagulation for at least 4 weeks before cardioversion may still have left atrial thrombus, especially when a non-vitamin K oral anticoagulant (NOAC) has been used. Following cardioversion, further anticoagulation may be needed depending on underlying risk factors for thromboembolism. In the absence of such risk factors (CHA_2DS_2-VASc score 0 for males or 1 for females), no oral anticoagulation is needed after cardioversion. In patients with AF >48 h or risk factors for thromboembolism, heparin is continued together with warfarin until the INR becomes 2–3 (for dosing see CAD), or a NOAC is administered immediately after cardioversion. Thereafter anticoagulation is continued for 4 weeks and then further anticoagulation depends on the presence of risk factors (Table 53.7).

Acute rate control When AF cannot be cardioverted or cardioversion is contraindicated (i.e. presence of left atrial thrombus), acute rate control (80–100 bpm) can be accomplished by IV:

- **Beta blockers**, or
- **Non-dihydropyridine calcium antagonists.**

In the setting of heart failure or hypotension, **amiodarone** IV or **digitalis**, under careful monitoring, may be used (Table 53.8). In pre-excitation, only amiodarone, ibutilide, and class IA are safe (see later). AF with slow ventricular rates may respond to atropine (0.5–2 mg IV), but temporary pacing may be required.

Table 53.4 Direct current cardioversion of AF

ESC 2010 GL on AF. Recommendations for direct current cardioversion (DCC)	
Immediate DCC when a rapid ventricular rate does not respond promptly to pharmacological measures in patients with AF and ongoing myocardial ischaemia, symptomatic hypotension, angina, or heart failure.	I-C
Immediate DCC for patients with AF involving pre-excitation when rapid tachycardia or haemodynamic instability is present.	I-B
Elective DCC to initiate a long-term rhythm control management strategy.	IIa-B
Pre-treatment with amiodarone, flecainide, propafenone, ibutilide, or sotalol to enhance success of DCC and prevent recurrent AF.	IIa-B
Repeated DCC in highly symptomatic patients refractory to other therapy.	IIb-C
Pre-treatment with beta blockers, diltiazem, or verapamil for rate control, although the efficacy of these agents in enhancing success of DCC or preventing early recurrence of AF is uncertain.	IIb-C
DCC is contraindicated in patients with digitalis toxicity.	III-C
AHA/ACC/HRS 2014 GL on AF. Direct current cardioversion	
Cardioversion for AF or atrial flutter to restore sinus rhythm. If unsuccessful, repeat cardioversion attempts may be made	I-B
Cardioversion for AF or atrial flutter with rapid ventricular response that does not respond to pharmacological therapies	I-C
Cardioversion for AF or atrial flutter and pre-excitation with haemodynamic instability	I-C
Repeat cardioversions in persistent AF when sinus rhythm is maintained for a clinically meaningful time period between procedures	IIa-C

ESC 2010 Guidelines for the management of atrial fibrillation. *Eur Heart J.* 2010;**31**:2369–429 with permission from Oxford University Press. AHA/ACC/HRS 2014 Guideline or the management of patients with atrial fibrillation. *J Am Coll Cardiol.* 2014;**64**:2246–80 with permission from Elsevier.

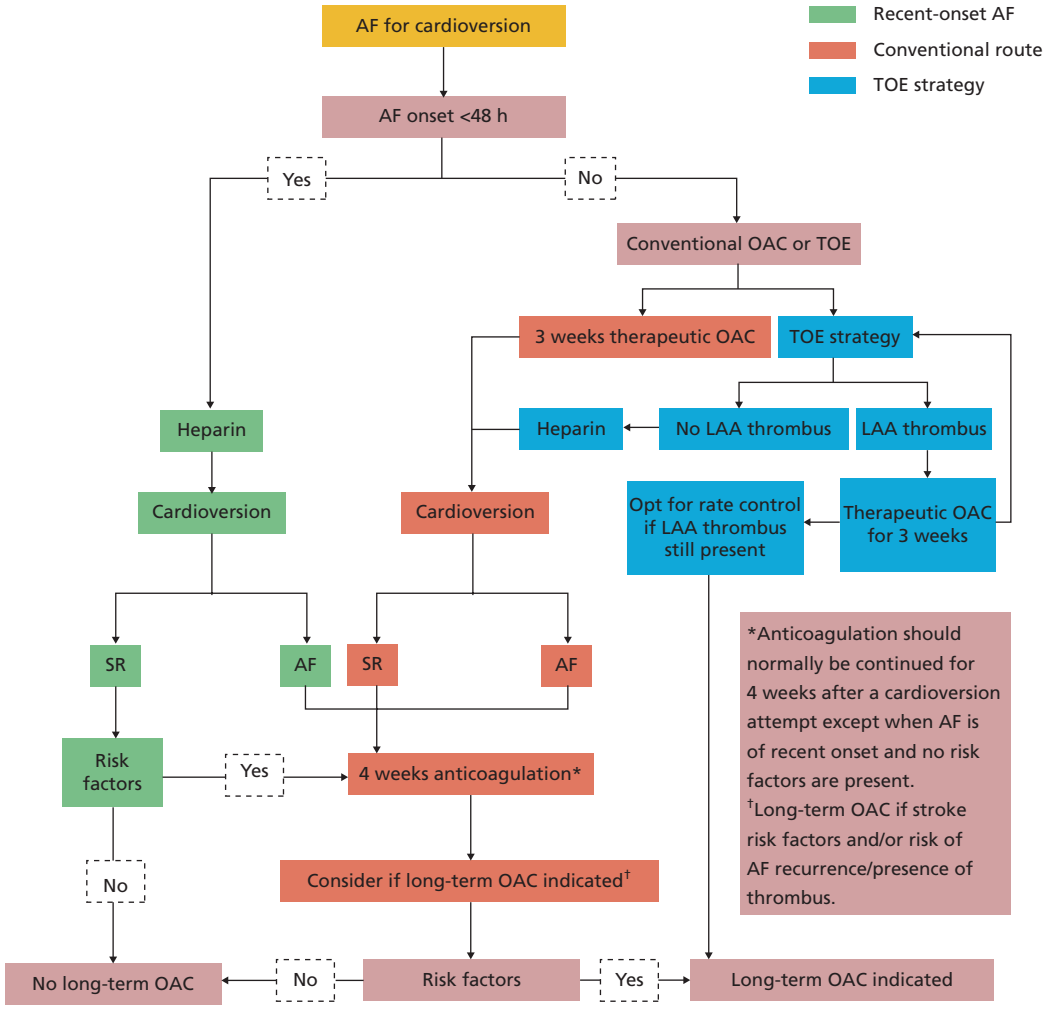


Figure 53.3 ESC 2010 GL on AF. Cardioversion of haemodynamically stable AF, the role of TOE-guided cardioversion, and subsequent anticoagulation strategy.

AF, atrial fibrillation; LA, left atrium; LAA, left atrial appendage; OAC, oral anticoagulant; SR, sinus rhythm; TOE, transoesophageal echocardiography.
ESC 2010 Guidelines for the management of atrial fibrillation. *Eur Heart J*. 2010;**31**:2369–429 with permission from Oxford University Press.

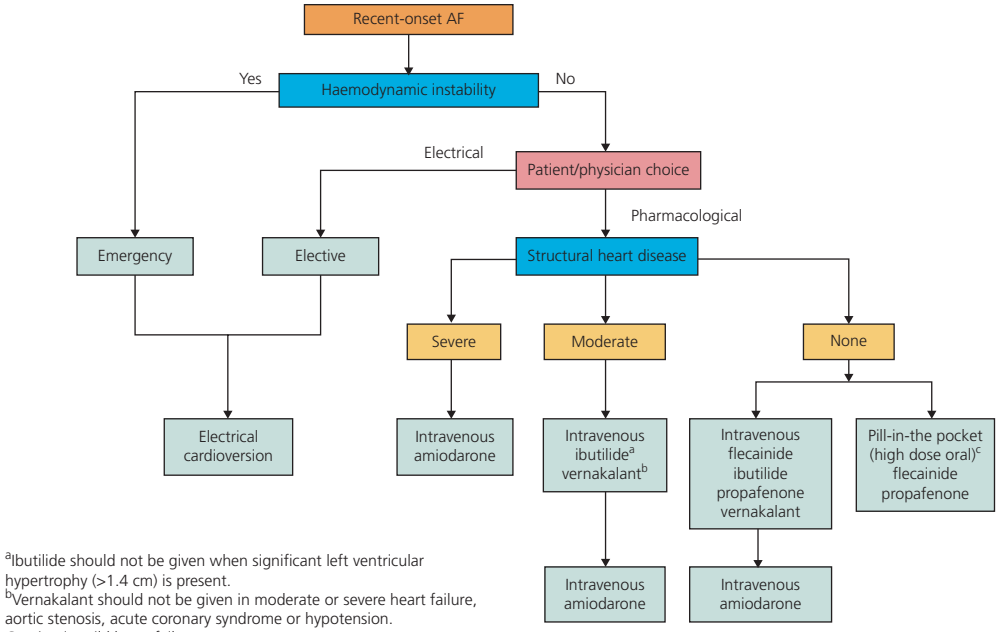


Figure 53.4 ESC 2012 update on AF. Indications for electrical and pharmacological cardioversion, and choice of antiarrhythmic drugs for pharmacological cardioversion in patients with recent-onset AF.

2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. *Europace*. 2012;**14**:1385–413.

Table 53.5 Pharmacological cardioversion of AF

ESC 2010 GL and 2012 update on AF	
IV flecainide, propafenone, ibutilide, or vernakalant for cardioversion of recent-onset AF when pharmacological cardioversion is preferred and there is no structural heart disease.	I-A
IV amiodarone in patients with recent-onset AF and structural heart disease.	I-A
A single high oral dose of flecainide or propafenone (the 'pill-in-the-pocket' approach) in selected patients with recent-onset AF and no significant structural heart disease, provided this treatment has been proven safe during previous testing in a medically secure environment.	IIa-B
Ibutilide in patients with recent-onset AF, structural heart disease, but without hypotension or manifest congestive heart failure. Serum electrolytes and the QTc interval must be within the normal range, and the patients must be closely monitored during, and for 4 h after, the infusion because of risk of proarrhythmia.	IIb-A
Vernakalant in AF ≤7 days and moderate structural heart disease (but without hypotension <100 mmHg, NYHA class III or IV heart failure, recent (<30 days) ACS, or severe aortic stenosis). It should be used with caution in patients with NYHA class I–II heart failure.	IIb-B
IV vernakalant for cardioversion of post-operative AF ≤3 days after cardiac surgery.	IIb-B
Digoxin.	III-A
Verapamil, sotalol, metoprolol.	III-B
Other beta-blocking agents and ajmaline are ineffective in converting recent-onset AF to sinus rhythm and are not recommended.	III-C
AHA/ACC/HRS 2014 GL on AF	
Flecainide, dofetilide, propafenone, and IV ibutilide for cardioversion of AF or atrial flutter provided contraindications are absent.	I-A
Amiodarone for cardioversion of AF.	IIa-A
Propafenone or flecainide ("pill-in-the-pocket") to terminate AF out of hospital once observed to be safe in a monitored setting.	IIa-B
Dofetilide should not be initiated out of hospital (QT prolongation risk).	III-B (Harm)

ESC 2010 Guidelines for the management of atrial fibrillation. *Eur Heart J*. 2010;**31**:2369–429 with permission from Oxford University Press.
AHA/ACC/HRS 2014 Guideline for the management of patients with atrial fibrillation. *J Am Coll Cardiol*. 2014;**64**:2246–80 with permission from Elsevier.
2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. *Europace*. 2012;**14**:1385–413.

Table 53.6 AHA/ACC/HRS 2014 GL on AF. Recommended drug doses for pharmacological cardioversion of AF

Drug	Route of administration	Dosage	Potential adverse effects
Amiodarone	Oral	600–800 mg daily in divided doses to a total load of up to 10 g, then 200 mg OD as maintenance	Phlebitis (IV), hypotension, bradycardia, QT prolongation, torsades de pointes (rare), GI upset, constipation, increased INR
	IV	150 mg over 10 min, then 1 mg/min for 6 h, then 0.5 mg/min for 18 h or change to oral dosing	
Dofetilide	Oral	CrCl (mL/min): Dose (mcg BID) >60: 500 40–60: 250 20–40: 125 <20: Not recommended	QT prolongation, torsades de pointes; adjust dose for renal function, body size, and age
Flecainide	Oral	200–300 mg x 1*	Hypotension, atrial flutter with 1:1 AV conduction, ventricular proarrhythmia; avoid in patients with CAD and significant structural heart disease
Ibutilide	IV	1 mg over 10 min; may repeat 1 mg once if necessary (weight <60 kg use 0.01 mg/kg)	QT prolongation, torsades de pointes, hypotension
Propafenone	Oral	450–600 mg x 1*	Hypotension, atrial flutter with 1:1 AV conduction, ventricular proarrhythmia; avoid in patients with CAD and significant structural heart disease

*Recommended given in conjunction with a beta blocker or non-dihydropyridine calcium channel antagonist administered ≥30 minutes before administering the Vaughan Williams Class IC agent.
AV, atrioventricular; BID, twice a day; CAD, coronary artery disease; CrCl, creatinine clearance; GI, gastrointestinal; INR, international normalized ratio; IV, intravenous; and OD, once daily.
AHA/ACC/HRS 2014 Guideline for the management of patients with atrial fibrillation. *J Am Coll Cardiol*. 2014;**64**:2246–80 with permission from Elsevier.

Table 53.7 Anticoagulation for cardioversion

ESC 2010 and 2012 GL Update on AF. Peri-cardioversion anticoagulation	
In AF of ≥48 h duration or when the duration of AF is unknown, OAC therapy (e.g. VKA with INR 2–3 or dabigatran) for ≥3 weeks prior to and for ≥4 weeks after cardioversion, regardless of the method (electrical or oral/IV pharmacological).	I-B
In patients with risk factors for stroke or AF recurrence, OAC therapy, whether with dose-adjusted VKA (INR 2–3) or a NOAC, should be continued lifelong, irrespective of the apparent maintenance of sinus rhythm following cardioversion.	I-B
For AF requiring immediate/emergency cardioversion because of haemodynamic instability, heparin (IV UFH bolus, followed by infusion, or weight-adjusted therapeutic dose LMWH) is recommended.	I-C
For patients with AF <48 h and at high risk of stroke, IV heparin or weight-adjusted therapeutic dose LMWH peri-cardioversion, followed by OAC with a VKA (INR 2.0–3.0) long-term.	I-B
As an alternative to anticoagulation prior to cardioversion, TOE-guided cardioversion to exclude thrombus in the left atrium or left atrial appendage.	I-B
For patients undergoing TOE-guided cardioversion who have no identifiable thrombus, cardioversion immediately after anticoagulation with heparin until OAC therapy has been established, which should be maintained for at least 4 weeks after cardioversion.	I-B
For patients undergoing a TOE-guided strategy in whom thrombus is identified, VKA (INR 2.0–3.0) for at least 3 weeks, followed by a repeat TOE to ensure thrombus resolution.	I-C
For atrial flutter undergoing cardioversion, anticoagulation is recommended as for patients with AF.	I-C
If thrombus resolution is evident on repeat TOE, cardioversion and OAC for 4 weeks or lifelong (if risk factors are present).	IIa-C
If thrombus remains on repeat TOE, an alternative strategy (e.g. rate control) may be considered.	IIb-C
For AF duration that is clearly <48 h and no thromboembolic risk factors.	IIb-C

(*Continued*)

Table 53.7 Continued

AHA/ACC/HRS 2014 GL on AF. Prevention of thromboembolism in patients with AF undergoing cardioversion	
With AF or atrial flutter for ≥48 h, or unknown duration, anticoagulation with warfarin (INR 2–3) for at least 3 wk prior to and 4 wk after cardioversion.	I-B
With AF or atrial flutter for >48 h or unknown duration requiring immediate cardioversion, anticoagulate as soon as possible and continue for at least 4 wk.	I-C
With AF or atrial flutter <48 h and high stroke risk, IV heparin or LMWH, or factor Xa or direct thrombin inhibitor, before or immediately after cardioversion, followed by long-term anticoagulation.	I-C
Following cardioversion of AF, long-term anticoagulation should be based on thromboembolic risk.	I-C
With AF or atrial flutter for ≥48 h or unknown duration and no anticoagulation for preceding 3 wk, perform a TOE prior to cardioversion, and then cardiovert if no LA thrombus is identified, provided anticoagulation is achieved before TOE and maintained after cardioversion for at least 4 wk.	IIa-B
With AF or atrial flutter ≥48 h, or unknown duration, anticoagulation with dabigatran, rivaroxaban, or apixaban for ≥3 wk prior to and 4 wk after cardioversion.	IIa-C
With AF or atrial flutter <48 h and low thromboembolic risk, IV heparin, LMWH, a new oral anticoagulant, or no antithrombotic for cardioversion.	IIb-C

ESC 2010 Guidelines for the management of atrial fibrillation. *Eur Heart J*. 2010;**31**:2369–429 with permission from Oxford University Press.
AHA/ACC/HRS 2014 Guideline for the management of patients with atrial fibrillation. *J Am Coll Cardiol*. 2014;**64**:2246–80 with permission from Elsevier.
2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. *Europace*. 2012;**14**:1385–413.

Table 53.8 AHA/ACC/HRS 2014 GL on AF. AF acute rate control common medication dosage

	Intravenous administration	Usual oral maintenance dose
Beta blockers		
Metoprolol tartrate	2.5–5.0 mg IV bolus over 2 min; up to 3 doses	25–100 mg BID
Metoprolol XL (succinate)	N/A	50–400 mg OD
Atenolol	N/A	25–100 mg OD
Esmolol	500 mcg/kg IV bolus over 1 min, then 50–300 mcg/kg/min IV	N/A
Propranolol	1 mg IV over 1 min, up to 3 doses at 2 min intervals	10–40 mg TID or QID
Nadolol	N/A	10–240 mg OD
Carvedilol	N/A	3.125–25 mg BID
Bisoprolol	N/A	2.5–10 mg OD
Non-dihydropyridine calcium channel antagonists		
Verapamil	(0.075–0.15 mg/kg) IV bolus over 2 min, may give an additional 10.0 mg after 30 min if no response, then 0.005 mg/kg/min infusion	180–480 mg OD (ER)
Diltiazem	0.25 mg/kg IV bolus over 2 min, then 5–15 mg/h	120–360 mg OD (ER)
Digitalis glycosides		
Digoxin	0.25 mg IV with repeat dosing to a maximum of 1.5 mg over 24 h	0.125–0.25 mg OD
Others		
Amiodarone	300 mg IV over 1 h, then 10–50 mg/h over 24 h	100–200 mg OD

BID, twice daily; ER, extended release; IV, intravenous; N/A, not applicable; OD, once daily; QID, four times a day; and TID, three times a day.
AHA/ACC/HRS 2014 Guideline for the management of patients with atrial fibrillation. *J Am Coll Cardiol*. 2014;**64**:2246–80 with permission from Elsevier.

Chronic therapy

Rhythm vs rate control

Randomized control trials have failed to detect significant mortality and cardiovascular morbidity differences between patients with rate (i.e. controlling ventricular response with the patient in AF) vs rhythm (i.e. maintenance of SR) control achieved with antiarrhythmic medication (Table 53.9).[100–106] This is rather surprising, in view of the deleterious effects of AF, and has been mainly attributed to the proarrhythmic effects of drugs that may negate any benefits conferred by maintenance of SR.[107,108] Assessment of quality of life was also rather inadequate in most trials. In the J-RHYTHM trial, fewer patients requested changes of assigned treatment strategy in the rhythm control vs the rate control group, which was accompanied by improvement in AF-specific quality of life scores.[104] Maintenance of SR also improved quality of life in the SAFE-T trial.[109] Finally, follow-up of most trials was relatively short. Superiority of rhythm control has been shown for certain patient groups. In the AFFIRM trial, patient ≥65 years and patients without a history of CHF had significantly better outcome with rate control therapy.[110] Improved survival with maintenance of sinus rhythm was also detected in the CHF-STAT (amiodarone in heart failure patients),[111] and DIAMOND (dofetilide in patients with LVEF <35%)[112] trials. In a recent extensive population-based, observational trial, rhythm control therapy was associated with lower rates of stroke/TIA, particularly among patients with moderate and high risk of stroke.[113] In the ATHENA trial, the primary outcome (first hospitalization due to cardiovascular events or death) occurred in 734 patients (31.9%) in the dronedarone group and in 917 patients (39.4%) in the placebo group, with a hazard ratio for dronedarone of 0.76 (p <0.001). Cardiovascular mortality was also reduced by dronedarone (3.9% vs 2.7%; p = 0.003).[114] However, dronedarone is contraindicated in patients with heart failure[115] and in permanent AF (see Drugs for rhythm control).[116] In patients with LV dysfunction, there is a component of AF-induced cardiomyopathy that is independent of an uncontrolled rate, and catheter ablation of AF may be beneficial even when there is good heart rate control.[117]

Recommendations are provided in Table 53.10.

Drugs for rate control

Beta blockers (such as metoprolol, bisoprolol, nebivolol, and carvedilol) are the safest drugs.

Verapamil and **diltiazem** are also safe but are contraindicated in heart failure. Diltiazem has been found superior to carvedilol and metoprolol in patients with permanent AF and preserved LV function.[118]

Digoxin is only effective at rest. Life-threatening proarrhythmia may occur, especially with overdosing in the elderly. In a recent analysis of the AFFIRM study, digoxin was associated with a significant increase in all-cause mortality in patients with AF after correcting for clinical characteristics and co-morbidities, regardless of gender or of the presence or absence of HF.[119] This could be due to relatively high serum digoxin levels (≥1.0 ng/mL), required by the study for rate control. In another report on the AFFIRM, however, with very careful propensity score matching, no evidence of increased mortality with digoxin was found in patients with paroxysmal or persistent AF,[120] and this was also the finding of a study on data from the ORBIT-AF registry.[121] However, increased mortality was also seen in a retrospective analysis of the ROCKET-AF trial,[122] in an observational study on data from the TREAT-AF trial regardless of cardiovascular comorbidities and concomitant therapies,[123] and in the retrospective ATRIA-CRVN study on patients without heart failure.[124] Increased mortality was also detected in a recent meta-analysis.[125] Thus, the issue is debatable.

Amiodarone IV is the drug of choice (together with IV beta blockers) for slowing the ventricular rate in patients with acute coronary syndromes. In stable patients with AF, it should not be used for rate response due to its thyroid and pulmonary toxicity, unless all other drugs have failed. Strict rate control (<80 bpm) has not been found superior to lenient rate control. (<110 bpm).[126]

Recommendations for drugs and doses are presented in Figure 53.5, and Tables 53.8 and 53.11.

AV nodal modification

In patients in whom drug or pulmonary vein ablation therapy has failed or there are signs of tachycardiopathy, **AV nodal catheter ablation or modification**, followed by **ventricular** or **biventricular pacing**, may be necessary (Table 53.12).[127,128] Septal RV or biventricular pacing if LVEF ≤35% are superior to apical RV pacing in this respect.[129] The increased risk of polymorphic VT and torsades that has been detected after complete AV nodal ablation (as opposed to modification) is probably transient, although 24–48 h monitoring may be needed.

Drugs for rhythm control

In a meta-analysis of 44 randomized trials with 11 322 patients, the efficacy of drugs, such as disopyramide, quinidine, flecainide, propafenone, amiodarone, dofetilide, and sotalol, for maintenance of SR was 40–60% per year. All drugs resulted in increased withdrawals due to side effects, and all, except amiodarone and propafenone, increased proarrhythmia. No drug reduced mortality, whereas disopyramide and quinidine increased

mortality.[108] In a subsequent meta-analysis, a trend for increased mortality was identified for sotalol and, possibly, amiodarone.[130]

Amiodarone is the most effective drug,[131] but its long-term use is limited by its toxic effects, mainly on the thyroid, lungs, and liver (especially at doses >200 mg od). The possibility of a trend towards increased mortality with its long-term use has also been raised.[130] It is the drug of choice in heart failure NYHA III and IV. Proarrhythmia is rare, but QT monitoring is advisable (Table 53.13). Although it inhibits the clearance of warfarin, a paradoxical increase in stroke has been reported in anticoagulated patients.[132]

Dronedarone is less effective as well as less toxic than amiodarone at least over 1 year follow-up (dronedarone vs placebo in ADONIS and EURIDIS trials).[133] It reduces hospitalization due to paroxysmal AF or atrial flutter (ATHENA trial),[114] even in the presence of ischaemic heart disease.[134] It is contraindicated in NYHA III or IV or recently decompensated (<4 weeks) heart failure (increased mortality in the ANROMEDA trial)[115] and in patients with permanent AF (PALLAS trial).[116] The PALLAS trial on patients with >2 years AF, 70% of whom had NYHA I–III heart failure, was stopped following increased cardiovascular mortality due to the drug.[116] Thus, dronedarone is not indicated in patients who cannot, or will not, be converted into normal sinus rhythm because it doubles the rate of cardiovascular death, stroke, and heart failure. It may cause creatinine level elevation (2.5% of patients) and, very rarely, severe hepatic impairment, although in a recent Swedish registry on patients with paroxysmal AF, no increased risk of death or liver disease was detected.[135] Although it mildly prolongs the QT, the risk of torsades is negligible.[130] It may be given in patients with recurrent AF for the maintenance of sinus rhythm (ESC 2012 I-A) and to reduce hospitalization for AF in patients in sinus rhythm with a history of non-permanent AF. Care is needed with concomitant administration of digoxin,[116] and this combination should be probably avoided.[3]

Beta blockers (other than sotalol) are safe but modestly effective.

Sotalol A beta blocker with class III properties, at high doses, is equally effective with amiodarone in converting AF to SR (24% vs 27%, respectively) but less effective than maintaining SR (approximately 30% vs 47% at 1 year, respectively).[109] Sotalol should not be used in the presence of ventricular hypertrophy or significant repolarization abnormalities.[136] The main concern is proarrhythmia due to QT prolongation, and a trend towards increased mortality has been reported,[130,137] although not validated in all studies.[138] Careful monitoring of the QT is advisable and discontinuation of the drug when QT >500 ms (see VT).

Flecainide approximately doubles the likelihood of maintaining sinus rhythm. It is contraindicated in coronary artery disease and LV dysfunction and cardiac hypertrophy or infiltration,[139] and should be stopped if the QRS increases by >25% (risk of monomorphic VT). Concomitant administration of beta blockers reduces proarrhythmic risk and controls ventricular rate in case of conversion to atrial flutter.[140] Caution is necessary when using sodium channel blocking drugs as monotherapy in athletes with AF. These drugs may lead to (slow) atrial flutter, with 1:1 conduction to the ventricles during high sympathetic tone. Short-term flecainide administration (4 weeks) after cardioversion is less effective than long-term treatment (80%), but can prevent recurrences of atrial fibrillation.[141]

Propafenone is safer and has a mild beta-blocking activity, but the same precautions as with flecainide should be taken.

Dofetilide has also been found useful and safe in patients with AF and impaired LV function (DIAMOND trial), since mortality was not different compared to controls (>50% in 3 years).[142]

Recommendations for drug usage and complications are presented in Tables 53.14 to 53.16, and Figures 53.6 and 53.7.

The primary goal of rhythm control drug therapy is to selectively prolong the refractory period in the atrium and avoid the risk of ventricular proarrhythmia. **Ranolazine** is an anti-ischaemic drug that was shown to reduce AF in the MERLIN-TIMI 36 trial. It blocks I_{Na}, I_{CaL}, and I_{Kr}, and it is postulated that the late sodium current contributes to the prolongation of the action potential duration associated with reduced I_{Kr} at slow heart rates.[143] Theoretically, inhibition of I_{Na} with ranolazine or vernakalant may reduce the risk of TDP associated with I_{Kr} inhibition by drugs, such as dofetilide or sotalol.[142] Combination therapy with amiodarone plus ranolazine or dronedarone plus ranolazine has been shown experimentally to have marked synergistic effects that result in atrium-selective blockade of sodium channels and suppression of AF.[144]

Table 53.9 Trials for rhythm control

Trial	Patients	Mean age (years)	Mean F-U (years)	Inclusion criteria	Primary outcome	P
PIAF (2000)	252	61.0	1.0	Persistent AF	Symptomatic improvement	0.32
AFFIRM (2002)	4060	69.7	3.5	Paroxysmal AF or persistent AF, age ≥65 years, or risk of stroke or death	All-cause mortality	0.08
RACE (2002)	522	68.0	2.3	Persistent AF or flutter for <1 years and 1–2 cardioversions over 2 years	Composite: cardiovascular death, CHF, severe bleeding, pacemaker implantation, thromboembolic events, severe adverse effects of antiarrhythmic drugs	0.11
STAF (2003)	200	66.0	1.6	Persistent AF, LA size >45 mm, CHF NYHA II–IV, LVEF <45%	Composite: overall mortality, cerebrovascular complications	0.99
HOT CAFÉ (2004)	205	60.8	1.7	Persistent AF, age 50–75 years	Composite: death, thromboembolism, major haemorrhage	>0.71
AF-CHF (2008)	1376	66	3.1	CHF, LVEF ≤35%, history of AF	Cardiovascular death	0.59
J-RHYTHM (2009)	823	64.7	1.6	Paroxysmal AF	Composite: total mortality, cerebral infarction, systemic embolism, major bleeding, hospitalization for heart failure, or physical/psychological disability	0.012

Table 53.10 ESC 2010 GL on AF. Recommendations for rate and rhythm control of AF

Rate control as the initial approach in elderly patients with AF and minor symptoms (EHRA score 1)	I-A
Rate control throughout a rhythm control approach to ensure adequate control of the ventricular rate during recurrences of AF.	I-A
Rhythm control in patients with symptomatic (EHRA score ≥2) AF despite adequate rate control.	I-B
Rhythm control in AF-related heart failure for improvement of symptoms.	IIa-B
Rhythm control as an initial approach in young symptomatic patients in whom catheter ablation treatment has not been ruled out.	IIa-C
Rhythm control in AF secondary to a trigger or substrate that has been corrected (e.g. ischaemia, hyperthyroidism).	IIa-C

ESC 2010 Guidelines for the management of atrial fibrillation. *Eur Heart J*. 2010;**31**:2369–429 with permission from Oxford University Press.

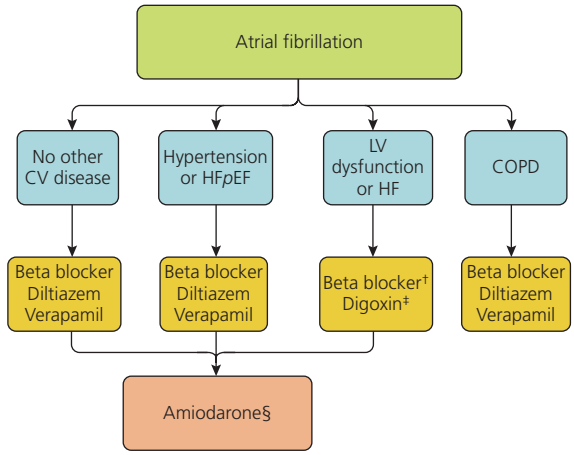


Figure 53.5 AHA/ACC/HRS 2014 GL on AF. Approach to selecting drug therapy for ventricular rate control.

Drugs are listed alphabetically.
† Beta blockers should be instituted following stabilization of patients with decompensated HF. The choice of beta blocker (cardio-selective, etc.) depends on the patient's clinical condition.
‡ Digoxin is not usually first-line therapy. It may be combined with a beta blocker and/or a non-dihydropyridine calcium channel blocker when ventricular rate control is insufficient and may be useful in patients with HF.
§ In part because of concern over its side-effect profile, use of amiodarone for chronic control of ventricular rate should be reserved for patients who do not respond to or are intolerant of beta blockers or non-dihydropyridine calcium antagonists.
COPD indicates chronic obstructive pulmonary disorder; CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; and LV, left ventricular.
AHA/ACC/HRS 2014 Guideline or the Management of Patients with Atrial Fibrillation. *J Am Coll Cardiol*. 2014;**64**:2246–80 with permission from Elsevier.

Table 53.11 Rate control of AF

ESC 2010 GL on AF. Acute rate control	
IV beta blockers or non-dihydropyridine calcium channel antagonists in the acute setting in the absence of pre-excitation to slow the ventricular response to AF, exercising caution in hypotension or heart failure.	I-A
IV digoxin or amiodarone in the acute setting to control the heart rate in concomitant heart failure or hypotension.	I-B
In pre-excitation, preferred drugs are class I antiarrhythmic drugs or amiodarone.	I-C
Beta blockers, non-dihydropyridine calcium channel antagonists, digoxin, and adenosine in pre-excited AF.	III-C
ESC 2010 and 2012 GL update on AF. Drugs for long-term rate control of AF	
Beta blockers, non-dihydropyridine calcium channel antagonists, digitalis, or a combination thereof in paroxysmal, persistent, or permanent AF. Choice individualized and dose modulated to avoid bradycardia.	I-B
In activity-related symptoms, the adequacy of rate control should be assessed during exercise, and therapy should be adjusted to achieve a physiological chronotropic response and to avoid bradycardia.	I-C
In pre-excitation AF or in patients with a history of AF, preferred drugs are propafenone or amiodarone.	I-C
Initiate treatment with a lenient rate control protocol, aimed at a resting heart rate <110 bpm.	IIa-B
Adopt a stricter rate control strategy when symptoms persist or tachycardiomyopathy occurs, despite lenient rate control: resting heart rate <80 bpm and heart rate during moderate exercise <110 bpm. After achieving the strict heart rate target, assess safety with 24 h Holter monitor.	IIa-B
Digoxin in heart failure and LV dysfunction and in sedentary (inactive) patients.	IIa-C
Oral amiodarone when other measures are unsuccessful or contraindicated.	IIb-C
Digitalis as the sole agent to control the rate of ventricular response in paroxysmal AF.	III-B
Dronedarone is not recommended in patients with permanent AF.	III-B

(*Continued*)

Table 53.11 Continued

AHA/ACC/HRS 2014 GL on AF. Rate control of AF	
Beta blocker or non-dihydropyridine calcium channel antagonist for paroxysmal, persistent, or permanent AF.	I-B
IV beta blockers or nondihydropyridine calcium channel blocker to slow ventricular heart rate in the acute setting in patients without pre-excitation. In haemodynamically unstable patients, electrical cardioversion.	I-B
In AF-related symptoms during activity, assess heart rate control during exertion, adjusting pharmacological treatment.	I-C
A heart rate control (resting heart rate <80 bpm) strategy for symptomatic management of AF.	IIa-B
IV amiodarone for rate control in critically ill patients without pre-excitation.	IIa-B
AV nodal ablation with permanent ventricular pacing when pharmacological management is inadequate and rhythm control is not achievable.	IIa-B
Lenient rate control strategy (resting heart rate <110 bpm) when patients remain asymptomatic and LV systolic function preserved.	IIb-B
Oral amiodarone for ventricular rate control when other measures are unsuccessful or contraindicated.	IIb-C
AV nodal ablation should not be performed without prior attempts to achieve rate control with medications.	III-C (harm)
Non-dihydropyridine, calcium channel antagonists in decompensated heart failure.	III-C (harm)
Digoxin, non-dihydropyridine, calcium channel antagonists, or amiodarone in pre-excitation and AF.	III-B (harm)
Dronedarone for rate control in permanent AF.	III-B (harm)

ESC 2010 Guidelines for the management of atrial fibrillation. *Eur Heart J*. 2010;**31**:2369–429 with permission from Oxford University Press.
AHA/ACC/HRS 2014 Guideline for the management of patients with atrial fibrillation. *J Am Coll Cardiol*. 2014;**64**:2246–80 with permission from Elsevier.
2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. *Europace*. 2012;**14**:1385–413.

Table 53.12 ESC 2010 GL on AF. Ablation of the AV node

When the rate cannot be controlled with pharmacological agents and when AF cannot be prevented by antiarrhythmic therapy or is associated with intolerable side effects and direct catheter-based or surgical ablation of AF is not indicated, has failed, or is rejected.	IIa-B
Patients with permanent AF and an indication for CRT (NYHA III or ambulatory class IV symptoms despite optimal medical therapy, LVEF <35%, QRS width ≥130 ms).	IIa-B
CRT non-responders in whom AF prevents effective biventricular stimulation and amiodarone is ineffective or contraindicated.	IIa-C
Biventricular stimulation after AV node ablation, in any type of AF and severely depressed LV function (LVEF ≤35%), and severe heart failure symptoms (NYHA III or IV).	IIa-C
When tachycardia-mediated cardiomyopathy is suspected and the rate cannot be controlled with pharmacological agents, and direct ablation of AF is not indicated, has failed, or is rejected.	IIb-C
Ablation of the AV node with consecutive implantation of a CRT device may be considered in permanent AF, LVEF ≤35%, and NYHA I or II symptoms on optimal medical therapy to control heart rate when pharmacological therapy is insufficient or associated with side effects.	IIb-C
Catheter ablation of the AV node without a prior trial of medication or catheter ablation for AF to control the AF and/or ventricular rate.	III-C
Recommendations for pacemakers after atrioventricular node ablation	
CRT pacemaker in any type of AF, moderately depressed LV function (LVEF ≤45%), and mild heart failure symptoms (NYHA II).	IIb-C
DDD pacemaker with mode-switch function in paroxysmal AF and normal LV function.	IIb-C
VVIR pacemaker in persistent or permanent AF and normal LV function.	IIb-C

ESC 2010 Guidelines for the management of atrial fibrillation. *Eur Heart J*. 2010;**31**:2369–429 with permission from Oxford University Press.

Table 53.13 Adverse reactions to amiodarone

Reaction	Incidence (%)	Diagnosis	Management
Pulmonary	2	Cough and/or dyspnoea, especially with local or diffuse opacities on high-resolution CT scan and decrease in DLCO from baseline	Usually, discontinue drug; corticosteroids may be considered in more severe cases; occasionally, can continue drug if levels high and abnormalities resolve; rarely, continue amiodarone with corticosteroid if no other option
Gastrointestinal tract	30	Nausea, anorexia, and constipation	Symptoms may decrease with decrease in dose
	15–30	AST or ALT level greater than 2 times normal	If hepatitis considered, exclude other causes
	<3	Hepatitis and cirrhosis	Consider discontinuation, biopsy, or both to determine whether cirrhosis is present
Thyroid	4–22	Hypothyroidism	L-thyroxine
	2–12	Hyperthyroidism	Corticosteroids, propylthiouracil, or methimazole; may need to discontinue drug; may need thyroidectomy
Skin	<10	Blue discoloration	Reassurance; decrease in dose
	25–75	Photosensitivity	Avoidance of prolonged sun exposure; sunblock; decrease in dose
Central nervous system	3–30	Ataxia, paraesthesiae, peripheral polyneuropathy, sleep disturbance, impaired memory and tremor	Often dose-dependent and may improve, or resolve, with dose adjustment
Ocular	<5	Halo vision, especially at night	Corneal deposits the norm; if optic neuropathy occurs, discontinue
	≤1	Optic neuropathy	Discontinue drug, and consult an ophthalmologist
	>90	Photophobia, visual blurring, and microdeposits	
Heart	5	Bradycardia and AV block	May need permanent cardiac pacing
	<1	Proarrhythmia	May need to discontinue the drug
Genitourinary	<1	Epididymitis and erectile dysfunction	Pain may resolve spontaneously

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLCO, diffusion capacity of carbon monoxide.
Data sourced from ESC 2010 Guidelines for the management of atrial fibrillation. *Eur Heart J*. 2010;**31**:2369–429 with permission from Oxford University Press.
Camm, John A *et al*. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J*. 2012;33 with permission from Oxford University Press.
AHA/ACC/HRS 2014 Guideline for the management of patients with atrial fibrillation. *J Am Coll Cardiol*. 2014;**64**:2246–80 with permission from Elsevier.

Table 53.14 Rhythm control of AF

ESC 2010 and 2012 GL update on AF. Drugs for rhythm control	
Depending on underlying heart disease:	
Amiodarone	I-A
Dronedarone	I-A
Flecainide	I-A
Propafenone	I-A
d,l-sotalol	I-A
Amiodarone is more effective in maintaining sinus rhythm than sotalol, propafenone, flecainide (by analogy), or dronedarone.	I-A
But, because of its toxicity profile, should generally be used when other agents have failed or are contraindicated.	I-C
Amiodarone in severe heart failure, NYHA III and IV, or recently unstable (decompensation within the prior month) NYHA class II.	I-B
Dronedarone or flecainide or propafenone or sotalol for patients without significant structural heart disease.	I-A
Beta blockers for prevention of adrenergic AF.	I-C
Other antiarrhythmic drug is considered if one antiarrhythmic drug fails to reduce the recurrence of AF to a clinically acceptable level.	IIa-C

(*Continued*)

Table 53.14 Continued

Dronedarone to reduce cardiovascular hospitalizations in patients with non-permanent AF and cardiovascular risk factors.	IIa-B
Beta blockers for rhythm (plus rate) control in patients with a first episode of AF.	IIa-C
Disopyramide in patients with vagally mediated AF.	IIb-B
Short-term (4 weeks) antiarrhythmic therapy after cardioversion may be considered in selected patients, e.g. those at risk for therapy-associated complications.	IIb-B
Dronedarone in patients with NYHA III and IV or with recently unstable (decompensation within the prior month) NYHA II heart failure.	III-B
Antiarrhythmic drug therapy for maintenance of sinus rhythm in patients with advanced sinus node disease or AV node dysfunction, unless they have a functioning permanent pacemaker.	III-C
AHA/ACC/HRS 2014 on AF. Pharmacological agents for preventing AF and maintaining sinus rhythm	
Before initiating antiarrhythmic drug therapy, treat precipitating or reversible causes of AF.	I-C
The following antiarrhythmic drugs are recommended, depending on underlying heart disease and comorbidities: a. Amiodarone; b. Dofetilide; c. Dronedarone; d. Flecainide; e. Propafenone; f. Sotalol.	I-A
Risks of the antiarrhythmic drug, including proarrhythmia, should be considered before initiating therapy.	I-C
Owing to its potential toxicities, amiodarone should only be used after consideration of risks and when other agents have failed or are contraindicated.	I-C
Continue current antiarrhythmic drug therapy in the setting of infrequent, well-tolerated recurrences of AF, when the drug has reduced the frequency or symptoms of AF.	IIb-C
A rhythm-control strategy with pharmacological therapy in patients with AF for the treatment of tachycardia-induced cardiomyopathy.	IIa-C
Antiarrhythmic drugs for rhythm control when AF becomes permanent.	III-C (harm)—(III-B for dronedarone)
Dronedarone should not be used in NYHA class III and IV heart failure or with an episode of decompensated heart failure in the past 4 weeks.	III-B (harm)

ESC 2010 Guidelines for the management of atrial fibrillation. *Eur Heart J*. 2010;**31**:2369–429 with permission from Oxford University Press.
2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. *Europace*. 2012;**14**:1385–413.

Table 53.15 AHA/ACC/HRS 2014 on AF. Dosage and safety considerations for maintenance of sinus rhythm in AF

Drug	Usual doses	Exclude/use with caution	Major pharmacokinetic drug interactions
Vaughan Williams Class IA			
Disopyramide	Immediate release: 100–200 mg once every 6 h Extended release: 200–400 mg once every 12 h	HF Prolonged QT interval Prostatism, glaucoma Avoid other QT interval-prolonging drugs	Metabolized by *CYP3A4*: caution with inhibitors (e.g., verapamil, diltiazem, ketoconazole, macrolide antibiotics, protease inhibitors, grapefruit juice) and inducers (e.g., rifampin, phenobarbital, phenytoin)
Quinidine	324–648 mg every 8 h	Prolonged QT interval Diarrhoea	Inhibits *CYP2D6*: ↑ concentrations of tricyclic antidepressants, metoprolol, antipsychotics; ↓ efficacy of codeine Inhibits P-glycoprotein: ↑ digoxin concentration
Vaughan Williams Class IC			
Flecainide	50–200 mg once every 12 h	Sinus or AV node dysfunction HF CAD Atrial flutter Infranodal conduction disease Brugada syndrome Renal or liver disease	Metabolized by *CYP2D6* (inhibitors include quinidine, fluoxetine, tricyclics; also genetically absent in 7–10% of population) and renal excretion (dual impairment can ↑↑ plasma concentration)

(*Continued*)

Table 53.15 Continued

Propafenone	Immediate release: 150–300 mg once every 8 h Extended release: 225–425 mg once every 12 h	Sinus or AV node dysfunction HF CAD Atrial flutter Infranodal conduction disease Brugada syndrome Liver disease Asthma	Metabolized by *CYP2D6* (inhibitors include quinidine, fluoxetine, tricyclics; also genetically absent in 7–10% of population)—poor metabolizers have ↑ beta blockade Inhibits P-glycoprotein: ↑ digoxin concentration Inhibits P-glycoprotein: ↑ warfarin concentration (↑ INR 25%)
Vaughan Williams Class III			
Amiodarone	Oral: 400–600 mg daily in divided doses for 2–4 wk; maintenance typically 100–200 mg OD IV: 150 mg over 10 min; then 1 mg/min for 6 h; then 0.5 mg/min for 18 h or change to oral dosing; after 24 h, consider decreasing dose to 0.25 mg/min	Sinus or AV node dysfunction Infranodal conduction disease Lung disease Prolonged QT interval	Inhibits most CYPs to cause drug interaction: ↑ concentrations of warfarin (↑ INR 0–200%), statins, many other drugs Inhibits P-glycoprotein: ↑ digoxin concentration
Dofetilide	125–500 mcg once every 12 h	Prolonged QT interval Renal disease Hypokalaemia Diuretic therapy Avoid other QT interval prolonging drugs	Metabolized by *CYP3A*: verapamil, HCTZ, cimetidine, ketoconazole, trimethoprim, prochlorperazine, and megestrol are contraindicated; discontinue amiodarone at least 3 mo before initiation
Dronedarone	400 mg once every 12 h	Bradycardia HF Long-standing persistent AF/flutter Liver disease Prolonged QT interval	Metabolized by *CYP3A*: caution with inhibitors (e.g., verapamil, diltiazem, ketoconazole, macrolide antibiotics, protease inhibitors, grapefruit juice) and inducers (e.g. rifampin, phenobarbital, phenytoin) Inhibits *CYP3A*, *CYP2D6*, P-glycoprotein: ↑ concentrations of some statins, sirolimus, tacrolimus, beta blockers, digoxin
Sotalol	40–160 mg once every 12 h	Prolonged QT interval Renal disease Hypokalaemia Diuretic therapy Avoid other QT interval prolonging drugs Sinus or AV nodal dysfunction HF Asthma	None (renal excretion)

AF indicates atrial fibrillation; AV, atrioventricular; CAD, coronary artery disease; HCTZ, hydrochlorothiazide; HF, heart failure; INR, international normalized ratio; IV, intravenous; and OD, once daily.
AHA/ACC/HRS 2014 Guideline for the management of patients with atrial fibrillation. *J Am Coll Cardiol*. 2014;**64**:2246–80 with permission from Elsevier.

Table 53.16 ESC 2010 GL on AF. Suggested doses and main caveats for commonly used antiarrhythmic drugs

ESC 2010 GL on AF. Suggested doses and main caveats for commonly used antiarrhythmic drugs

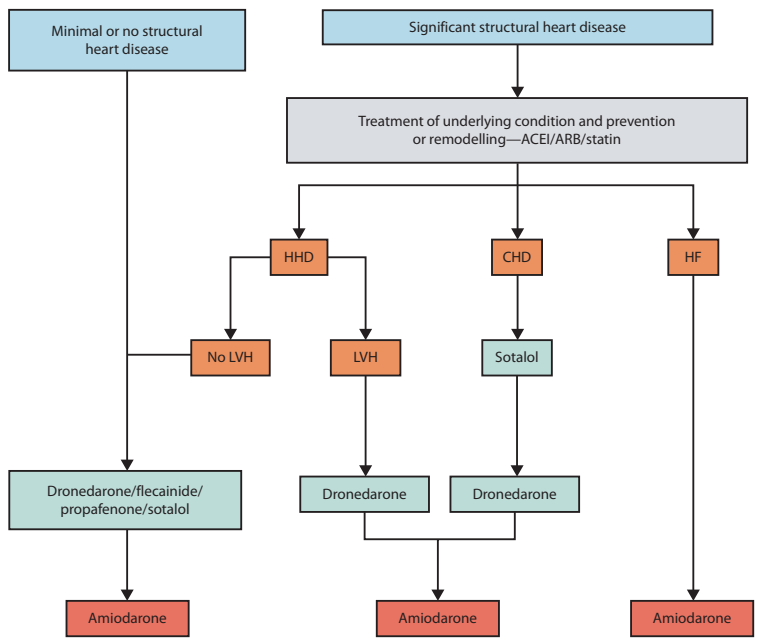
Drug	Dose	Main contraindications and precautions	ECG features prompting lower dose or discontinuation	AV nodal slowing
Disopyramide	100–250 mg tds	Contraindicated in systolic heart failure Caution when using concomitant therapy with QT-prolonging drugs	QT interval >500 ms	None
Flecainide	100–200 mg bd	Contraindicated if creatinine clearance <50 mg/mL, in coronary artery disease, reduced LV ejection fraction	QRS duration increase >25% above baseline	None
Flecainide XL	200 mg od	Caution in the presence of conduction system disease		

(*Continued*)

Table 53.16 Continued

Propafenone	150–300 mg tds	Contraindicated in coronary artery disease, reduced LV ejection fraction	QRS duration increase >25% above baseline	Slight
Propafenone SR	225–425 mg bd	Caution in the presence of conduction system disease and renal impairment		
d.l-Sotalol	80–160 mg bd	Contraindicated in the presence of significant LV hypertrophy, systolic heart failure, pre-existing QT prolongation, hypokalaemia creatinine clearance <50 mg/mL. Moderate renal dysfunction requires careful adaptation of dose	QT interval >500 ms	Similar to high-dose beta blockers
Amiodarone	600 mg od for 4 weeks, 400 mg od for 4 weeks, then 200 mg od	Caution when using concomitant therapy with QT-prolonging drugs, heart failure. Dose of vitamin K antagonists and of digitoxin/digoxin should be reduced.	QT interval >500 ms	10–12 bpm in AF
Dronedarone	400 mg bd	Contraindicated in NYHA class III–IV or unstable heart failure, during concomitant therapy with QT-prolonging drugs, powerful CYP3A4 inhibitors, and creatinine clearance <30 mg/mL. Dose of digitoxin/digoxin should be reduced. Elevations in serum creatinine of 0.1–0.2 mg/dL are common and do not reflect reduced renal function.	QT interval >500 ms	10–12 bpm in AF

AF, atrial fibrillation; AV, atrioventricular; bpm, beats per minute; CYP, cytochrome P; ECG, electrocardiogram; LV, left ventricular; NYHA, New York Heart Association.
ESC 2010 Guidelines for the management of atrial fibrillation. *Eur Heart J*. 2010;**31**:2369–429 with permission from Oxford University Press.



ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; HHD = hypertensive heart disease; CHD = coronary heart disease; HF = heart failure; LVH = left ventricular hypertrophy; NYHA = New York Heart Association. Antiarrhythmic agents are listed in alphabetical order within each treament box.

Figure 53.6 ESC 2012 update on AF. Choice of antiarrhythmic drug, according to underlying pathology.

2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. *Europace*. 2012;**14**:1385–413.

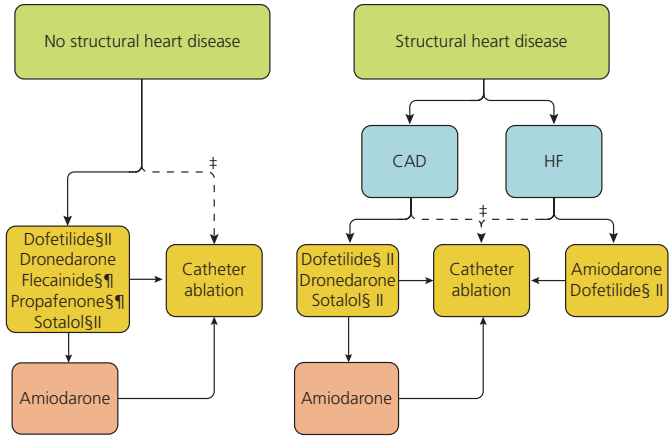


Figure 53.7 AHA/ACC/HRS 2014 GL on AF. Strategies for rhythm control in patients with paroxysmal and persistent AF.

Catheter ablation is only recommended as first-line therapy for patients with paroxysmal AF (Class IIa recommendation).
Drugs are listed alphabetically.
‡ Depending on patient preference when performed in experienced centres.
§ Not recommended with severe LVH (wall thickness >1.5 cm).
‖ Should be used with caution in patients at risk for torsades de pointes ventricular tachycardia.
¶ Should be combined with AV nodal blocking agents.
AF indicates atrial fibrillation; CAD, coronary artery disease; HF, heart failure; and LVH, left ventricular hypertrophy.
AHA/ACC/HRS 2014 Guideline or the Management of Patients with Atrial Fibrillation. *J Am Coll Cardiol.* 2014;**64**:2246–80 with permission from Elsevier.

Anticoagulation

Adjusted-dose warfarin and antiplatelet agents reduce stroke by approximately 60% and 20%, respectively, in patients with AF.[145] In general, oral anticoagulation is preferred in patients with CHA_2DS_2-VASc score ≥2 and no anticoagulation in patients with score 0 (Table 53.17 and Figure 53.8). These criteria are superior for selection of anticoagulation than detection of atrial tachyarrhythmias by implantable devices such as ICDs.[146] Patients with congenital heart disease and AF should receive anticoagulation regardless of other risk factors.[147] Anticoagulation in patients with one stroke risk factor (CHA_2DS_2-VASc score 1 for men and 2 in women), should be individualized since the risk of stroke is low. Low risk patients (score 0 for male and 1 for female) have a truly low risk of stroke, but there is a significant increase in the events rate in the presence of an additional risk factor, and in this case anticoagulation is indicated.[148–150] Patients older than 65 years, and especially women, are at high risk of ischaemic stroke,[151] and anticoagulation reduces mortality.[152,153] The risk of bleeding is assessed by schemes, such as the HAS-BLED, ATRIA and HEMORR2HAGES.[154] A HAS-BLED score ≥3 indicates 'high risk' (Table 53.18). A history of falls should not be considered an absolute contraindication to anticoagulation.[150] New oral anticoagulants are now recommended for non-valvular AF as a potential alternative to warfarin.[155] Nonsteroidal anti-inflammatory drugs (NSAID) increase the risk of both serious bleeding and thromboembolism in anticoagulated patients with AF.[156]

Aspirin The protective value of acetylsalicylic acid as monotherapy has been questioned, and it may even increase the risk of ischaemic stroke in the elderly.[157,158] Warfarin is superior to aspirin in the elderly (>75 years), offering a 52% reduction in yearly risk of a combined endpoint of stroke, intracranial haemorrhage, and peripheral embolism (1.8% vs 3.8%) (BAFTA trial).[152] Thus, aspirin for stroke prevention in AF should be limited to patients who refuse any form of oral anticoagulation,[3] or, perhaps, to those with $CHAD_2DS_2$-VASC score 1.[1]

Aspirin and clopidogrel offer increased protection compared to aspirin alone,[1] albeit at an increased risk of major bleeding,[159] and are preferred when warfarin is contraindicated. Still, however, aspirin and clopidogrel offer less protection than warfarin (relative risk 1.44 for stroke, peripheral embolism, MI, and vascular death).[159] In patients who sustain an ischaemic stroke despite INR 2–3, targeting a higher INR should be considered (3–3.5), rather than adding an antiplatelet agent, since major bleeding risk starts at INR >3.5.[2]

Warfarin is a racemic mixture of isomers that inhibits synthesis of vitamin K-dependent coagulation factors. The effective dose of warfarin varies significantly among individuals, due to genetic variations in its receptor, metabolism via the cytochrome P450 system, and interactions with other drugs, vitamins, and green vegetables. Despite anticoagulation of more elderly patients with AF,

intracerebral haemorrhage is considerably lower than in the past, ranging from 0.1 to 0.6%. The risk increases with INR >3.5–4. Recommended INR values for AF are 2–3. Pharmacogenetic testing for guiding doses, by means of genotyping for variants CYP2C9 and VKORG1 that are associated with reduced clearance and thus a decrease in warfarin requirement, is not clinically useful.[160] Patients initiating warfarin may be at an increased risk of stroke during the first 30 days of treatment, probably due to rapid deactivation of proteins S and C, two endogenous anticoagulants.[161] In high risk cases, warfarin should be started with concomitant LMW heparin administration for the initial 3–5 days of treatment. Increased levels of coronary calcification has been recently reported in patients on long-term therapy with vitamin K antagonists.[162]

Non-vitamin K antagonist oral anticoagulants (NOACs) They are ***direct thrombin (dabigatran)*** or ***factor Xa (rivaroxaban, apixaban, edoxaban) inhibitors***. Thrombin catalyses the final step in the coagulation cascade by converting fibrinogen to fibrin. Factor Xa, in conjunction with factor Va, mediates activation of prothrombin to thrombin. In patients with **non-valvular AF** (ie no mechanical valves or rheumatic mitral disease), they offer a relative 50% reduction in the risk of intracranial haemorrhage and haemorrhagic stroke compared to warfarin that is also maintained in the elderly. There are no clear interactions with food, and no need for frequent laboratory monitoring and dose adjustments.[163,164] In the elderly (≥75 years) apixaban and edoxaban also offer a reduced rate of gastrointestinal bleeding compared to warfarin. Rivaroxaban offers a similar risk whereas dabigatran (both 150 mg bd and 110 mg bd) is associated with an increased risk of gastrointestinal bleeding.[165] Anticoagulation with these agents has a considerably higher cost than warfarin.[166] NOACs are contraindicated in patients with rheumatic mitral stenosis and mechanical heart valves.[167] It should also be noted that all major clinical trials have been tried in patients without severe renal impairment (CrCl <25–30 mL/min), and renal function should always be considered, especially with dabigatran (Table 53.19). They are not indicated in patients on haemodialysis because they may precipitate inadvertent bleeding.[168] Renal function declines with anticoagulation by approximately 1.16 ml/min GFR, and this may be more pronounced with warfarin than dabigatran due to inhibition of vitamin K-dependent gamma-carboxyglutamic acid (Gla/MPG).[169] NOACs interact with inhibitors (or inducers) of P-glycoprotein transporters and cytochrome P450 (CYP)3A4 (Table 53.19). Caution is required when they are coadministered with drugs such as verapamil, amiodarone, and dronedarone. In patients taking warfarin, switching to a new agent is appropriate when the INR is <2. Mode of action of novel oral anticoagulants in the coagulation cascade is presented in Figure 53.9. A comparison of new anticoagulants is presented in Tables 53.19 and 53.20. A practical guide by EHRA has been recently published and a web site has been created (www.NOACforAF.eu).[170]

Dabigatran is preferred to warfarin for nonvalvular AF by the ESC and the Canadian Cardiovascular Society.

In 2010, the FDA approved dabigatran at a dose of 150 mg bd (CrCl >30 mL/min) or 75 mg bd (CrCl 15–30 mL/min) based on the results of the Re-LY trial (Table 53.20).[166,171] Doses of 75 mg twice daily were approved for patients with chronic kidney disease stage 4 (eGFR<30 but ≥15 ml/min). However, in the long-term RELY-ABLE trial, during 2.3 years of continued treatment with dabigatran, there was a higher rate of major bleeding with dabigatran 150 mg twice daily in comparison with 110 mg, and similar rates of stroke and death.[172] The European Medicines Agency (EMA) has approved both the 110 mg bd and 150 mg bd doses for non-valvular AF. Elective cardioversion may be performed in patients taking dabigatran for at least 3 weeks.[3] Dabigatran is excreted via the kidneys, and no dosing recommendation is given for clearance <15 mL/min. In the elderly a reduced dose is reasonable (110 or 75 mg bd),[173] especially for those >80 years old. It can be safely used together with aspirin.[171,174] A higher risk of major and gastrointestinal haemorrhage, compared to warfarin, has been seen in African-Americans and patients with chronic kidney disease, but still the risk of intracranial haemorrhage is lower.[175] The main side effect is dyspepsia and stomach pain (11%) and transaminase elevations 0.9–2%, although with a frequency similar to that caused by warfarin. There is no evidence of liver toxicity as happened with ximelagatran. A trend in the RE-LY study towards more myocardial infarctions in the dabigatran arm, as compared to warfarin, was not confirmed in a subsequent post hoc analysis.[176] A recent meta-analysis of seven trials, including the RE-LY, detected a higher risk of myocardial infarction (1.19% vs 0.79%; p = 0.03),[177] and this was also observed in the recent RE-MEDY trial.[178] However, in the recent Danish Registry report (4,978 patients on dabigatran and 8,936 patients on warfarin), rates of mortality, pulmonary embolism, and myocardial infarction were lower with dabigatran, compared to warfarin. Stroke/systemic embolism, and major bleeding rates were similar in the two groups.[179]

Anticoagulant effect Thrombin time in diluted plasma (dilute TT—Hemoclot direct thrombin inhibitor assay) and ecarin clotting time (ECT) are precise methods to assess the anticoagulant effect of dabigatran. aPTT and PT are prolonged by dabigatran but the correlation is not linear to guide dosage.[180] However, in the presence of a normal aPTT dabigatran is unlikely to contribute to bleeding, and aPTT can be used in emergencies as a rough estimate.[181]

Antidotes Specific antidotes are under study.[182] *Idarucizumab*, a monoclonal antibody fragment, completely reverses the anticoagulant effect of dabigatran within minutes and has been shown safe in initial clinical trials (2.5 g IV infusions no more than 15 min apart).[183, 184]

Idarucizumab for reversal of dabigatran was approved by the FDA in October 2015. *Aripazine* binds in a similar way to the new oral factor Xa inhibitors and to dabigatran, but further clinical experience is needed (see below). Non-specific procoagulant agents such as *3- or 4-factor prothrombin complex concentrates (PCCs)* (4-PCC, 50 IU/kg, Kcentra) and *activated factor VIIa* (FEIBA) may also be used as antidotes.[155,185–187] PCCs are pooled plasma products that contain significant concentrations of 3 factors (II, IX, and X) or 4 factors (II, VII, IX, and X) and vitamin K–dependent proteins. Both 3- and 4-factor prothrombin complex concentrates (PCC) mostly or completely reverse the effects of dabigatran on thromboelastometry variables and PT but not on aPTT.[187] In emergencies, gastric lavage in recent drug ingestion, haemodialysis, oral charcoal within 2 hours following dabigatran ingestion, desmopressin, packed red cells in anaemia, platelet transfusions in patients receiving concurrent antiplatelet therapies, and fresh frozen plasma in the presence of dilutional coagulopathy or disseminated intravascular coagulation may also be tried as general measures.[188]

Apixaban, an oral factor Xa inhibitor, is approved in Europe and Canada, and by the FDA for nonvalvular AF, and is possibly the most cost-effective new oral anticoagulant.[166,189] Apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial haemorrhage in patients with nonvalvular atrial fibrillation for whom vitamin K antagonist therapy was unsuitable (apixaban vs aspirin, AVERROES trial).[190] In the ARISTOTLE trial, apixaban was found superior to warfarin in preventing embolic or haemorrhagic stroke, and resulted in less bleeding and lower mortality (11% reduction, p = 0.047) (Tables 53.19 to 53.21).[191] Benefits were seen in both paroxysmal and persistent/permanent AF,[192] as well in a cohort of patients with valvular disease (mainly MR and TR).[193] Rates of intracranial bleeding were significantly lower in patients treated with apixaban than with warfarin regardless of renal function.[194] Benefits of apixaban are irrespective of concomitant aspirin use,[195] or of patients' age.[196] A substudy of the ARISTOTLE trial has also shown that cardioversion of AF can be safely performed in apixaban-treated patients.[197] The drug is metabolized in the liver via P450-dependent and -independent mechanisms, and 25% is excreted renally. It should not be used in severe hepatic impairment. Apixaban is not recommended in patients receiving concomitant treatment with strong inhibitors of both CYP3A4 and P-glycoprotein, such as azole antimycotics and HIV protease inhibitors, and should also be used with caution in patients taking rifampicin, phenytoin, carbamazepine, and phenobarbital. Diltiazem results in increased Xa inhibitor levels. There are limited clinical data on patients with a CrCl of 15 to 29 mL/min, and the drug is not recommended in patients with a CrCl of <15 mL/min.

Anticoagulant effect Anti-factor Xa assays may be used as estimates of the anticoagulant effect. aPTT and PT are prolonged by apixaban but they cannot be used to guide dosage since the correlation is not linear, especially with PT.[180] Diluted prothrombin time appears as the best test to use in emergency situations.[181]

Antidotes Andexanet alfa a recombinant protein that binds and sequestersfactor Xa inhibitors has been successfully tried for apixaban (ANNEXA-A trial) and rivaroxaban (ANNEXA-R trial).[182] It is given as 300 mg IV bolus that can be followed by an infusion of 4 mg/min for 120 min. Constipation, dysgeusia, flushing and urticarial are rare side effects. *Aripazine* has also been successfully tried for edoxaban. *Four-factor PCCs* (50IU/kg, Kcentra) can also been used.[186] Apixaban is not removed by dialysis, being protein bound. Gastric lavage in recent drug ingestion, and platelet and fresh frozen plasma transfusions may also be tried as general measures.

Rivaroxaban, an oral factor Xa inhibitor, has been approved by the FDA for nonvalvular AF. In the ROCKET-AF trial, rivaroxaban was not inferior to warfarin (INR 2–3) in patients with nonvalvular AF for the prevention of stroke or systemic embolism, and offered a lower rate of intracranial bleeding, but a higher rate of gastrointestinal bleeding (Tables 53.19–53.21).[198] In a substudy of this trial, rivaroxaban demonstrated equal safety and efficacy with warfarin in patients >75 years old.[199] The half-life of rivaroxaban is 7–11 hours, but factor Xa is inhibited for up to 24 hours, allowing once daily dosage. Its bioavailability increases with food. The drug is metabolized in the liver via P450-dependent and -independent mechanisms and is not recommended in patients receiving concomitant treatment with strong inhibitors of both CYP3A4 and glycoprotein inhibitors (see apixaban). The drug is not recommended in patients with a CrCl of <15 mL/min.

Anticoagulant effect Anti-factor Xa assays are used as estimates of the anticoagulant effect.[3] APTT and PT are prolonged by rivaroxaban but they cannot be used to guide dosage as the correlation is not linear.[180] However, with a prolonged PT, bleeding can be attributed to rivaroxaban, and PT can be used as a rough estimate in case of emergencies.[181]

Antidotes Andexanet alfa a recombinant protein that binds and sequestersfactor Xa inhibitors has been successfully tried for apixaban (ANNEXA-A trial) and rivaroxaban (ANNEXA-R trial).[182] It is given as 300 mg IV bolus that can be followed by an infusion of 4 mg/min for 120 min. Constipation, dysgeusia, flushing and urticarial are rare side effects. *Aripazine* has also been successfully tried for edoxaban. *Four-factor PCCs* (50IU/kg, Kcentra) have also been used as antidote to rivaroxaban.[185] Gastric lavage in recent drug ingestion, and platelet and fresh frozen plasma transfusions may also been tried as general measures.

Edoxaban was also non-inferior to warfarin with respect to prevention of stroke or systemic embolism and was associated with significantly lower rates of bleeding and death from cardiovascular causes (ENGAGE AF-TIMI 48 trial), and is now approved by FDA. Both the 30 and 60 mg doses were not inferior to warfarin, but in the intention to treat

analysis with the 60 mg dose there was a trend favouring edoxaban.[200] Amiodarone increases edoxaban plasma levels via P-glycoprotein inhibition, and the lower dose should be used in patients on amiodarone.[201] In patients with AF, edoxaban appears to demonstrate greater efficacy compared with warfarin in patients who were vitamin K antagonists naive than vitamin K antagonists experienced.[202]

Antidotes Specific antidotes are under study.[182] *Aripazine* (PER977, 100–200 mg), a synthetic molecule that binds specifically to unfractionated heparin and low-molecular-weight heparin, reversed edoxaban within 10 to 30 minutes.[203] *Andexanet alfa* has been successfully tried for rivaroxaban. Gastric lavage in recent drug ingestion, and platelet and fresh frozen plasma transfusions may also be tried as general measures. *Four-factor PCCs* (50IU/kg, Kcentra) have also been found effective for reversing edoxaban.[204]

Betrixaban has also been found equivalent to warfarin.[205]

Transition between NOACs/warfarin

Transitioning from one anticoagulant to another is a high-risk period for both strokes and bleeding. A reasonable strategy is to reduce the NOAC to half dose, start warfarin, and stop the NOAC when the INR is ≥2. When the patient is on warfarin, the NOAC is started after cessation of therapy and three-daily INR measurements to detect a value <2.[206]

PCI in patients on oral anticoagulants

Patients with AF in the absence of an acute coronary syndrome do not need additional aspirin.[3] Patients undergoing PCI need additional antiplatelet therapy that is associated with an increased risk of bleeding. A detailed discussion and recommendations are presented in Chapter 28.

Perioperative anticoagulation

Warfarin Usually, major surgical procedures require an INR of at least <1.5. Warfarin has a half-life of 36–42 h and should be stopped for 4–5 days before surgery.[207] In urgent cases, oral or IV vitamin K (1–2 mg) may be considered. In need of urgent reversal, prothrombin plasma concentrate may also be added, and is preferable to fresh frozen plasma.[208] Bridging to UFH or LMWH that is discontinued ≥12 h before and restarted 24 h after the operation has been recommended only in patients with certain mechanical heart valves and high risk of thrombosis (see Table 23.7 of Chapter 23). In a recent meta-analysis, however, heparin bridging for invasive procedures and surgery in patients receiving vitamin K antagonists for AF, prosthetic heart valves, or VTE conferred a >5-fold increased risk for bleeding, whereas the risk of thromboembolic events was not significantly different between bridged and non-bridged patients.[209] The use of therapeutic dose LMWH was associated with an increased risk of bleeding compared with prophylactic or intermediate dose.[209] Thus, bridging is not required, and especially in patients at low risk of thrombosis. It appears to be safer without interrupting warfarin (see Chapter 70).[210–212] In the continued-warfarin group, the INR on the day of surgery should be ≤3, except for patients with one or more mechanical valves, for whom an INR ≤ 3.5 or less is permitted (BRUISE CONTROL trial).[204] In patients with AF, surgery can be safely accomplished with an INR <1.8 (BRIDGE trial).[211] In patients with AF, normal renal function and platelet count platelet count >100 × 109/L, even major surgery can be safely accomplished with warfarin cessation without bridging when the INR is <1.8 (BRIDGE trial). Warfarin is then resumed the evening after the procedure.[212] There are limited data on safety of cardiac surgery or other major surgery with a very high risk of thromboembolism and bleeding in patients who are on warfarin. Currently, these patients are bridged with heparin prior to surgery. In the need of emergent CABG, fresh frozen plasma and vitamin K may be used to reduce the risk of bleeding.

Non-vitamin K antagonist anticoagulants Depending on the risk of bleeding and renal function, pre-operative interruption of NOACs for 24–96 h has been recommended. (Table 53.22).[170,213] There has been recent evidence that continuation or short interruption of NOACs are safe strategies for most invasive procedures.[214] Bridging with heparin is, on most occasions, not necessary and may increase the risk of bleeding.[214] In a recent analysis of data from the RE-LY trial, interruption of dabigatran (2 days) or warfarin (5 days) for allowance of surgery was not associated with a significant occurrence of stroke and systemic embolism, although heparin bridging was used in <80% of patients on dabigatran, and there was no difference in major bleeding between the two treatment groups.[215] However, discontinuation of rivaroxaban in the ROCKET AF for at least 3 days was associated with a higher incidence of stroke compared to discontinuation of warfarin.[216] Thus, in patients with a $CHADS_2DS_2$-VASC score >4, i.e. >5% annual risk of stroke, bridging therapy with LMWH should be considered. Procedures with low haemorrhagic risk (dental extraction, skin biopsy, cataract surgery) can be safely performed without interruption of NOACs, especially if they are carried out 12 h after last dosing. For pacemaker and ICD implantation a 24 h discontinuation with reinitiation 48 h after implantation (24 h in patients with a $CHADS_2DS_2$-VASC score >4) is recommended.[217,170] If urgent surgery or intervention is required, the risk of bleeding must be weighted against the clinical need for the procedure.

Dilute TT for dabigatran and anti-Xa assays for Xa inhibitors are used to assess anticoagulant activity. aPTT and PT may also be used as rough estimates of the anticoagulant activity of dabigatran and rivaroxaban, respectively.[218] Sensitive PT may be used as a rough estimate of the anticoagulation intensity of all factor Xa inhibitors. Specific coagulation test (dTT for dabigatran; chromogenic assays for factor Xa inhibitors) can also be considered, but no

clinical experience exists.[170] Surgery or intervention should be deferred, if possible, until at least 12 h and ideally 24 h after the last dose. Non-specific antihaemorrhagic agents, such as recombinant human activated factor VIIa or prothrombin complex concentrates, should probably not be given for prophylactic reversal due to their uncertain benefit-risk.[219] Reinitiation of these agents should be delayed for 24–48 hours and once complete haemostasis is assured, since within 1 to 2 hours of reinitiation, the patient will be anticoagulated. For procedures with immediate and complete haemostasis, NOACs can be resumed 6–8 h after the intervention.[170]

Resumption of anticoagulation following bleeding

Recent data suggest that anticoagulation should be restarted following discharge after an episode of GI bleeding.[220] However, this study was too small for definitive conclusions.

Table 53.17 Prevention of thromboembolism

ESC 2012 Update on AF. Prevention of thromboembolism in non-valvular AF	
General	I-A
Antithrombotic therapy for all patients with AF, except in those at low risk (lone AF, aged <65 years, or with contraindications).	
The choice of the antithrombotic therapy should be based upon the absolute risks of stroke/thromboembolism and bleeding.	I-A
The CHA_2DS_2-VAS_c score is recommended as a means of assessing stroke risk in non-valvular AF.	I-A
In patients with a CHA_2DS_2-VAS_c score of 0 (i.e. aged <65 years with lone AF) who are at low risk, with none of the risk factors, no antithrombotic therapy.	I-B
In patients with a CHA_2DS_2-VAS_c score of ≥2, OAC therapy with: adjusted dose VKA (INR 2–3) or a direct thrombin inhibitor (dabigatran) or an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban) unless contraindicated.	I-A
In patients with a CHA_2DS_2-VAS_c score of 1, OAC therapy with: adjusted dose VKA (INR 2–3) or a direct thrombin inhibitor (dabigatran) or an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban), based upon an assessment of the risk of bleeding complications and patient preferences	IIa-A
No antithrombotic therapy in female patients who are aged <65 and have lone AF (but still have a CHA_2DS_2-VAS_c score of 1 by virtue of their gender)	IIa-B
When patients refuse the use of any oral anticoagulation (whether VKAs or NOACs), antiplatelet therapy should be considered, using combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily (where there is a low risk of bleeding) or, less effectively, aspirin 75–325 mg daily.	IIa-B
NOACs	
When dose-adjusted VKA (INR 2–3) cannot be used due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either a direct thrombin inhibitor (dabigatran) or an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban) is recommended.	I-B
Where OAC is recommended, one of the NOACs, either a direct thrombin inhibitor (dabigatran) or an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban).	IIa-A
Where dabigatran is prescribed, a dose of 150 mg bd is preferred to 110 mg bd, with the latter dose recommended in: Elderly patients aged ≥80 Concomitant use of interacting drugs (e.g. verapamil) High bleeding risk (HAS-BLED score ≥3) Moderate renal impairment (CrCl 30–49 mL/min)	IIa-B
Where rivaroxaban is being considered, a dose of 20 mg od is preferred to 15 mg od, with the latter dose recommended in: High bleeding risk (HAS-BLED score ≥3) Moderate renal impairment (CrCl 30–49 mL/min)	IIa-C
Annual baseline and subsequent regular assessment of renal function (by CrCl) in patients following initiation of any NOAC, but 2–3 times per year in those with moderate renal impairment.	IIa-B
NOACs (dabigatran, rivaroxaban, and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min).	III-A
Bleeding	
Assessment of the risk of bleeding when prescribing antithrombotic therapy (whether with VKA, NOAC, aspirin/clopidogrel, or aspirin).	I-A
The HAS-BLED score should be considered to assess bleeding risk. A score ≥3 indicates 'high risk', and some caution and regular review is needed, following the initiation of antithrombotic therapy (with OAC or antiplatelet therapy).	IIa-A
Correctable risk factors for bleeding (e.g. uncontrolled blood pressure, labile INRs if the patient was on a VKA, concomitant drugs (aspirin, NSAIDs, etc.), alcohol, etc.) should be addressed.	IIa-B
Use of the HAS-BLED score should be used to identify modifiable bleeding risks but should not be used on its own to exclude patients from OAC therapy.	IIa-B
The risk of major bleeding with antiplatelet therapy (with aspirin-clopidogrel combination therapy, and especially in the elderly, also with aspirin monotherapy) should be considered as being similar to OAC.	IIa-B

(*Continued*)

Table 53.17 Continued

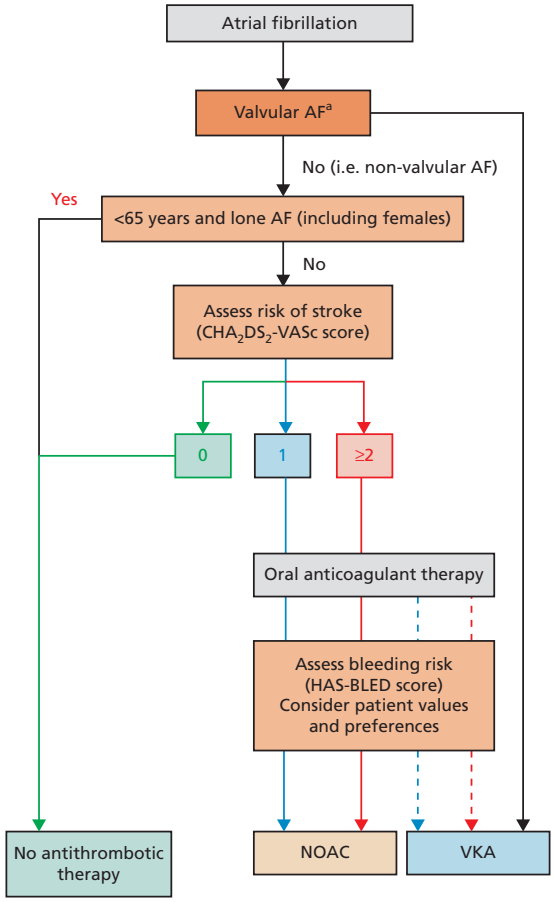
ESC 2010 GL on AF. Prevention of thromboembolism in AF (additional recommendations)	
For patients with mechanical heart valves, the target intensity of anticoagulation with a VKA should be based on the type and position of the prosthesis, maintaining an INR of at least 2.5 in the mitral position and at least 2.0 for an aortic valve.	I-B
Antithrombotic therapy for patients with atrial flutter as for those with AF.	I-C
The selection of antithrombotic therapy should be considered using the same criteria, irrespective of the pattern of AF (i.e. paroxysmal, persistent, or permanent).	IIa-A
Interruption of VKA (with subtherapeutic anticoagulation for up to 48 h), without substituting heparin as 'bridging' anticoagulation therapy in patients without mechanical prosthetic heart valves or not at high risk for thromboembolism, and who are undergoing surgical or diagnostic procedures that carry a risk of bleeding.	IIa-C
'Bridging' anticoagulation with therapeutic doses of either LMWH or UFH during the temporary interruption of VKA therapy should be considered in patients with a mechanical prosthetic heart valve or at high risk for thromboembolism who are undergoing surgical or diagnostic procedures.	IIa-C
Following surgical procedures, resumption of VKA therapy at the 'usual' maintenance dose (without a loading dose) on the evening of (or the next morning after) surgery, assuming there is adequate haemostasis.	IIa-B
Re-evaluation at regular intervals of the benefits, risks, and need for antithrombotic therapy should be considered.	IIa-C
In patients with AF presenting with acute stroke or TIA, management of uncontrolled hypertension before antithrombotic treatment is started and cerebral imaging (CT or MRI) performed to exclude haemorrhage.	IIa-C
In the absence of haemorrhage, VKA should be considered ~2 weeks after stroke, but, in the presence of haemorrhage, anticoagulation should not be given.	IIa-C
In the presence of a large cerebral infarction, delaying the initiation of anticoagulation, given the risk of haemorrhagic transformation.	IIa-C
In patients with AF and an acute TIA, VKA as soon as possible in the absence of cerebral infarction or haemorrhage.	IIa-C
UFH or subcutaneous LMWH when surgical procedures require interruption of VKA for longer than 48 h in high-risk patients.	IIb-C
In patients who sustain ischaemic stroke or systemic embolism during treatment with usual intensity VKA (INR 2.0–3.0), raising the intensity of the anticoagulation to a maximum target INR of 3.0–3.5, rather than adding an antiplatelet agent.	IIb-C
AHA/ACC/HRS 2014 GL on AF. Prevention of thromboembolism	
Antithrombotic therapy based on shared decision-making, discussion of risks of stroke and bleeding, and patient's preferences.	I-C
Antithrombotic therapy selection based on risk of thromboembolism irrespective of paroxysmal, persistent or permanent AF.	I-B
CHA2DS2-VASc score recommended to assess stroke risk.	I-B
Warfarin recommended with mechanical heart valves. Target INR should be based on the type and location of prosthesis.	I-B
INR should be determined at least weekly during initiation of therapy and monthly when anticoagulation is stable.	I-A
With prior stroke, TIA, or CHA2DS2-VASc score ≥2, oral anticoagulants recommended. Options include:	
Warfarin	I-A
Dabigatran, rivaroxaban, or apixaban	I-B
With warfarin, determine INR at least weekly during initiation and monthly when stable.	I-A
Direct thrombin or factor Xa inhibitor recommended, if unable to maintain therapeutic INR.	I-C
Re-evaluate the need for anticoagulation at periodic intervals.	I-C
Bridging therapy with LMWH or UFH with a mechanical heart valve if warfarin is interrupted. Decisions regarding bridging therapy should balance the risks of stroke and bleeding.	I-C
Without a mechanical heart valve, bridging therapy decisions should balance stroke and bleeding risks against the duration of time patient will not be anticoagulated.	I-C
Evaluate renal function prior to initiation of direct thrombin or factor Xa inhibitors, and re-evaluate when clinically indicated and at least annually.	I-B
For atrial flutter, antithrombotic therapy as for AF.	I-C
With nonvalvular AF and CHA2DS2-VASc score of 0, omit antithrombotic therapy.	IIa-B
With CHA2DS2-VASc score ≥2 and end-stage CKD (CrCl <15 mL/min) or on haemodialysis, prescribe warfarin for oral anticoagulation.	IIa-B
With nonvalvular AF and a CHA2DS2-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin.	IIb-C
With moderate-to-severe CKD and CHA2DS2-VASc scores of ≥2, direct thrombin or factor Xa inhibitors at reduced doses.	IIb-C
For PCI, BMS may be considered to minimize duration of DAPT.	IIb-C
Following coronary revascularization in patients with CHA2DS2–VASc score of ≥2, use clopidogrel concurrently with oral anticoagulants, but without aspirin.	IIb-B

(*Continued*)

Table 53.17 Continued

Direct thrombin, dabigatran, and factor Xa inhibitor, rivaroxaban, are not recommended with AF and end-stage CKD or on haemodialysis.	III-C (no benefit)
Direct thrombin inhibitor, dabigatran, should not be used with a mechanical heart valve.	III-B (harm)

OAC, oral anticoagulation with VKA (vitamin K antagonists). NOACs, non-vitamin K oral anticoagulants, i.e. dabigatran, rivaroxaban, apixaban.
For prevention of thromboembolism in AF in the context of heart failure, see Chapter 31 on heart failure.
AF indicates atrial fibrillation; BMS, bare-metal stent; CKD, chronic kidney disease; CrCl, creatinine clearance; DAPT, dual antiplatelet therapy; INR, international normalized ratio; LMWH, low-molecular-weight heparin; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack; and UFH, unfractionated heparin.
ESC 2010 Guidelines for the management of atrial fibrillation. *Eur Heart J*. 2010;**31**:2369–429 with permission from Oxford University Press.
2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. *Europace*. 2012;**14**:1385–413 with permission from Oxford University Press.
AHA/ACC/HRS 2014 Guideline for the Management of Patients with Atrial Fibrillation. *J Am Coll Cardiol*. 2014;**64**:2246–80 with permission from Elsevier.



Antiplatelet therapy with aspirin plus clopidogrel, or—less effectively—aspirin only, should be considered in patients who refuse any OAC or cannot tolerate anticoagulants for reasons unrelated to bleeding. If there are contraindications to OAC or antiplatelet therapy, left atrial appendage occlusion, closure or excision may be considered.
Colour: CHA_2DS_2-VASc; green = 0, blue = 1, red ≥2
Line: solid = best option; dashed = alternative option.
AF = atrial fibrillation; CHA_2DS_2-VASc = see text; HAS-BLED = see text; NOAC = novel oral anticoagulant; OAC = oral anticoagulant; VKA = vitamin K antagonist.
[a]Includes rheumatic valvular disease and prosthetic valves.

Figure 53.8 ESC 2012 update on AF. Choice of anticoagulant.

2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. Europace. 2012;**14**:1385–413.

Table 53.18 The HAS-BLED bleeding risk score

Letter	Clinical characteristic	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2

'Hypertension' is defined as systolic blood pressure >160 mmHg.
'Abnormal kidney function' is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 mmol/L.
'Abnormal liver function' is defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin >2 × upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 × upper limit normal, etc.).
'Bleeding' refers to previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia, etc.
'Labile INRs' refers to unstable/high INRs or poor time in therapeutic range (e.g. <60%).
Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse, etc.
Lip GY, *et al*. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS -BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR , Elderly, Drugs/Alcohol Concomitantly) score. *J Am Coll Cardiol*. 2011;**57**:173–80 with permission from Elsevier.

Table 53.19 Oral anticoagulants for AF

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dose	Variable od	150 mg bd 110 mg bd if CrCl <50 ml/min or >75 years of age 75 mg bd if CrCl 15–30 ml/min	20 mg od 15 mg bd if CrCl <50 ml/min	2.5–5 mg bd 2.5 mg bd if 2 of 3 criteria: Cr ≥1.5 mg/dL, ≥80 years of age, body weight ≤60 kg	60 mg od 30 mg if CrCl ≤50 ml/min
Target	Vitamin K-dependent factors	Thrombin (factor II)	Factor Xa	Factor Xa	Factor Xa
Half-life	40 h	12–14 h	9–13 h	8–11 h	8–10 h
Renal clearance	0	80%	60%	25%	40%
Onset of action	3–5 h	2 h	2.5–4 h	3 h	1–5 h
Anticoagulation monitoring	INR 2–3	Not required	Not required	Not required	Not required
Interactions	Multiple	P-gp	P-gp, CYP3A4	P-gp, CYP3A4	P-gp, CYP3A4
Antidote	Vitamin K	idarucizumab, 3- and 4-factor PCCs	andexanet alfa, aripazine, 3- and 4-factor PCCs	andexanet alfa, aripazine, 3- and 4-factor PCCs	andexanet alfa, aripazine, 3- and 4-factor PCCs

Dabigatran is eliminated via the P-glycoprotein (P-gp) transporter, while the Xa inhibitors are eliminated via P-gp and cytochrome P450 (CYP)3A4 activity. Their dosage should be reduced with co-administration of P-gp or CYP3A4 inhibitors, and they should be used with caution or avoided with administration of P-gp or CYP3A4 inducers.
P-gp inhibitors include verapamil, diltiazem, amiodarone, dronedarone, quinidine, erythromycin, clarithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, ciclosporin, grapefruit juice.
P-gp inducers include rifampicin, St. John's wort, carbamazepine, phenytoin, phenobarbital, trazodone.
CYP3A4 inhibitors include ketoconazole, itraconazole, voriconazole, posaconazole, fluconazole, chloramphenicol, clarithromycin, verapamil and diltiazem, HIV protease inhibitors (e.g., ritonavir, atanazavir).
CYP3A4 inducers include phenytoin, carbamazepine, phenobarbital, rifampicin, and St. John's wort (*Hypericum perforatum*).

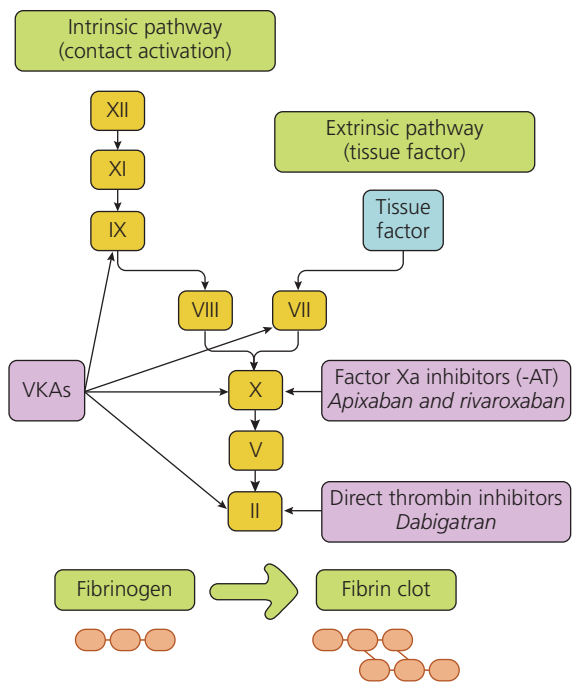


Figure 53.9 AHA/ACC/HRS 2014 GL on AF. Coagulation cascade.

AT indicates antithrombin and VKAs, vitamin K antagonists.
AHA/ACC/HRS 2014 Guideline or the Management of Patients with Atrial Fibrillation. *J Am Coll Cardiol*. 2014;**64**:2246–80 with permission from Elsevier.

Table 53.20 New oral anticoagulants (NOACs) vs warfarin in non-valvular AF

Trial	Dose of NOAC	NOAC (%/y)	Warfarin (%/y)	*P*
		Stroke/systemic embolism		
RELY	Dabigatran 110 mg bd	1.53	1.69	0.34
	Dabigatran 150 mg bd	1.11	1.69	<0.001
ROCKET-AF	Rivaroxaban 15–20 mg od[a]	2.1	2.4	0.12
ARISTOTLE	Apixaban 2.5–5 mg bd[b]	1.27[c]	1.60[c]	0.01
ENGAGE-AF-TIMI 48	Edoxaban 60 mg od	1.57	1.8	0.08
	Edoxaban 30 mg od[d]	2.04	1.8	0.1
		Intracranial haemorrhage		
RELY	Dabigatran 110 mg bd	0.12	0.38	<0.001
	Dabigatran 150 mg bd	0.10	0.38	<0.001
ROCKET-AF	Rivaroxaban 15–20 mg od	0.5	0.7	0.02
ARISTOTLE	Apixaban 2.5–5 mg bd	0.24	0.47	<0.001
ENGAGE-AF-TIMI 48	Edoxaban 60 mg od	0.26	0.47	<0.001
	Edoxaban 30 mg od	0.16	0.47	<0.001
		Major bleeding		
RELY	Dabigatran 110 mg bd	2.71	3.36	<0.003
	Dabigatran 150 mg bd	3.11	3.36	0.31
ROCKET-AF	Rivaroxaban 20 mg od	3.6	3.4	0.58
ARISTOTLE	Apixaban 2.5–5 mg bd	2.13	3.09	<0.001
ENGAGE-AF-TIMI 48	Edoxaban 60 mg od	2.75	3.43	<0.001
	Edoxaban 30 mg od	1.61	3.43	<0.001
		Total mortality		
RELY	Dabigatran 110 mg bd	3.75	4.13	0.13
	Dabigatran 150 mg bd	3.64	4.13	0.051
ROCKET-AF	Rivaroxaban 20 mg od	4.5	4.9	0.15
ARISTOTLE	Apixaban 2.5–5 mg bd	3.52	3.94	0.047
ENGAGE-AF-TIMI 48	Edoxaban 60 mg od	3.99	4.35	0.08
	Edoxaban 30 mg od	3.80	4.35	0.006

a: 15 mg od if CrCl 40–49 ml/min.
b: 2.5 mg bd if ≥2 of the following: age ≥80 y, BW <60 kg, creatinine ≥1.5 mg/dl.
c: This number includes both embolic and haemorrhagic strokes.
d: 30 mg od if CrCl 30–50 ml/min, BW <60 kg, concomitant verapamil or quinidine.
BW: body weight, CrCl: creatinine clearance.

Table 53.21 EHRA 2015 practical guide on the use of new oral anticoagulants. Possible measures in case of bleeding

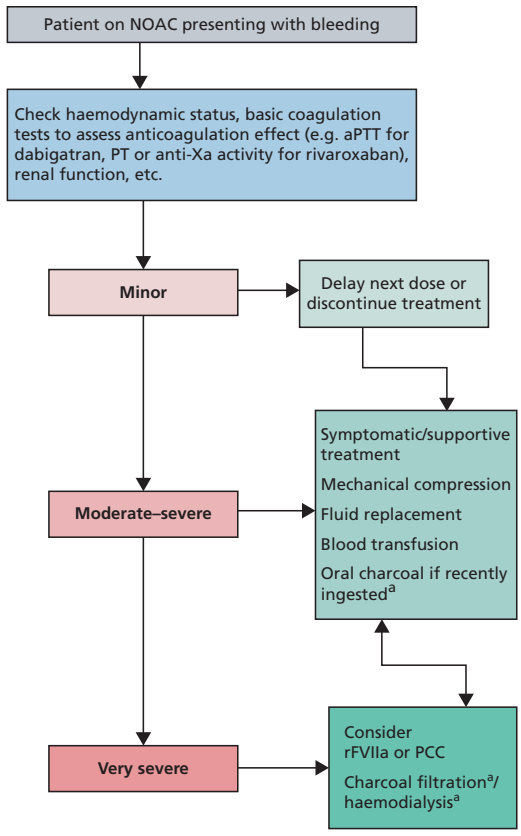
	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apibaxan, edoxaban, rivaroxaban)
Non-life-threatening bleeding	Inquire last intake + dosing regimen Estimate normalization of haemostasis Normal renal function: 12–24 h CrCl 50–80 mL/min: 24–36 h CrCl 30–50 mL/min: 36–48 h CrCl <30 mL/min: ≥ 48 h Maintain diuresis Local haemostatic measures Fluid replacement (colloids if needed) RBC substitution if necessary Platelet substitution (in case of thrombocytopenia ≤ 60 × 10^9/L or thrombopathy) Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvant Desmopressin can be considered in special cases (coagulopathy or thrombopathy) Consider dialysis (preliminary evidence–65% after 4h) Charcoal haemoperfusion not recommended (no data)	Inquire last intake + dosing regimen Normalization of haemostatis: 12–24 h Local haemostatic measures Fluid replacement (colloids if needed) RBC substitution if necessary Platelet substitution (in case of thrombocytopenia ≤ 60 × 10^9/L or thrombopathy) Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvant Desmopressin can be considered in special cases (coagulopathy or thrombopathy)
Life-threatening bleeding	All of the above Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence) Activated PCC 50 IE/kg; max 200 IE/kg/day: no strong data about additional benefit over PCC. Can be considered before PCC if available Activated factor Vii (rFVIIa; 90 µg/kg); no data about additional benefit + expensive (only animal evidence)	All of the above Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence) Activated PCC 50 IE/kg; max 200 IE/kg/day: no strong data about additional benefit over PCC. Can be considered before PCC if available Activated factor VII (rFVIIa; 90 µg/kg); no data about additional benefit + expensive (only animal evidence)

RBC, red blood cells; CrCl, creatinine clearance; PCC, prothrombin complex concentrate.
Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2015;**17**:1467–507.

Table 53.22 EHRA 2015 practical guide on the use of new oral anticoagulants: Last intake of NOAC before elective surgical intervention

No important bleeding risk and/or adequate local haemostasis possible: Perform 12–24 h after last intake				
	Dabigatran		**Apixaban/Rivaroxaban**	
	Low risk	High risk	Low risk	High risk
CrCl ≥ 80 mL/min	≥24	≥48	≥24	≥48
CrCl 50–80 mL/min	≥36	≥72	≥24	≥48
CrCl 30–50 mL/min	≥48	≥96	≥24	≥48
CrCl 15–30 mL/min	not indicated		≥36	≥48

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace*. 2015;**17**:1467–507.



aPTT = activated partial thromboplastin time; NOAC = novel oral anticoagulant; PCC = prothrombin complex concentrate; PT = prothrombin time; rFVIIa = activated recombinant factor VII. [a]With dabigatran.

Figure 53.10 ESC 2012 GL on AF. Management of bleeding in patients taking NOACs.

2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. *Europace*. 2012;**14**:1385–413.

Management of stroke

Ischaemic stroke

Patients presenting within 4.5 h after the onset of ischaemic stroke should be considered for IV rt-PA (0.9 mg/kg, with 10% bolus, and the remainder over 60 min, maximum dose 90 mg). Diffusion-weighted magnetic resonance imaging and non-enhanced computed tomography are the most sensitive and specific methods for detecting ischaemic stroke and excluding intracerebral haemorrhage.[221] They are necessary before intravenous rtPA to exclude intracranial haemorrhage (absolute contraindication) and to determine whether CT hypodensity or MRI hyperintensity of ischaemia are present. Criteria for ***fibrinolysis*** are presented in Table 53.23. Of note, age >80 years is not an exclusion criterion provided it can be given within the first 3 h.[221] Fibrinolysis does not increase the risk of intracranial haemorrhage when INR is ≤1.7. Tenecteplase (0.25 mg per kilogram, administered as a single bolus, with a maximum dose of 25 mg), a more fibrin-selective agent, is superior to alteplase in patients subjected to fibrinolyis within 6 h after the onset of ischaemic stroke,[222] but this was not verified in another comparison within 4.5 h after stroke.[223] Anticoagulants and antiplatelet agents should be withheld for the first 24 h following fibrinolysis. Labetalol (10–20 mg IV over 1–2 minutes, may be repeated once), or nicardipine (5 mg/h IV, titrate up by 2.5 mg/h every 5–15 minutes, maximum 15 mg/h) are recommended only when the blood pressure exceeds 180/110 mmHg.[221] However, in patients who are not candidates for fibrinolysis, blood pressure lowering in acute stroke is not established to be useful with systolic blood pressure of 140–220 mmHg and without evidence of non-stroke end-organ damage, with the possible exception of an early (<6 h) BP-lowering strategy.[224] Thus, treatment of hypertension in this setting should be individualized. In patients who are candidates for fibrinolysis, a pretreatment BP <180/110 mmHg is mandatory.

Fibrinolysis offers a recanalization rate of <50%, and large thrombi in vessels such as the distal internal carotid artery or the first segment of the middle cerebral artery respond poorly.[225] ***Intraarterial, catheter-based treatment*** administered within 6 hours after acute ischaemic stroke using aspiration and stent retrievers has improved neurologic recovery and reduced mortality compared to IV fibrinolysis, especially in the presence of a proximal cerebral arterial occlusion and a small infarct or salvageable brain tissue on CT.[226] It can be delivered with or without concomitant IV fibrinolysis, and preliminary data suggest that they might be useful up to 8 h[227] or even 12 h[228] after symptoms onset.

In patients who present with stroke while taking new anticoagulants, if the aPTT is prolonged in a patient taking dabigatran (or the prothrombin time with an Xa inhibitor), it should be assumed that the patient is anticoagulated, and thrombolysis should not be administered.[3,221] Since dabigatran 150 mg bd resulted in a significant reduction in both ischaemic and haemorrhagic stroke, should the acute ischaemic stroke occur whilst the patient is taking dabigatran 110 mg bd, or rivaroxaban or apixaban (none of which significantly reduced ischaemic stroke, compared with warfarin, in their respective trials), the use of dabigatran 150 mg bd instead may be reasonable, but no direct data exist.[3] If anticoagulation is unsuitable or not feasible, dual antiplatelet therapy is recommended for secondary prevention (CHANCE trial).[229] Reinitiation of anticoagulation following a non-fibrinolysed ischaemic stroke should be within 14 days after the onset of symptoms (AHA/ASA 2014 GL for prevention of stroke IIa-B), since the risk of early recurrence is as high as 8%.[230] In patients with a TIA, anticoagulation can be initiated 1 day after the onset of neurological symptoms for small infarcts, and 3 to 12 following large infarcts (Figure 53.11).[170] However, in the presence of high risk

Table 53.23 Management of acute ischaemic stroke. AHA/ASA 2013 GL on acute ischaemic stroke. Inclusion and exclusion characteristics of patients with ischaemic stroke who could be treated with IV alteplase within 3 hours from symptom onset

Inclusion criteria
Diagnosis of ischaemic stroke causing measurable neurological deficit
Onset of symptoms <3 h before beginning treatment
Aged ≥18 years
Exclusion criteria
Significant head trauma or prior stroke in previous 3 months
Symptoms suggest subarachnoid haemorrhage
Arterial puncture at non-compressible site within previous 7 days
History of previous intracranial haemorrhage
Recent intracranial or intraspinal surgery
Elevated blood pressure (systolic ≥185 mmHg or diastolic ≥110 mmHg)
Active internal bleeding
Acute bleeding diathesis, including, but not limited to:
Platelet count ≤100 000/mm^3
Heparin received within 48 hours, resulting in abnormally elevated aPTT greater than the upper limit of normal
Current use of anticoagulant, with INR >1.7 or PT >15 s
Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)
Blood glucose concentration <50 mg/dL (2.7 mmol/L)
CT demonstrates multilobar infarction (hypodensity > 1/3 cerebral hemisphere)
Relative exclusion criteria
Recent experience suggests that under some circumstances—with careful consideration and weighting of risk to benefit—patients may receive fibrinolytic therapy despite 1 or more relative contraindications. Consider risk to benefit of IV alteplase administration carefully if any of these relative contraindications are present:
Only minor or rapidly improving stroke symptoms (clearing spontaneously)
Pregnancy
Seizure at onset with postictal residual neurological impairments
Major surgery or serious trauma within previous 14 days
Recent gastrointestinal or urinary tract haemorrhage (within previous 21 days)
Recent acute myocardial infarction (within previous 3 months)

The checklist includes some FDA-approved indications and contraindications for administration of IV alteplase for acute ischaemic stroke. Recent guideline revisions have modified the original FDA-approved indications. A physician with expertise in acute stroke care may modify this list.
Onset time is defined as either the witnessed onset of symptoms or the time last known normal if symptom onset was not witnessed.
In patients without recent use of oral anticoagulants or heparin, treatment with IV alteplase can be initiated before availability of coagulation test results but should be discontinued if INR is >1.7 or PT is abnormally elevated by local laboratory standards.
In patients without history of thrombocytopenia, treatment with IV alteplase can be initiated before availability of platelet count but should be discontinued if platelet count is <100 000/mm^3.
aPTT indicates activated partial thromboplastin time; CT, computed tomography; ECT, ecarin clotting time; FDA, Food and Drug Administration; INR, international normalized ratio; IV, intravenous; PT, partial thromboplastin time; and TT, thrombin time.
Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association.

for haemorrhagic conversion (ie large infarct, haemorrhagic transformation on initial imaging, uncontrolled hypertension, or haemorrhage tendency), it is reasonable to delay initiation of oral anticoagulation beyond 14 days (AHA/ASA 2014 GL for prevention of stroke IIa-B).[230] Elective non-cardiac surgery may best be avoided for 9 months following a stroke.[231]

Intracerebral haemorrhage

In the case of intracerebral haemorrhage, reversal of anticoagulation (INR<1.3) is needed. Intensive treatment to lower the blood pressure with a target systolic level of <180 mmHg is recommended,[232] but there has been evidence that values <160–140 mmHg may reduce haematoma enlargement and improve functional outcomes.[233,234] After

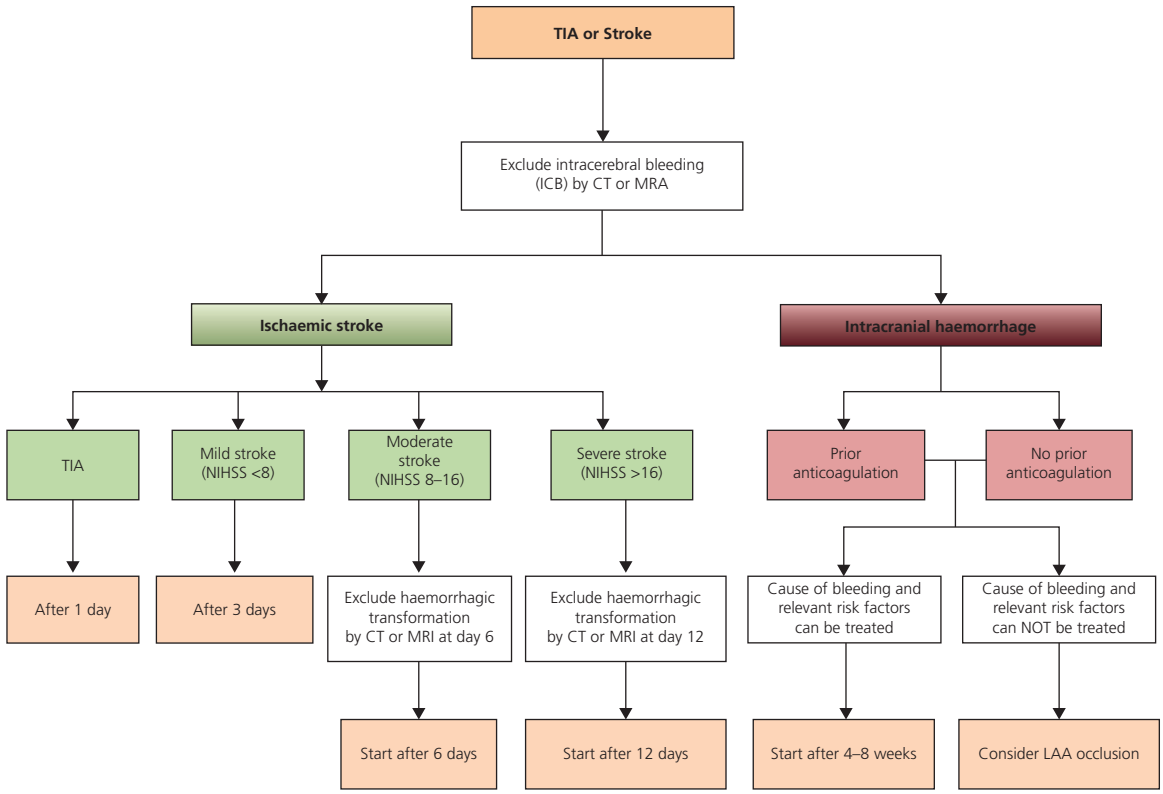


Figure 53.11 EHRA 2015 guide on NOACS. Flowchart for the initiation or re-initiation of anticoagulation after TIA/stroke or intracerebral haemorrhage.

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace*. 2015;**17**:1467–507.

documentation of cessation of bleeding low-dose heparin may be started 1-4 days from onset.[232] Oral anticoagulant treatment may also be started within 2 weeks since it is associated with a significant reduction in ischaemic stroke/all-cause mortality rates.[235] NOACs are probably preferred if the haemorrhage happened on warfarin.

Catheter ablation

Left atrial catheter ablation (Figure 53.12 and Table 53.24) offers improved rates of SR maintenance compared to antiarrhythmic therapy.[236] Success rates in RCTs are 57% and 77% following a single and multiple procedures, respectively, compared to 52% with antiarrhythmic drug therapy.[237] In the MANTRA-PAF trial, 85% of ablated patients vs 71% medically treated patients with PAF were free of AF in 2 years ($p = 0.004$), but the cumulative burden of AF during that time was not significantly different on an intention-to-treat analysis (36% of patients initially assigned to medication eventually had ablation).[238] In RAAFT-2, 45% of patients with PAF were free of arrhythmia 2 years following ablation, compared with 28% of patients on antiarrhythmic therapy.[239] In the SARA trial on patients with persistent AF, 70% of patients were free of arrhythmia at one year following ablation, compared to 44% on patients treated with drugs. However, no symptomatic improvement was detected.[240] Current catheter ablation strategies fall into two broad categories: pulmonary vein isolation to prevent AF initiation, and atrial substrate modification to impede AF perpetuation.[60] With these approaches, single-procedure 5-year success rates are approximately 60–80% in patients with paroxysmal AF subjected to a second (40%) or a third (10%) procedure in experienced centres.[241,242] However, in real-world registries, success rates may be <50% at 1 year, especially in patients with persistent AF.[243] PV isolation is achieved with PV antral ablation assisted by dedicated circumferential catheters or circumferential PV isolation with the assistance of electroanatomic mapping or by cryoablation with a balloon. Additional linear lesions along the roof of the left atrium, connecting the superior aspects of the left and right upper PV isolation lesions, and along the region between the mitral annulus and the left inferior PV (mitral isthmus) and the intervenous ridge, or ablation of complex fractionated electrograms carry a potentially

increased risk of complications or proarrhythmia, and their value is not established in patients with paroxysmal or persistent AF.[244–247] Novel techniques of autonomic denervation by targeting areas with fractionated atrial activity or the anatomic areas of the major ganglionated autonomic plexi are also under study.[64] Oral amiodarone treatment for 2 months following ablation reduces atrial arrhythmia-related hospitalization and cardioversion rates during the blanking period but does not significantly reduce recurrence of atrial tachyarrhythmias at the 6-month follow-up.[248]

Performance of AF ablation without interruption of warfarin (with an INR 2–3) and with additional use of UFH (aiming at ACT>300) is safe and associated with less thrombotic complications, without increasing the risk of pericardial effusion or other major bleeding events.[249] Thus, warfarin may be continued; UFH or LMWH is given during ablation to achieve an ACT >300 s, and when ACT<250 s sheaths are removed. Patients undergoing catheter ablation have a similar incidence of thromboembolic events with dabigatran and major bleeding compared to warfarin, with low event rates overall.[250] Most probably, a minimally interrupted strategy with cessation of dabigatran 24 h before the procedure (or 48 h if creatinine clearance is 30–50 mL/min), use of heparin during the procedure, and resumption 4 h after achieving haemostasis are safe.[251] There has also been evidence in favour of uninterrupted rivaroxaban and concomitant use of heparin, as recommended with warfarin, during AF ablation.[252] Warfarin or a new oral anticoagulant is recommended for all patients for at least 2 months following an AF ablation procedure. Decisions regarding the use of anticoagulation >2 months following ablation should be based on the patient's risk factors for stroke and not on the presence or type of AF. Discontinuation of anticoagulation therapy-post ablation is generally not recommended in patients who have a CHADS score ≥2. Following ablation, aggressive control of weight, blood pressure, lipids, blood sugar, and sleep apnoea is important for a favourable outcome.[253]

Complications of catheter ablation occur in 3.5–10% of cases and are mainly dependent on the operator's experience (<25 procedures per year), age of the patient (>80 years), female gender, $CHADS_2$ score of ≥2, and adopted techniques.[243,254,255] Tamponade occurs in 0.67% (in men) to 1.24% (in women), 16% of which require surgical intervention.[256] Other complications of radiofrequency ablation are pericardial effusion (0.6%), TIA (0.3%), stroke (0.3%), myocardial infarction (0.1%), vascular complications (1.2%), and atrio-oesophageal perforation (0.016%). Post-procedure neurocognitive dysfunction has also been reported and depends on ablation techniques and anticoagulation strategies.[257] The reported in-hospital mortality with AF ablation is 0.06–0.3% and is mainly due to tamponade or atrio-oesophageal fistulae, stroke, and massive

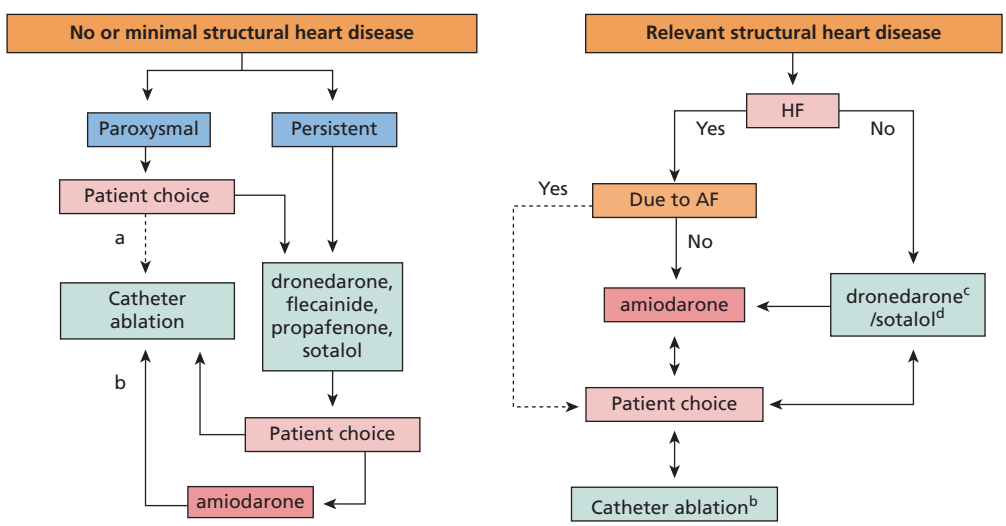


Figure 53.12 ESC 2012 update on AF. Antiarrhythmic drugs and/or left atrial ablation for rhythm control in AF.

AF indicates atrial fibrillation; HF, heart failure; Heart failure due to AF = tachycardiomyopathy.

[a]*Usually pulmonary vein isolation is appropriate.*

[b]More extensive left atrial ablation may be needed.

[c]Caution with coronary heart disease.

[d]Not recommended with left ventricular hypertrophy.

2012 focused update of the ESC Guidelines for the management of atrial fibrillation. *Europace*. 2012;**14**:1385–413 with permission from Oxford University Press.

Table 53.24 Recommendations for left atrial ablation

ESC 2012 GL update on AF	
Paroxysmal AF in patients with symptomatic recurrences on antiarrhythmic drug therapy (amiodarone, dronedarone, flecainide, propafenone, sotalol) and who prefer further rhythm control therapy when performed by an electrophysiologist who has received appropriate training and is performing the procedure in an experienced centre.	I-A
Catheter ablation of AF should target isolation of the pulmonary veins.	IIa-A
Catheter ablation of AF should be considered as first-line therapy in selected patients with symptomatic paroxysmal AF as an alternative to antiarrhythmic drug therapy, considering patient choice, benefit, and risk.	IIa-B
When catheter ablation of AF is planned, continuation of oral anticoagulation with a VKA should be considered during the procedure, maintaining an INR close to 2.0.	IIa-B
When AF recurs within the first 6 weeks after catheter ablation, a watch-and-wait rhythm control therapy should be considered.	IIa-B
AHA/ACC/HRS 2014 GL on AF. Catheter ablation to maintain sinus rhythm	
Symptomatic paroxysmal AF refractory or intolerant to at least1 class I or III antiarrhythmic medication when a rhythm control strategy is desired.	I-A
Assessment of the procedural risks and outcomes relevant to the individual patient prior to consideration of AF catheter ablation.	I-C
Selected patients with symptomatic persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication.	IIa-A
Recurrent symptomatic paroxysmal AF, prior to therapeutic trials of antiarrhythmic drug therapy, after weighing risks and outcomes of drug and ablation therapy.	IIa-B
Symptomatic long-standing (>12 months) persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication, when a rhythm control strategy is desired.	IIb-B
Prior to initiation of antiarrhythmic drug therapy with a class I or III antiarrhythmic medication for symptomatic persistent AF, when a rhythm control strategy is desired.	IIb-C
AF catheter ablation should not be performed in patients who cannot be treated with anticoagulant therapy during and following the procedure.	III-C (Harm)
AF catheter ablation to restore sinus rhythm should not be performed with the sole intent of obviating the need for anticoagulation.	III-C (Harm)

AHA/ACC/HRS 2014 GL on AF. Complications of radiofrequency catheter ablation for AF

Complication	Symptoms/signs	Treatment
Air embolism	Acute ischemia, cardiac arrest, AV block, hypotension	Supplemental oxygen, fluids, CPR, or pacing if indicated
Atrial-esophageal fistula	Usually 1–4 wk after ablation, dysphagia, unexplained fever, chills, sepsis, neurological events (septic emboli)	CT or MRI of esophagus, avoiding endoscopy, immediate surgical correction
Cardiac tamponade/perforation	Abrupt or gradual fall in BP	Pericardiocentesis, emergent surgical drainage if pericardiocentesis fails
Phrenic nerve injury resulting in diaphragmatic paralysis	Shortness of breath, elevated hemidiaphragm	None, usually resolves spontaneously
Iatrogenic atrial flutter	Tachycardia	Cardioversion, antiarrhythmic drugs, or repeat ablation
Gastric motility disorder	Nausea, vomiting, bloating, abdominal pain	Depends on severity of symptoms
Mitral valve injury requiring surgery	Entrapment of catheter	Advance sheath with gentle catheter retraction, surgical removal
MI	Chest pain, ST changes, hypotension	Standard therapy
Pericarditis	Chest pain, typical quality	NSAIDs, colchicine, steroids
Pulmonary vein stenosis	Shortness of breath, cough, hemoptysis	PV dilation/stent or no therapy
Radiation injury	Pain and reddening at radiation site, can present late	Treat as burn injury
Stroke or TIA	Neurological deficit	Consider lysis therapy

(*Continued*)

Table 53.24 Continued

Vascular access complication		
Femoral pseudo aneurysm	Pain or pulsatile mass at groin	Observation, compression, thrombin injection, possible surgery
Arteriovenous fistula	Pain, bruit at groin site	Observation, compression, possible surgery
Hematoma	Pain, swelling	Compression
Death	N/A	N/A

AF indicates atrial fibrillation; AV, atrioventricular; BP, blood pressure; CPR, cardiopulmonary resuscitation; CT, computed tomography; MI, myocardial infarction; MRI, magnetic resonance imaging; N/A, not applicable; NSAIDs, non-steroidal anti-inflammatory drugs; PV, pulmonary valve; and TIA, transient ischaemic attack.
Camm, John A *et al*. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J*. 2012;**33** with permission from Oxford University Press.
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pneumonia. Atrio-oesophageal fistulae usually occur following extensive ablation of the posterior atrial wall, and carry a 55% mortality despite surgical repair.[258] Use of irrigated tip catheters, with continuous fluid administration through catheter sheaths, meticulous anticoagulation with UFH without interruption of oral anticoagulation therapy, and avoidance of posterior wall lesions in the presence of a CT-assessed atrial-oesophageal distance <2 mm are necessary to eliminate the risk of stroke and oesophageal damage.[259] Circumflex coronary artery injury may occur following extensive ablation near the distal coronary sinus and the base of the left atrial appendage as well as in the anterior left atrium. It may result in VF or sinus dysfunction requiring permanent pacing.[260] Pulmonary vein stenosis occurs with ostial ablation (1% incidence of stenosis that requires intervention[238]) but not with antral or circumferential lesions. Iatrogenic arrhythmias may occur in 4–20% of cases, being higher with linear or fractionated electrogram ablation techniques.[261,262] Usually they are macroreentrant (perimitral or roof-dependent) and rarely focal, and respond to catheter ablation (see Chapter 51), although they do not always require repeated ablation.[261] Cryoballoon-mediated PV isolation is equally effective to radiofrequency irrigated ablation, and theoretically might reduce thromboembolic complications or ablation-induced atrial tachycardias, but is associated with 2-6% risk of phrenic nerve palsy that is usually reversible.[263,264]

Surgical ablation

Since its introduction, the MAZE procedure has gone through three modifications (Maze I, II, and III), using cut-and-sew techniques that ensure transmural lesions to isolate the PV, connect these dividing lines to the mitral valve annulus, and create electrical barriers in the RA that prevent macro-reentrant rhythms from becoming sustained. Success rates of around 70–95% have been reported.[265] Risks include death (< 1% when performed as an isolated procedure), the need for permanent pacing (with right-sided lesions), recurrent bleeding requiring reoperation, impaired atrial transport function, delayed atrial arrhythmias (especially atrial flutter), and atrio-oesophageal fistula. Variations of the MAZE procedure, using minimally invasive thoracoscopic approaches and radiofrequency or cryoablation energy, have also been successfully used. In patients with dilated left atrium and hypertension or failed prior catheter ablation, a minimally invasive approach has been found superior to catheter ablation in achieving freedom from left atrial arrhythmias after 12 months of follow-up but at a higher procedural adverse event rate.[266]

Surgical ablation of AF may also be considered in patients with symptomatic AF undergoing cardiac surgery, especially when mitral valve procedures are undertaken in experienced centres. In the US, concomitant surgical ablation is performed in approximately 60% of patients with AF who undergo mitral valve operations.[267] Surgical ablation (PVI isolation and linear lesions), performed in patients with AF undergoing surgery for coronary artery or valve disease, improved the likelihood of SR but did not reduce total mortality, stroke rate, and the incidence of heart failure (PRAGUE-12).[268] In the CTSN trial, the addition of PV isolation or Maze to mitral valve surgery significantly increased the rate of freedom from atrial fibrillation at 1 year among patients with persistent or long-standing persistent AF (63 vs 29%), but the risk of implantation of a permanent pacemaker was also increased.[269] The value of minimally invasive surgical ablation of AF without concomitant cardiac surgery in patients with symptomatic AF after failure of catheter ablation is not established (Table 53.25).

Left atrial appendage closure

The left atrial appendage is considered the main (but not the only) site of thrombus formation in AF. Recently, minimally invasive epicardial techniques and interventional trans-septal techniques have been developed for occlusion

Table 53.25 Recommendations for surgical ablation of AF

ESC 2010 GL on AF	
Surgical ablation of AF in patients with symptomatic AF undergoing cardiac surgery.	IIa-A
Surgical ablation of AF in patients with asymptomatic AF undergoing cardiac surgery if feasible with minimal risk.	IIb-C
Minimally invasive surgical ablation of AF without concomitant cardiac surgery in patients with symptomatic AF after failure of catheter ablation.	IIb-C
AHA/ACC 2014 GL on valvular heart disease. Intervention for AF	
A concomitant maze procedure* at the time of mitral valve repair or replacement for treatment of chronic, persistent AF.	IIa-C
A full biatrial maze procedure, when technically feasible, at the time of mitral valve surgery, is preferred to a lesser ablation procedure, in patients with chronic, persistent AF.	IIa-B
Concomitant maze procedure or pulmonary vein isolation at the time of cardiac surgical procedures other than mitral valve surgery in patients with paroxysmal or persistent AF that is symptomatic or associated with a history of emboli on anticoagulation.	IIb-C
Catheter ablation for AF should not be performed in patients with severe MR when mitral repair or replacement is anticipated, with preference for the combined maze procedure plus mitral valve repair.	III-B
AHA/ACC/HRS 2014 GL on AF. Surgery maze procedures: recommendations	
Patients with AF undergoing cardiac surgery for other indications.	IIa-C
A stand-alone AF surgical ablation procedure for selected patients with highly symptomatic AF not well managed with other approaches.	IIb-B

* The term 'maze procedure' properly refers to a specific biatrial procedure creating a defined set of conduction block lesions performed 'cut and sew' ('maze III') or with tissue ablation technologies including cryoablative or radiofrequency ('maze IV').
AHA/ACC/HRS 2014 Guideline or the Management of Patients with Atrial Fibrillation. *J Am Coll Cardiol*. 2014;**64**:2246–80 with permission from Elsevier.
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of the appendage orifice to reduce the stroke risk.[270] Data on the safety and efficacy of this approach are rather insufficient. In the PROTECT AF trial, left appendage closure with the Watchman device was non-inferior to ongoing warfarin therapy with regard to prevention of stroke, systemic embolism, and cardiovascular death. However, the closure arm sustained an increased number of procedure-related safety events, mainly pericardial tamponade and procedure-related stroke.[271] Adverse effects were lower in the PREVAIL trial in which left appendage occlusion was noninferior to warfarin for ischaemic stroke, although non-inferiority was not achieved for overall efficacy.[272] In March 2015, the FDA approved the Watchman device for patients who have a reason to avoid oral anticoagulation. Percutaneous closure is indicated in patients with a high stroke risk and contraindications for long-term oral anticoagulation (ESC 2012 GL on AF, IIb-B).[3,273,274] The usefulness of closure of the left atrial appendage in patients with ischaemic stroke, or TIA and AF, is uncertain (AHA/ASA 2014 GL for prevention of stroke, IIb-B).[230] Surgical excision of the LAA may be considered in patients undergoing open heart surgery (ESC 2012 GL on AF and AHA/ACC/HRS 2014 GL on AF, IIb-C).[3]

Atrial pacing

Atrial-based pacing is associated with a lower risk of AF and stroke than ventricular-based pacing in patients requiring pacemakers for bradyarrhythmias, but the value of pacing as a primary therapy for prevention of recurrent AF has not been proven.[275] Pacing in the interatrial septum, instead of the appendage, as well as anti-tachycardia algorithms for suppression of ectopic activity have produced promising results,[276,277] but the evidence is still inconclusive. There are no hard data to support the use of biatrial or multisite right atrial pacing for prevention of AF.

Upstream therapy

Upstream therapy to prevent or delay myocardial remodelling associated with hypertension, heart failure, or inflammation (e.g. after cardiac surgery) may defer the development of new AF (primary prevention) or, once established, its rate of recurrence or progression to permanent AF (secondary prevention) (Table 53.26).[278]

ACEIs/ARBs There has been compelling evidence supporting the role of RAAS in the genesis and perpetuation of AF. Experimental studies have demonstrated the beneficial effects of ACEIs and ARBs on AF prevention; however, clinical studies on the efficacy of such therapeutic interventions have produced variable results, depending on the clinical background of treated patients.[279,280] In patients with heart failure and/or LV hypertrophy, ACEIs and ARBs appear particularly useful for primary prevention of AF. Although meta-analyses of secondary prevention trials also suggest significant risk reduction after cardioversion with the use of

Table 53.26 AF upstream therapy

ESC 2010 GL on AF. Recommendations for secondary prevention of AF with 'upstream' therapy	
Pre-treatment with ACEIs and ARBs in patients with recurrent AF and receiving antiarrhythmic drug therapy.	IIb-B
ARBs or ACEIs for prevention of recurrent paroxysmal AF or in patients with persistent AF undergoing electrical cardioversion in the absence of significant structural heart disease if these agents are indicated for other reasons (e.g. hypertension).	IIb-B
ESC 2010 GL on AF. Recommendations for primary prevention of AF with 'upstream' therapy	
ACEIs and ARBs in patients with heart failure and reduced ejection fraction.	IIa-A
ACEIs and ARBs in patients with hypertension, particularly with LV hypertrophy.	IIa-B
Statins after CABG, isolated or in combination with valvular interventions.	IIa-B
Statins in patients with underlying heart disease, particularly heart failure.	IIb-B
Upstream therapies with ACEIs, ARBs, and statins for primary prevention of AF in patients without cardiovascular disease.	III-C
AHA/ACC/HRS 2014 GL on AF. Upstream therapy for primary prevention of new-onset AF	
An ACE inhibitor (ACEI) or angiotensin-receptor blocker (ARB) in patients with heart failure with reduced LVEF.	IIa-B
ACEI or ARB in the setting of hypertension.	IIb-B
Statin therapy after coronary artery surgery.	IIb-A
ACEI, ARB or statins not beneficial in patients without cardiovascular disease.	III-B (no benefit)

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ACEIs and ARBs, no effect was detected in large secondary prevention trials.[281,282] These agents are indicated for primary prevention in patients with hypertension or heart failure, but their value in secondary prevention is unproven.

Despite experimental evidence for a potential role of **statins**, **omega fatty acids**, and **steroids**, their clinical value is not proven.[283,284]

AF in specific conditions

Post-operative AF

AF is the most common complication after cardiac surgery, 30% after CABG, 40% after valve surgery, and 50% after combined CABG and valve surgery, with a peak incidence of post-operative AF between post-operative days 2 and 4.[2] Anticoagulation is necessary for AF persisting longer than 48 h (Table 53.27). In general, minimization of inotropes and optimization of fluid and electrolyte status (especially hypokalaemia and hypomagnesaemia) should be considered in all patients.[285] **Beta blocker** therapy is most effective when provided both before and after cardiac surgery;[286] withdrawal of beta blockers is a significant risk factor for the development of post-operative AF and should be avoided. Treatment should be started at least 1 week before surgery with a beta 1 blocker without intrinsic sympathomimetic activity. Prophylactic **amiodarone** started orally before the operation also decreases the incidence of post-operative AF and reduces the incidence of stroke in most,[286,287] but not all, studies.[288] IV amiodarone is the drug of choice for pharmacologic conversion of post-operative AF.[285] Recently, perioperative infusion of **carperitide,** a renin-angiotensin-aldosterone system inhibitor with strong natriuretic activity, reduced postoperative AF.[289] **IV magnesium** and **steroids** have also been beneficial.[290,291] **Colchicine** (1 mg bd on the third post-op day, followed by 0.5 mg bd (0.25 bd in patients <70 kg)) for 1 month reduced the incidence of AF by 45% (COPPS substudy).[292] Use of **statins** has also been found to reduce post-operative AF.[293] There is also limited evidence that routine atrial or biatrial pacing reduces AF.[294]

Acute coronary syndromes

AF occurs in 2–21% of patients with ACS and indicates increased in-hospital and long-term mortality (see Chapter 28),[295] particularly when occurring >30 days after MI.[296] Recommendation for the management of AF are presented in Chapter 28.

Heart failure

AF constitutes a strong and independent risk factor for the development of heart failure, and both conditions frequently coexist, partly because of common risk factors.[297] Beta blockers are the cornerstone of therapy in patients with systolic heart failure, and confer a 27% reduction in the incidence of new-onset AF.[298] The rhythm control strategy has not been shown to be superior to rate control in heart failure patients with AF.[106] However, catheter ablation may lead to improvement in LV function, exercise tolerance, and quality of life with restoration of SR,[299] and is superior to AV nodal ablation and biventricular pacing.[300] It is also preferable to a rate-control strategy with beta blockers and/or digoxin by means of symptoms and neurohormonal status,[301] and to amiodarone by means

Table 53.27 Post-operative AF

ESC 2010 GL on AF. Prevention of post-operative AF	
Oral beta blockers for patients undergoing cardiac surgery in the absence of contraindications.	I-A
If used, beta blockers (or other oral antiarrhythmic drugs for AF management) are to be continued until the day of surgery.	I-B
Restoration of sinus rhythm by DCC in patients who develop post-operative AF and are haemodynamically unstable.	I-B
Ventricular rate control in patients with AF without haemodynamic instability.	I-C
Preoperative administration of amiodarone as prophylactic therapy for patients at high risk for post-operative AF.	IIa-A
Unless contraindicated, antithrombotic/anticoagulation medication for post-operative AF considered when the duration of AF is >48 h.	IIa-A
If sinus rhythm is restored successfully, anticoagulation for a minimum of 4 weeks but more prolonged in the presence of stroke risk factors.	IIa-B
Antiarrhythmic medications for recurrent or refractory post-operative AF in an attempt to maintain sinus rhythm.	IIa-C
Sotalol after cardiac surgery but is associated with risk of proarrhythmia.	IIb-A
Biatrial pacing after cardiac surgery.	IIb-A
Corticosteroids after cardiac surgery but are associated with risk.	IIb-B
AHA/ACC/HRS 2014 GL on AF. Postoperative cardiac and thoracic surgery	
Beta blocker in post-operative AF unless contraindicated.	I-A
A nondihydropyridine calcium channel blocker when a beta blocker is inadequate to achieve rate control in postoperative AF.	I-B
Preoperative administration of amiodarone as prophylactic therapy for patients at high risk for postoperative AF.	IIa-A
Restore sinus rhythm pharmacologically with ibutilide or direct-current cardioversion in patients who develop postoperative AF, as advised for nonsurgical patients.	IIa-B
Antiarrhythmic medications to maintain sinus rhythm in recurrent or refractory postoperative AF.	IIa-B
Antithrombotic medication in postoperative AF.	IIa-B
Cardioversion for well-tolerated, new-onset postoperative AF (with rate control and anticoagulation) if AF does not revert spontaneously to sinus rhythm during follow-up.	IIa-C
Prophylactic sotalol for patients at risk of developing AF following cardiac surgery.	IIb-B
Colchicine postoperatively to reduce AF following cardiac surgery.	IIb-B

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AHA/ACC/HRS 2014 Guideline for the management of patients with atrial fibrillation. *J Am Coll Cardiol*. 2014;**64**:2246–80 with permission from Elsevier.

of reduced AF burden and mortality (AATAC trial).[302] Addition of single-antiplatelet therapy to warfarin in patients with heart failure, AF, and vascular disease is not associated with additional benefit in thromboembolic or coronary risk, but increases bleeding risk.[303]

Recommendations are provided in Chapter 32 on heart failure.

Valve disease

AF is frequently seen in mitral and progressed aortic valve disease. Paroxysmal or persistent AF constitutes an indication for percutaneous or surgical intervention in mitral valve disease (Table 53.28). Successful catheter ablation may reduce functional MR with restoration of SR.[66]

Hyperthyroidism

AF occurs in 10–25% of patients, with hyperthyoidism especially in men and the elderly.[4] Treatment is aimed primarily at restoring a euthyroid state, which may be associated with a spontaneous reversion to sinus rhythm. If a rhythm control strategy is selected, thyroid function should be normalized prior to cardioversion to reduce the risk of recurrence (Table 53.29). Amiodarone may cause both hyper- and hypothyroidism. Hypothyroidism typically occurs within the first 1–24 months, and the prevalence is as high as 22%, especially in patients with anti-thyroid antibodies (Table 53.29).[304] There are two types of amiodarone-induced hyperthyroidism: type I, where there is an excess iodide-induced production of T4 and T3; and type II, where there is a destructive thyroiditis with a transient excess release of T4 and T3 and, later, reduced thyroid function. Although amiodarone may be continued when hypothyroidism has been successfully treated with replacement therapy, it is necessary to discontinue amiodarone if hyperthyroidism develops. Thyrotoxicosis may also occur after cessation of amiodarone therapy.

Wolff–Parkinson–White syndrome

The incidence of SCD in patients with Wolff–Parkinson–White syndrome ranges from 0 to 0.6% per year.[1] Markers

Table 53.28 ESC 2010 GL on AF. AF in valvular disease

OAC therapy (INR 2.0–3.0) in patients with mitral stenosis and AF (paroxysmal, persistent, or permanent).	I-C
OAC therapy (INR 2.0–3.0) in patients with AF and clinically significant mitral regurgitation.	I-C
Percutaneous mitral balloon valvotomy for asymptomatic patients with moderate or severe mitral stenosis and suitable valve anatomy who have new-onset AF in the absence of LA thrombus.	IIa-C
Early mitral valve surgery in severe mitral regurgitation, preserved LV function, and new-onset AF, even in the absence of symptoms, particularly when valve repair is feasible.	IIa-C

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Table 53.29 Hyperthyroidism

ESC 2010 GL on AF. AF in hyperthyroidism	
Antithrombotic therapy, based on the presence of other stroke risk factors in patients with active thyroid disease.	I-C
Beta blocker to control the rate of ventricular response in patients with AF complicating thyrotoxicosis, unless contraindicated.	I-C
When a beta blocker cannot be used, a non-dihydropyridine calcium channel antagonist (diltiazem or verapamil) to control the ventricular rate in thyrotoxicosis.	I-C
If a rhythm control strategy is desirable, it is necessary to normalize thyroid function prior to cardioversion, as otherwise the risk of relapse remains high.	I-C
Once a euthyroid state is restored, recommendations for antithrombotic prophylaxis are the same as for patients without hyperthyroidism.	I-C
AHA/ACC/HRS 2014 GL on AF. Hyperthyroidism	
Beta blockers to control ventricular rate in patients with AF complicating thyrotoxicosis unless contraindicated.	I-C
When a beta blocker cannot be used, a nondihydropyridine calcium channel antagonist to control the ventricular rate.	I-C

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of increased risk are short R-R intervals during pre-excited AF (<250 ms), a history of symptomatic tachycardia, the presence of multiple APs, or Ebstein's anomaly. AV nodal blocking agents are contraindicated in WPW syndrome. Recommendations are provided in Chapter 55.

Hypertrophic cardiomyopathy

Patients with hypertrophic cardiomyopathy (HCM) are at greater risk of developing AF compared with the general population, and around 20–25% develop AF, with an annual incidence of 2%.[2] AF is associated with increased risk for mortality, stroke, and severe functional disability, particularly in patients with outflow obstruction, ≤50 years of age, or those developing chronic AF.[305] A rhythm control strategy with catheter ablation seems preferable.[306] Additional antiarrhythmic drugs may be necessary, and amiodarone or disopyramide may be reasonable, although no controlled studies are available. Fast AF may also predispose to haemodynamic collapse and VF, and electrical or pharmacological cardioversion is indicated in the absence of atrial thrombus in patients presenting with acute-onset AF. When myectomy is considered, addition of MAZE-III procedure may also eliminate AF without increased perioperative mortality. Recommendations are provided in Chapter 37.

Chronic obstructive pulmonary disease

AF is common in patients with chronic lung disease and has adverse prognostic implications in the context of acute exacerbations associated with hypoxia. Treatment of the underlying pulmonary disease and correction of metabolic imbalance are the primary considerations, as antiarrhythmic therapy and electrical cardioversion are likely to be ineffective until respiratory decompensation has been corrected. Multifocal atrial tachycardia is common in severe COPD and may be mistaken for AF. Agents used to relieve bronchospasm, such as theophylline and beta-adrenergic agonists, may precipitate AF, and controlling the rate of ventricular response may be difficult in this situation. Non-selective beta blockers, propafenone, and adenosine are generally contraindicated in patients with bronchospasm, and non-dihydropyridine calcium channel antagonists are the preferred alternative (Table 53.30). Beta 1 selective blockers (e.g. nebivolol, bisoprolol, and metoprolol), in small doses, are also tolerated and effective.[307]

Renal failure patients undergoing dialysis

In an extensive, retrospective cohort study on dialysis patients with AF, warfarin did not reduce stroke risk and

Table 53.30 Pulmonary disease

ESC 2010 GL on AF. AF in pulmonary disease	
Correction of hypoxaemia and acidosis as initial management for patients who develop AF during an acute pulmonary illness or exacerbation of chronic pulmonary disease.	I-C
DCC in patients with pulmonary disease who become haemodynamically unstable as a consequence of AF.	I-C
A non-dihydropyridine calcium channel antagonist (diltiazem or verapamil) to control the ventricular rate in patients with obstructive pulmonary disease who develop AF.	IIa-C
Beta 1 selective blockers (e.g. bisoprolol), in small doses, as an alternative for ventricular rate control.	IIa-C
Theophylline and beta-adrenergic agonist agents in bronchospastic lung disease.	III-C
Non-selective beta blockers, sotalol, propafenone, and adenosine in obstructive lung disease.	III-C
AHA/ACC/HRS 2014 GL on AF. Pulmonary diseases	
A nondihydropyridine calcium channel antagonist to control the ventricular rate in chronic obstructive pulmonary disease.	I-C
Direct-current cardioversion in patients who become haemodynamically unstable as a consequence of new onset AF.	I-C

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Table 53.31 ESC 2010 GL on AF. Recommendations for AF in athletes

When a 'pill-in-the-pocket' approach with sodium channel blockers is used, sport cessation for as long as the arrhythmia persists and until 1–2 half-lives of the antiarrhythmic drug used have elapsed.	IIa-C
Isthmus ablation in competitive or leisure time athletes with documented atrial flutter, especially when therapy with flecainide or propafenone is intended.	IIa-C
Where appropriate, AF ablation to prevent recurrent AF in athletes.	IIa-C
When a specific cause for AF is identified in an athlete (such as hyperthyroidism), it is not recommended to continue participation in competitive or leisure time sports until correction of the cause.	III-C
It is not recommended to allow physical sports activity when symptoms due to haemodynamic impairment (such as dizziness) are present.	III-C

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was associated with a higher bleeding risk.[308] Thus, the issue is controversial but apixaban 2.5 mg bd or warfarin but with careful INR monitoring should be used in patients with high CHA2DS2-VASc scores.

Other conditions

AF in ACHD is discussed in Chapter 52. AF in valve disease and genetic channelopathies is discussed in the relevant chapters.

Athletes

The intensity of physical activity displays a U-shaped relationship with incident AF, which may indicate that the positive antiarrhythmic effects of physical activity are partially negated when exercise is too strenuous.[35,309] For practical purposes, only the pill-in-the pocket approach and catheter ablation are acceptable treatment options (Table 53.31).

AF in pregnancy

AF is rare during pregnancy in women without previously detected AF and without pre-existing heart disease.[2,67] However, AF or atrial flutter occurs in 1.3% of patients with structural heart disease with a peak at the end of the second trimester and is associated with unfavourable maternal outcome and lower fetal birth weight.[310] In patients with previously diagnosed AF, 52% experience new episodes during pregnancy. AF during pregnancy is well tolerated in most patients without congenital or valvular disease, but more fetal complications occur in those women who develop arrhythmias during pregnancy.

Rate control drugs Beta blockers cross the placenta and are associated with various adverse effects, including intrauterine growth retardation, neonatal respiratory depression, bradycardia, and hypoglycaemia, especially if treatment is initiated early in pregnancy (i.e. 12–24 weeks). No association with low weight for gestational age has been found for labetalol (started after the 6th week of gestation) as opposed to atenolol (see Chapter 25). Digoxin crosses the placenta freely, and digitalis intoxication in the mother has been associated with fetal death. Oral verapamil and diltiazem are most probably safe (Table 53.32). Sotalol, flecainide, or propafenone are second-choice drugs.

Drugs for atrial fibrillation conversion IV ibutilide or flecainide is usually effective and may be considered, although the experience during pregnancy is limited.[311,312] Amiodarone may cause neonatal hypothyroidism (9% of newborns), hyperthyroidism, goitre, and growth retardation. All drugs should, if possible, be avoided during the period of organogenesis in the first trimester of pregnancy.

Table 53.32 ESC 2010 GL on AF. AF in pregnancy

DCC can be performed safely at all stages of pregnancy and is recommended in patients who are haemodynamically unstable due to AF and whenever the risk of ongoing AF is considered high for the mother or for the fetus.	I-C
Protection against thromboembolism throughout pregnancy in AF patients with a high thromboembolic risk; the choice of agent (heparin or warfarin) according to the stage of pregnancy.	I-C
Oral VKA is from the second trimester until 1 month before expected delivery.	I-B
Subcutaneous LMWH during the first trimester and during the last month of pregnancy. Alternatively, UFH to prolong the aPTT to 1.5 times the control.	I-B
Beta blocker or a non-dihydropyridine calcium channel antagonist if rate control is necessary. During the first trimester of pregnancy, the use of beta blockers must be weighed against the potential risk of negative fetal effects.	IIa-C
IV flecainide or ibutilide if arrhythmia conversion is mandatory and DCC considered inappropriate in haemodynamically stable patients with structurally normal hearts.	IIb-C
Digoxin if rate control is indicated and beta blockers or non-dihydropyridine calcium channel antagonists are contraindicated.	IIb-C

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Direct current cardioversion Several case reports have demonstrated successful cardioversion of maternal AF, without harm to the fetus. Prior anticoagulation or TOE exclusion of left atrial thrombus is mandatory when AF is >48 h, and anticoagulation is maintained for 4 weeks. In AF <48 h, one IV UH or LMWH is given pericardioversion. Energy requirements in pregnant and non-pregnant women are similar.

Anticoagulation is recommended in patients with ≥2 risk points of the $CHADS_2$ score or 2 risk points of the CHA_2DS_2VASC score.[312] Vitamin K antagonists can be teratogenic in up to 7% of fetuses and, in many cases, should be substituted with UFH or LMWH for the first trimester.[312] Warfarin may be used in the second trimester at an only slightly elevated teratogenic risk. Warfarin crosses the placenta freely, and the fetus may be overdosed, even when the mother is in the therapeutic INR range. LMWH does not cross the placenta barrier and has been used for treatment and prophylaxis of venous thromboembolism during pregnancy without adverse fetal effects. Perhaps the most practical policy is to recommend subcutaneous administration of weight-adjusted therapeutic doses of LMWH during the first trimester and during the last month of pregnancy (Table 53.32). The new oral thrombin antagonists, such as dabigatran, have shown fetotoxicity at high doses and should not be used.[312]

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Chapter 54

Atrioventricular junctional tachycardias

Atrioventricular nodal reentrant tachycardia

Definition

Atrioventricular nodal reentrant tachycardia (AVNRT) denotes reentry in the area of the AV node. Several models have been proposed to explain the mechanism of the arrhythmia in the context of the complex anatomy of the AV node and its atrial extension.[1,2]

Epidemiology

AVNRT represents the most common regular supraventricular arrhythmia in the human.[3] The arrhythmia is more prevalent in women.

Pathophysiology

The concept of dual AV nodal pathways as the substrate for AVNRT dates from 1956 when Moe and colleagues demonstrated evidence of a dual AV conduction system in dogs. It was postulated that a dual conduction system was present, one having a faster conduction time and longer refractory period (fast pathway), the other having a slower conduction time and shorter refractory period (slow pathway) (Figure 54.1). At a critical coupling interval, the premature impulse blocks in the faster pathway and conducts in the, still excitable, slow pathway, causing a sudden jump in the AV conduction time. Following that, the impulse returns to the atria, supposedly via the fast pathway which has then recovered, and an atrial echo beat or sustained tachycardia results (Figure 54.2).[1] Denes and colleagues, in 1973, ascribed episodes of paroxysmal supraventricular tachycardia to AV node reentry due to the presence of dual atrioventricular nodal pathways and, using His bundle recordings and the atrial extrastimulus method, demonstrated sudden prolongation of the AH interval in a patient with dual atrioventricular nodal pathways (so-called atrioventricular conduction jumps).[1] In approximately 6% of patients with AV nodal reentry, antegrade conduction is thought to proceed over the slow pathway, and may result in an atypical form of AVNRT (Figure 54.3). In these patients, antegrade conduction curves are not discontinuous. This pattern of conduction as well as a potentially incessant nature can also be seen in the presence of concealed septal accessory pathways with decremental properties.[3]

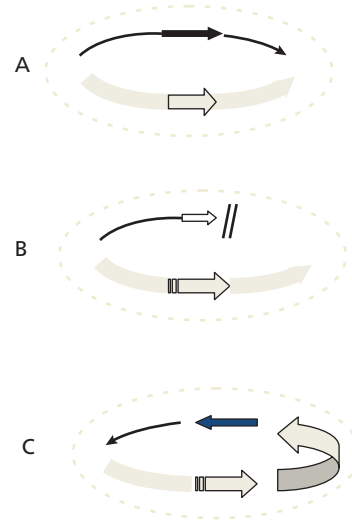

Figure 54.1 Theoretical depiction of the AV nodal reentrant circuit. During sinus rhythm, the impulse penetrates both the fast and slow pathways (A). A premature beat results in conduction block of the fast pathway and propagation through the slow pathway (B). An earlier impulse encounters more delay in the slow pathway in a way that the blocked fast pathway has recovered when the now retrograde impulse arrives and tachycardia begins (C).

The concept of longitudinally dissociated dual AV nodal pathways that conduct around a central obstacle with proximal and distal connections can provide explanations for many aspects of the electrophysiological behaviour of these tachycardias, but several obscure points remain. These pathways have not been demonstrated histologically, the exact circuit responsible for the reentrant tachycardia is unknown, and critical questions still remain unanswered. Consequently, several attempts to provide a reasonable hypothesis based on anatomic or anisotropic models have appeared.[4,5] There has been considerable evidence that the right and left inferior extensions of the human AV node and the atrio-nodal inputs they facilitate may provide the anatomic substrate of the slow pathway,[6,7] and a comprehensive model of the tachycardia circuit for all forms of atrioventricular nodal reentrant tachycardia based on the concept of atrio-nodal inputs has been proposed (Figure 54.4).[1] Still, however, the exact circuit of AVNRT remains elusive.

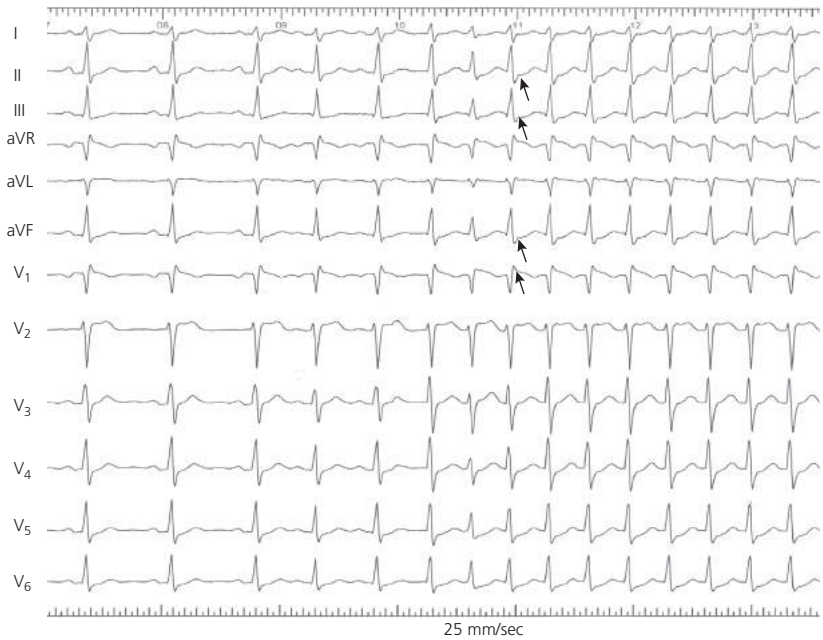

Figure 54.2 Induction of typical AVNRT by atrial ectopy. The first three beats are sinus beats. The next two are atrial ectopics conducted with a short PR (apparently over the fast pathway). The next atrial ectopic is conducted with a prolonged PR over the slow pathway, due to antegrade block of the fast pathway, and initiates AVNRT by returning retrogradely through the fast pathway that has recovered. Retrograde P waves are more prominent in lead V_1 and especially the inferior leads (arrows).

Katritsis DG, Camm AJ. Atrioventricular nodal reentrant tachycardia. *Circulation*. 2010;**122**:831–40 with permission from Wolters Kluwer.

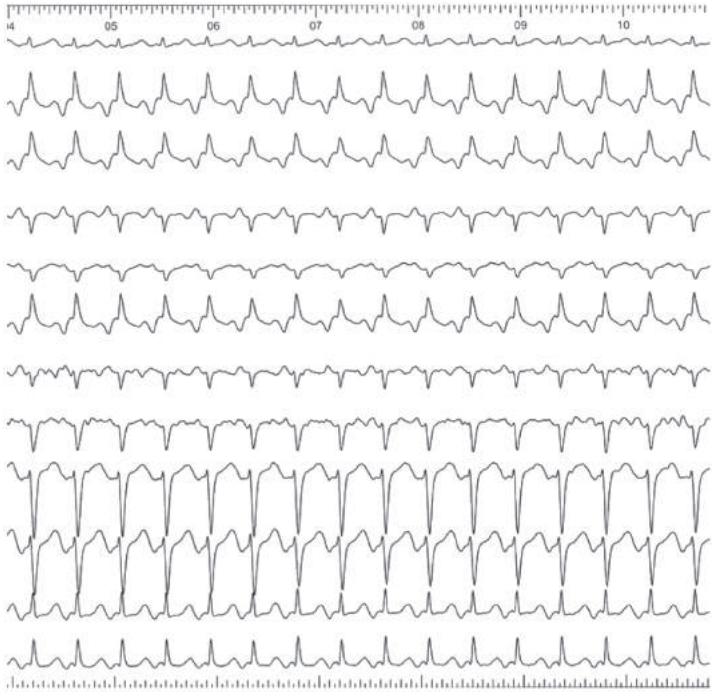

Figure 54.3 Long RP tachycardia due to atypical AVNRT. Note negative P waves in inferior leads, but positive P wave in lead V_1.

Presentation

Reentrant atrioventricular tachycardias tend to appear first in youth, and the attacks recur throughout life as **regular palpitations of sudden onset and offset**. Occasionally, certain events, such as physical exercise, emotional upset, indigestion, or alcohol consumption, precipitate attacks. Polyuria, probably indicating increased ANP levels, may be present during or after a prolonged attack. AVNRT may result in AF that usually, although not invariably, is eliminated following catheter ablation of AVNRT.[8]

Diagnosis

ECG morphologies

Typically, AVNRT is a narrow complex tachycardia, i.e. QRS duration less than 120 ms (Figure 54.2), unless an aberrant conduction, which is usually of the RBBB type, or a previous conduction defect exists. Tachycardia-related ST depression, as well as RR interval variation, may be seen. RR alternans may be seen but are more common in AVRT.

In the **typical form** of AVNRT (also called slow-fast AVRNT), abnormal (retrograde) P waves are constantly related to the QRS and, in the majority of cases, are indiscernible or very close to the QRS complex RP >PR.

Thus, P waves are either masked by the QRS complex or seen as a small terminal P' wave that is not present during sinus rhythm (Figure 54.5).

In the **atypical form** of AVNRT, P waves are clearly visible before the QRS, i.e. RP > PR denoting a **'long RP tachycardia'**, and are negative or shallow in leads II, III, aVF, and V_6 but positive in V_1.

Other causes of long RP tachycardia are presented in Table 54.1.

Although AV dissociation is usually not seen, it can occur since neither the atria nor the ventricles are necessary for the reentry circuit. If the tachycardia is initiated by atrial ectopic beats, the initial (ectopic) P wave usually differs from the subsequent (retrograde) P waves (Figure 54.2).

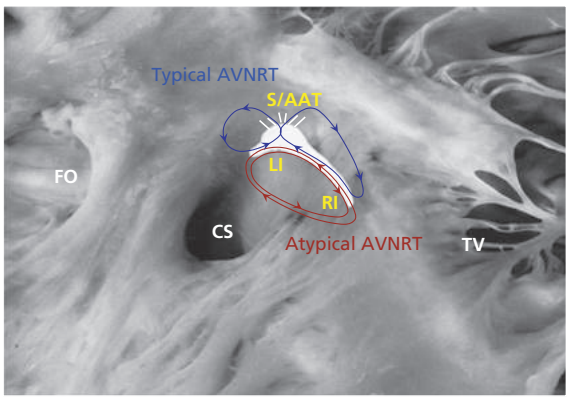

Figure 54.4 Proposed circuit of AVNRT. During typical AVNRT (slow-fast), right- or left-sided circuits may occur with antegrade conduction through the inferior inputs and retrograde conduction through the superior inputs (S) or the anisotropic atrionodal transitional area (AAT). In atypical AVNRT conduction occurs anterogradely through one of the inferior inputs, left (LI) or right (RI) and retrogradely through the inferior inputs and retrogradely through the other one. Depending on the orientation of the circuit we may record the so-called 'fast-slow' or 'slow-slow' types.

Katritsis DG, *et al*. Atypical atrioventricular nodal reentrant tachycardia: prevalence, electrophysiologic characteristics, and tachycardia circuit. *Europace*. 2015;**17**:1099–106 with permission from Oxford University Press.

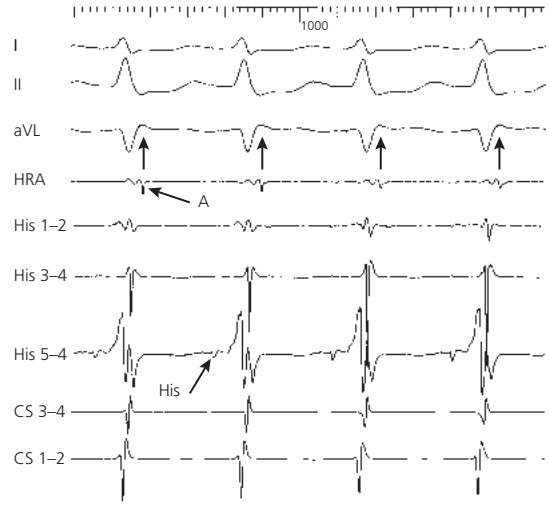

Figure 54.5 Electrograms during slow-fast AVNRT. The A-H interval (as measured from the A on the HRA electrode to the His on the His bundle electrode) is longer than the H-A. Small P waves at the end of QRS correspond to retrograde atrial conduction (small arrows).

I, ECG lead I, lead I of the surface ECG; II, ECG lead II, lead II of the surface ECG; aVL, lead aVL of the surface ECG; HRA, high right atrium; His, His bundle; CS, coronary sinus; A, atrial electrogram; His: His bundle electrogram.

Table 54.1 Long RP tachycardias

1. Sinus tachycardia
2. Atrial tachycardia
3. Atypical atrioventricular nodal reentrant tachycardia
4. Atrioventricular reentrant tachycardia due to slowly conducting concealed accessory pathways

Electrophysiologic classification

The recognition of the fact that AVNRT may present with atypical retrograde atrial activation has made diagnosis of the arrhythmia, as well as classification attempts, more complicated. Heterogeneity of both fast and slow conduction patterns has been well described, and all forms of AVNRT may display anterior, posterior, and middle, or even left, atrial retrograde activation patterns.

Typical AVNRT In the ***slow-fast type*** of AVNRT, the onset of atrial activation appears prior to, at the onset of, or just after the QRS complex, thus maintaining an atrial-His/His-atrial ratio (AH/HA) >1 (Figure 54.5). The VA interval measured from the onset of ventricular activation on surface ECG to the earliest deflection of the atrial activation in the His bundle electrogram is ≤60. Although, typically, the earliest retrograde atrial activation is being recorded at the His bundle electrogram, detailed mapping studies have demonstrated that posterior, or even left, septal fast pathways may occur in up to 7.6% in patients with typical AVNRT.[9,10,11]

Atypical AVNRT Atypical AVNRT is seen in approximately 6% of all AVNRT cases.[12] It is traditionally classified as fast-slow or slow-slow, but criteria used are not unanimously accepted.[13] In the so-called ***fast-slow type*** of AVNRT, retrograde atrial electrograms begin well after ventricular activation with an AH/HA ratio <1, indicating that retrograde conduction is slower than antegrade conduction. The AH interval is less than 185–200 ms. The VA interval, measured from the onset of ventricular activation on surface ECG to the earliest deflection of the atrial activation in the His bundle electrogram, is >60 ms. Earliest retrograde atrial activation is traditionally reported at the base of the triangle of Koch, near the coronary sinus ostium. Detailed mapping of retrograde atrial activation in a large series of patients, however, has produced variable results, with eccentric atrial activation at the lower septum or even the distal coronary sinus.[11,14,15] In the ***slow-slow type***, the AH/HA ratio is >1, and the AH interval > 200 ms, but the VA interval is >60 ms, suggesting that two slow pathways are utilized for both anterograde and retrograde activation. Earliest retrograde atrial activation is usually at the coronary sinus ostium, but variants of left-sided atrial retrograde activation (distal coronary sinus) have also been published.[2]

The distinction between 'fast-slow' and 'slow-slow' forms is of no practical significance and certain cases of atypical AVNRT cannot be classified according to described criteria. AVNRT can be classified as typical or atypical according to the HA interval or, when a His bundle electrogram is not reliably recorded, according to the VA interval measured on the His bundle recording electrode (Table 54.2).[13]

Table 54.2 Classification of AVNRT types. Variable earliest retrograde atrial activation has been described for all types

Conventional classification			
	AH/HA	**VA (His)**	**Usual ERAA**
Typical AVNRT			
Slow-fast	>1	<60 ms	RHis, CS os, LHis
Atypical AVNRT			
Fast-slow	<1	>60 ms	CS os, LRAS, dCS
Slow-slow	>1	>60 ms	CS os, dCS
New proposed classification			
	HA	**VA (His)**	**AH/HA**
Typical AVNRT	≤70 ms	≤60 ms	>1
Atypical AVNRT	>70 ms	>60 ms	Variable

AH, atrial to His interval; HA, His to atrium interval; VA, interval measured from the onset of ventricular activation on surface ECG to the earliest deflection of the atrial activation in the His bundle electrogram; ERAA, earliest retrograde atrial activation; RHis, His bundle electrogram recorded from the right septum; LHis, His bundle electrogram recorded from the left septum; LRAS, low right atrial septum; CS os, ostium of the coronary sinus; dCS, distal coronary sinus.
Atypical AVNRT has been traditionally classified as fast-slow (HA>70 ms, VA>60, AH/HA<1, and AH<200 ms) or slow-slow (HA>70 ms, VA>60 ms, AH/HA>1, and AH>200 ms). Not all of these criteria are always met and atypical AVNRT may not be sub-classified accordingly.
AH: atrial to His interval, HA: His to atrium interval, VA: interval measured from the onset of ventricular activation on surface ECG to the earliest deflection of the atrial activation on the His bundle electrogram.
Katritsis DG, Camm AJ. Atrioventricular nodal reentrant tachycardia. *Circulation*. 2010;**122**:831–40 with permission from Wolters Kluwer.
Katritsis DG, Josephson ME. Classification of electrophysiological types of atrioventricular nodal re-entrant tachycardia: a reappraisal. *Europace*. 2013;Apr 23.

Differential diagnosis

In the presence of a **narrow-QRS tachycardia**, AVNRT should be differentiated from: *atrial tachycardia orthodromic atrioventricular reentrant tachycardia* (AVRT) due to a septal accessory pathway. Atrial tachycardia is usually a narrow-QRS tachycardia. Conduction with aberration or over a bystanding pathway are rare possibilities. Narrow-QRS AVRT in the absence of overt pre-excitation, i.e. Wolff–Parkinson–White syndrome, is due to a concealed accessory pathway that is responsible for orthodromic tachycardia.

When a **wide-QRS tachycardia** is encountered and ventricular tachycardia is excluded, the possible diagnoses are:

- *AVNRT with aberrant conduction* due to bundle branch block
- *Atrial tachycardia with aberrant conduction* due to bundle branch block
- *AVNRT with a bystanding accessory pathway*
- *Antidromic AVRT due to an accessory pathway.*

Aberrant conduction, although rare, can be seen in AVNRT and is usually of the RBBB type. However, cases of LBBB have been reported.

Although differential diagnosis is usually accomplished at electrophysiology study, several electrocardiographic criteria may indicate AVNRT, and they are specific but modestly sensitive.[3]

- In case of relatively delayed retrograde conduction that allows the identification of retrograde P waves, a pseudo r deflection in lead V1 and a pseudo S wave in the inferior leads are more common in AVNRT rather than in AVRT due to an accessory pathway or atrial tachycardia.
- A difference of RP intervals in lead V1 and III > 20 ms is also indicative of AVNRT rather than AVRT due to a posteroseptal pathway.
- The presence of a notch in lead aVL has also been found as a reliable criterion suggesting AVNRT, while a pseudo R in aVR was shown to have higher sensitivity and specificity than an R in V1.
- The documentation of preexcited beats as well as AV dissociation during tachycardia are useful diagnostic criteria. AV block or AV dissociation due to block, although uncommon and short-lasting, or a coexisting arrhythmia such as atrial fibrillation may be seen during AVNRT and exclude AVRT.
- Tachycardia cycle length (CL) variability ≥15 ms is common in SVT. A change in atrial CL that predicts the change in subsequent ventricular CL strongly favours AT or atypical AVNRT. A change in atrial CL that is predicted by the change in the preceding ventricular CL favours typical AVNRT or AVRT. Conversely, changing R-R intervals with a fixed V-A interval excludes atrial tachycardia.

Therapy

In acute episodes of AVNRT that do not respond to Valsalva manoeuvres, intravenous adenosine is the treatment of choice. Alternatively, a single dose of oral diltiazem (120 mg) and a beta-blocker (i.e. propranolol 80 mg) may be tried.[16] Chronic administration of antiarrhythmic drugs (such as beta-blockers, non-dihydropyridine calcium channel blockers, flecainide, or propafenone) may be ineffective in up to 50% of cases (Tables 54.3 and 53.4, and Figures 54.6 and 54.7).[2] Thus,

Table 54.3 ACC/AHA/ESC 2003 GL on SVT. Recommendations for long-term treatment of patients with recurrent AVNRT

Poorly tolerated AVNRT with haemodynamic intolerance	
Catheter ablation	I-B
Verapamil, diltiazem, beta-blockers, sotalol, amiodarone	IIa-C
Flecainide, propafenone (not in CAD/low LVEF)	IIa-C
Recurrent symptomatic AVNRT	
Catheter ablation	I-B
Verapamil	I-B
Diltiazem, beta-blockers	I-C
Digoxin (overridden by enhanced sympathetic tone)	IIb-C
Recurrent AVNRT unresponsive to beta-blockade or calcium channel blocker and patient not desiring RF ablation	
Flecainide, propafenone, sotalol	IIa-B
Amiodarone	IIb-C
AVNRT with infrequent or single episode in patients who desire complete control of arrhythmia	
Catheter ablation	I-B

(*Continued*)

Table 54.3 Continued

Documented PSVT with only dual AV-nodal pathways or single echo beats demonstrated during electrophysiological study and no other identified cause of arrhythmia	
Verapamil, diltiazem, beta-blockers, flecainide, propafenone	I-C
Catheter ablation	I-B
Infrequent, well-tolerated AVNRT	
No therapy	I-C
Vagal manoeuvres	I-B
Pill-in-the-pocket	I-B
Verapamil, diltiazem, beta-blockers	I-B
Catheter ablation	I-B

ACC/AHA /ESC 2003 Guidelines for the management of patients with supraventricular arrhythmias. *Eur Heart J*. 2003;**24**:1857–97, with permission from Oxford University Press.

catheter ablation is the current treatment of choice. Slow pathway ablation or modification is effective in both typical and atypical AVNRT. Usually, a combined anatomical and mapping approach is employed with ablation lesions delivered at the inferior or mid-part of the triangle of Koch, either from the right or the left septal side.[17,18] Multicomponent atrial electrograms or low amplitude potentials, although not specific for the identification of slow pathway conduction, are successfully used to guide ablation at these areas. This approach offers a success rate of 95%, is associated with a risk of 0.5–1% AV block, and has an approximately 4% recurrence rate. There is no procedure-related mortality.[19,20] Advanced age is not a contraindication for slow pathway ablation.[21] The pre-existence of first-degree heart block may carry a higher risk for late AV block and, avoidance of extensive slow pathway ablation is preferable in this setting.[22] Cryoablation may carry a lower risk of AV block, but it is rather negligible and this mode of therapy is associated with a significantly higher recurrence rate.[23]

Table 54.4 ACC/AHA/HRS 2015 GL on SVT. AVNRT

Acute treatment	
Vagal maneuvers	I-B-R
Adenosine	I-B-R
Synchronized cardioversion for hemodynamically unstable patients when adenosine and vagal maneuvers do not terminate the tachycardia or are not feasible	I-B-NR
Synchronized cardioversion for hemodynamically stable patients when pharmacological therapy is ineffective or contraindicated	I-B-NR
IV beta blockers, diltiazem, or verapamil for hemodynamically stable patients	IIa-B-R
Oral beta blockers, diltiazem, or verapamil for hemodynamically stable patients	IIb-C-LD
IV amiodarone for hemodynamically stable patients when pharmacological therapy is ineffective or contraindicated	IIb-C-LD
Ongoing management	
Verapamil or diltiazem in patients who are not candidates for catheter ablation	I-B-R
Catheter ablation of the slow pathway	I-B-NR
Beta blockers in patients who are not candidates for catheter ablation	I-B-R
Flecainide or propafenone in patients without structural heart disease or ischemic heart disease and not candidates for, or prefer not to undergo, catheter ablation and in whom beta blockers, diltiazem, or verapamil are ineffective or contraindicated	IIa-B-R
Clinical follow-up without pharmacological therapy or ablation in minimally symptomatic patients	IIa-B-NR
Sotalol or dofetilide or digoxin or amiodarone in patients who are not candidates for catheter ablation	IIb-B-R
Self-administered ("pill-in-the-pocket") acute doses of oral beta blockers, diltiazem, or verapamil for infrequent, well-tolerated episodes of AVNRT	IIb-C-LD

ACC/AHA/HRS 2015 Guideline for the management of adult patients with supraventricular tachycardia. *J Am Coll Cardiol*. 2015; doi:10.1016/j.jacc.2015.08.856 with permission from Elsevier.

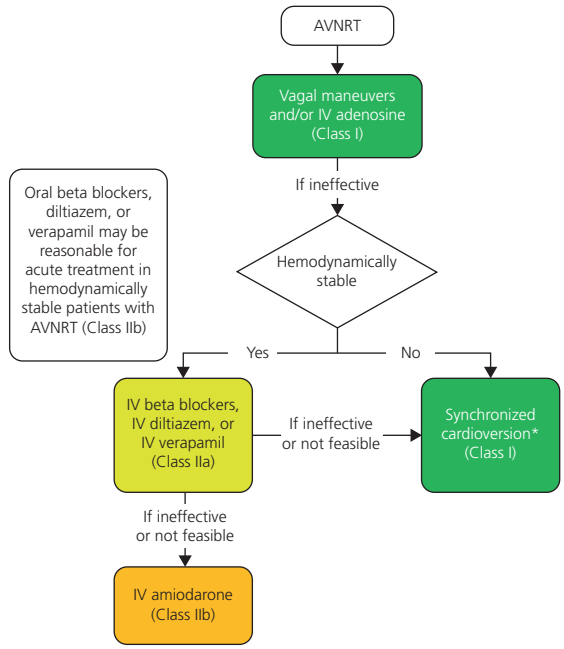

Figure 54.6 ACC/AHA.HRS 2015 GL on SVT. Acute treatment of AVNRT.

Drugs listed alphabetically.
*For rhythms that break or recur spontaneously, synchronized cardioversion is not appropriate.
ACC/AHA/HRS 2015 Guideline for the management of adult patients with supraventricular tachycardia. *J Am Coll Cardiol*. 2015;doi:10.1016/j.jacc.2015.08.856 with permission from Elsevier.

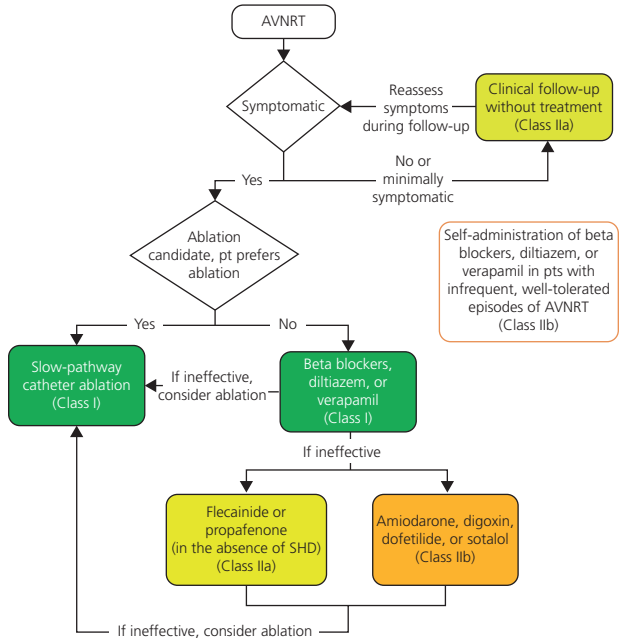

Figure 54.7 ACC/AHA.HRS 2015 GL on SVT. Ongoing management of AVNRT.

Drugs listed alphabetically.
SHD: structural heart disease (including ischemic heart disease).
ACC/AHA/HRS 2015 Guideline for the management of adult patients with supraventricular tachycardia. *J Am Coll Cardiol*. 2015;doi:10.1016/j.jacc.2015.08.856 with permission from Elsevier.

Non-reentrant junctional tachycardias

Non-reentrant junctional tachycardias are rare, but should be recognized because catheter ablation conveys a higher risk of AV block than in AVNRT (5–10%) (Tables 54.5 and 54.6, and Figure 54.8).

Non-paroxysmal junctional tachycardia was frequently diagnosed in the past as a junctional rhythm of gradual onset and termination, with a rate between 70 and 130 beats/min, and was considered a typical example of digitalis-induced delayed after-depolarizations and triggered activity in the AV node. Myocardial ischaemia, hypokalaemia, COPD, and myocarditis are also associated conditions.

Table 54.5 ACC/AHA/ESC GL on SVT 2003. Recommendations for treatment of focal and non-paroxysmal junctional tachycardia syndromes

Focal junctional tachycardia	
Beta-blockers	IIa-C
Flecainide	IIa-C
Propafenone (paediatric pts)	IIa-C
Sotalol (paediatric pts)	IIa-C
Amiodarone (paediatric pts)	IIa-C
Catheter ablation	IIa-C
Non-paroxysmal junctional tachycardia	
Reverse digitalis toxicity	I-C
Correct hypokalaemia	I-C
Treat myocardial ischaemia	I-C
Beta-blockers, calcium channel blockers	IIa-C

ACC/AHA /ESC 2003 Guidelines for the management of patients with supraventricular arrhythmias. *Eur Heart J*. 2003;**24**:1857–97, with permission from Oxford University Press.

Table 54.6 ACC/AHA/HRS 2015 GL on SVT. Junctional tachycardia (JT)

Acute treatment	
IV beta blockers in symptomatic junctional tachycardia	IIa-C-LD
IV diltiazem, procainamide, or verapamil in junctional tachycardia	IIa-C-LD
Ongoing management	
Beta blockers	IIa-C-LD
Diltiazem or verapamil	IIa-C-LD
Flecainide or propafenone in patients without structural heart disease or ischemic heart disease	IIb-C-LD
Catheter ablation when medical therapy is not effective or contraindicated	IIb-C-LD

ACC/AHA/HRS 2015 Guideline for the management of adult patients with supraventricular tachycardia. *J Am Coll Cardiol*. 2015;doi:10.1016/j.jacc.2015.08.856 with permission from Elsevier.

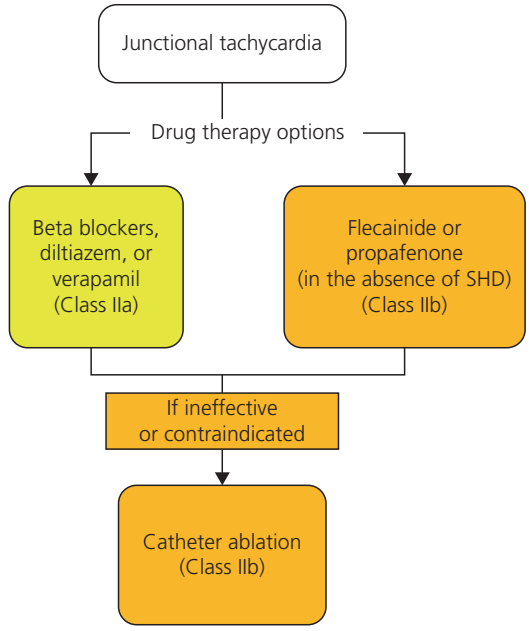

Figure 54.8 ACC/AHA.HRS 2015 GL on SVT. Ongoing management of junctional tachycardia.

Drugs listed alphabetically.
SHD: structural heart disease (including ischaemic heart disease).
ACC/AHA/HRS 2015 Guideline for the management of adult patients with supraventricular tachycardia. *J Am Coll Cardiol*. 2015;doi:10.1016/j.jacc.2015.08.856 with permission from Elsevier.

Focal junctional tachycardia is an uncommon arrhythmia that arises from abnormal automaticity at the AV node or proximal His bundle. In children it may be seen as a congenital arrhythmia or, more often, early after infant open heart surgery.[24] It can also be seen in adult patients with a structurally normal heart.[25] The usual electrocardiographic finding is a narrow QRS tachycardia with AV dissociation. Occasionally, the tachycardia might be irregular, thus resembling atrial fibrillation. Focal catheter ablation at the site of the earliest atrial activation is possible, but carries a lower success rate and a higher risk of AV block compared to AVNRT.[26]

Non-reentrant atrioventricular nodal tachycardia caused by **simultaneous multiple nodal pathway conduction** is an uncommon mechanism of AV nodal tachycardia and has been associated with repetitive retrograde concealment or 'linking' phenomena.[2] These are expressed in the form of ventricular pauses with consistent AV relationship after the pause.

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Chapter 55

Atrioventricular reentrant tachycardias

Definitions

The anatomical basis for atrioventricular reentrant tachycardia (AVRT) is an abnormal connection (accessory pathway) between atrial and ventricular myocardium. One limb of the reentrant circuit is the AV node, and the other is the anomalous connection. The term **pre-excitation** refers to activation of the ventricle by an impulse arising in the atrium, earlier than would be expected if conduction occurred via the normal atrioventricular conduction pathway. The term was first used to describe electrocardiographic abnormalities in patients with typical **Wolff–Parkinson–White (WPW) syndrome**, i.e. short PR interval (<120 ms), prolonged QRS (>120 ms), with an initial delta wave and paroxysmal tachycardia (Figure 55.1).

Epidemiology

WPW syndrome is the second most common cause of paroxysmal supraventricular tachycardia in most parts of the world, and is the most common cause in China, being responsible for more than 70% of cases.[1] In Western countries, the prevalence of WPW syndrome is 0.1–0.3%, and there is 4-fold increase of this in family members of WPW patients.[1]

Pathophysiology

The atrioventricular connections (previously known as bundles of Kent), when fully operating, produce the typical **WPW syndrome**. Atrio-nodal bypass tracts (previously known as James fibres) are considered to result in the so-called **Lown–Ganong–Levine syndrome**, i.e. short PR and normal QRS, although there is no histologic evidence for the existence of this entity. Accessory pathways capable of conduction in the antegrade direction may produce pre-excitation during sinus rhythm, and the reentrant circuit can use either the AV node or the pathway as the antegrade limb. In the first case, the AVRT is called **orthodromic** and is narrow complex (Figure 55.2), unless showing RBBB or, less usually, LBBB aberration. In the second case, the AVRT is **antidromic** and pre-excited, i.e. wide complex (Figure 55.3). Pre-excited AVRT, in which an accessory

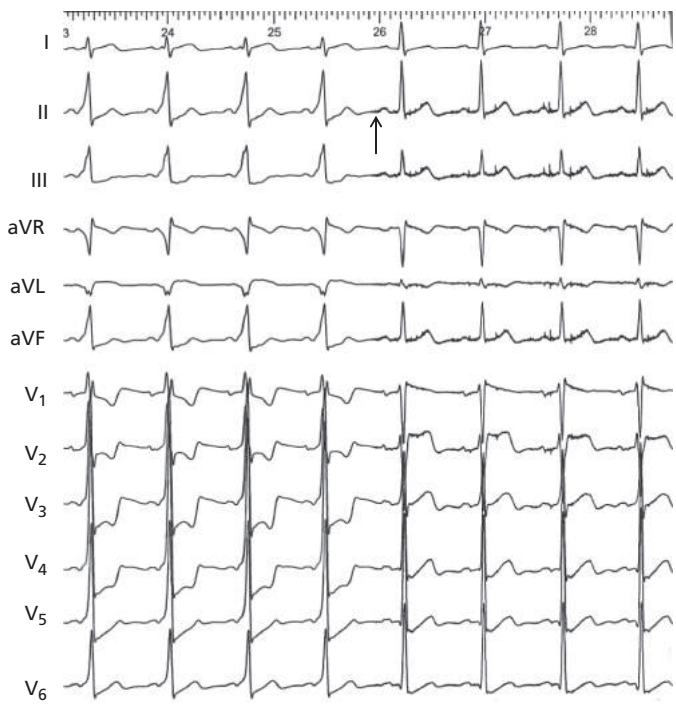

Figure 55.1 Wolff–Parkinson–White syndrome due to a left lateral accessory pathway. Application of radiofrequency energy during catheter ablation (arrow) results in loss of pre-excitation and restoration of normal conduction.

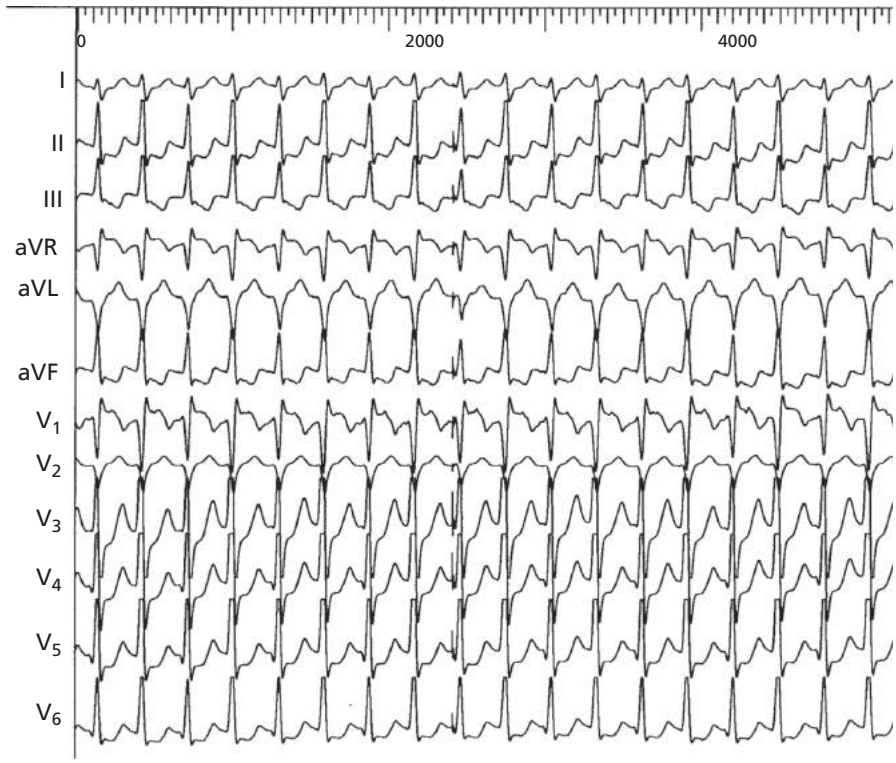

Figure 55.2 Orthodromic AVRT due to a concealed posteroseptal pathway.

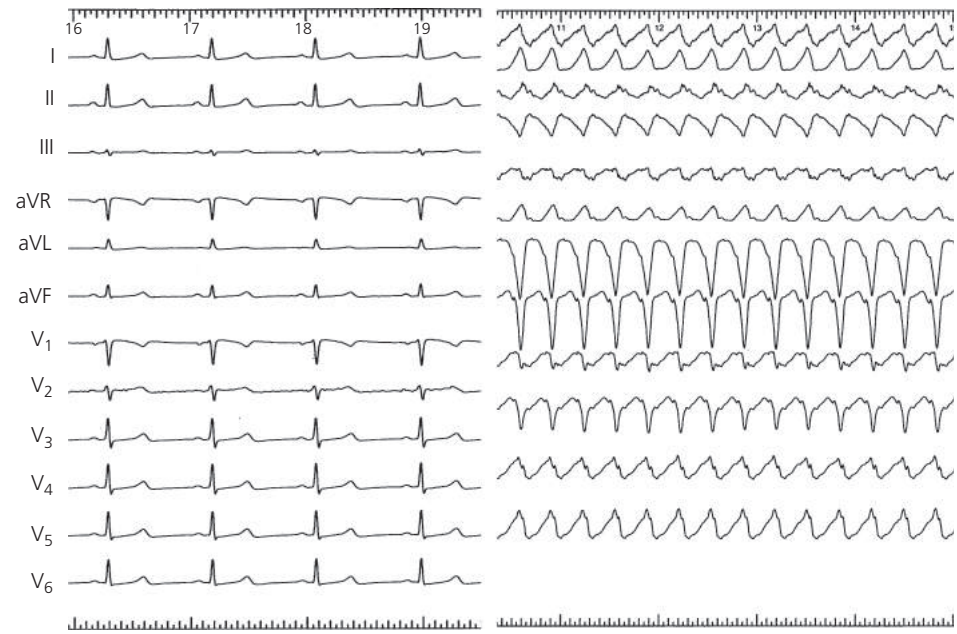

Figure 55.3 Antidromic AVRT due to an atriohisian Mahaim pathway. Note that ECG is normal during sinus rhythm (left panel). Antidromic AVRT due to an atriofascicular pathway usually produces a horizontal or superior QRS axis, but normal axis may also occur, depending on the way of insertion into the right bundle and fusion over the left anterior fascicle.

atrioventricular connection is used as the antegrade limb and the AV node or a second pathway serves as the retrograde limb of the circuit, has been clinically documented in less than 5% of patients with WPW syndrome and may be induced in less than 10% in the EP laboratory.[2] This usually happens in patients with multiple pathways or with free wall pathways located, at least, >4 cm from the AV node, although, in children, it may be seen even with septal pathways.[2] If the pathway conducts only in the retrograde direction, the so-called **concealed accessory pathway**, the ECG during sinus rhythm is normal and only orthodromic AVRT can be produced. Approximately 8% of accessory pathways display decremental antegrade or retrograde conduction. The term **permanent junctional reciprocating tachycardia** (PJRT) refers to orthodromic AVRT due to a slowly conducting, concealed, and usually septal pathway. There is incessant SVT, usually with negative P waves in the inferior leads and a long RP interval. **Mahaim** pathways are **atriofascicular** or (rarely) **nodoventricular** pathways, characterized by decremental conduction that results in gradual increase of the atrioventricular interval, simultaneous with the development of left bundle branch block. Antidromic and, rarely, orthodromic tachycardias may be induced with possible VA block in the case of a nodoventricular fibre.

Aetiology

Accessory pathways are a congenital disorder. Rarely, atrioventricular connections can be iatrogenic following a Fontan operation.[3] A missense mutation in the gene that encodes the gamma 2 regulatory subunit of AMP-activated protein kinase (PRKAG2) has been associated with ventricular preexcitation and conduction disease.[4] A particular mutation in PRKAG2 has also been associated with Mahaim (nodoventricular fibres).[4] A novel form of WPW syndrome is associated with microdeletion in the region of gene BMP2 that encodes the bone morphogenetic protein-2, a member of the transforming growth factor (TGF-β) gene superfamily, and affects the development of annulus fibrosus. It is characterized by variable cognitive deficits, dysmorphic features, and prolonged AV conduction on atrial pacing.[4]

Presentation

Patients present due to **sudden onset and offset episodes of palpitations** or with **pre-excited AF** (ie, AF with wide-QRS–up to 30%). During AF, antegrade conduction over the accessory pathway results in a wide QRS complex tachyarrhythmia which may be mistaken for ventricular tachycardia. Up to 50% of patients with WPW syndrome are asymptomatic,[5] and diagnosis is made after an incidental ECG. Loss of antegrade conduction capacity occurs with time in up to 30% of patients,[5] but, when pre-excitation remains, the frequency of tachycardia increases with age.[6]

WPW predisposes to development of AF which may, or may not, be eliminated following ablation of the pathway.[7,8] The risk of cardiac arrest/VF in WPW syndrome is 0.0024 per person-years,[9] and the reported incidence of sudden death ranges between 0 and 0.0015 per person-years.[9–11]

Diagnosis

Patients with concealed pathways, as well as some with Mahaim fibres, have completely normal resting ECG. Antegradely conducting pathways may produce the typical WPW pattern or may be latent. Latent pathways, when conducting antegradely, may be revealed by infusion of adenosine or sometimes isoprenaline. In approximately 1.3% of cases of WPW syndrome, more than one accessory pathway is present.[12] Left free wall pathways are the most common, followed by posteroseptal, right free wall, and anteroseptal. Right-sided pathways are found in 10% of patients with Ebstein's anomaly. Several guides for the localization of the pathway from the surface ECG have been proposed (Figure 55.4).[13]

Risk stratification in WPW syndrome

The clinical significance of pre-excitation is related to the common association with arrhythmias, such as atrioventricular reentrant tachycardias and atrial fibrillation. Atrial fibrillation associated with the WPW syndrome may be life-threatening, especially if the accessory pathway has a short refractory period, allowing a very rapid ventricular rate or resulting in ventricular fibrillation. The issues of risk stratification and need for catheter ablation still remain controversial. A meta-analysis has demonstrated a very low incidence of life-threatening arrhythmia and sudden death (0.0012 per patient-years) in patients with asymptomatic pre-excitation, that is doubled in children compared to adults.[11] In patients with symptomatic pre-excitation the risk of sudden cardiac death is also low, approximately 0.0015 per patient-years.[10] Symptomatic patients have a 7% risk of developing fast AF, with the shortest pre-excited RR interval ≤250 ms, and a 1.4% risk of haemodynamic collapse or cardiac arrest resulting from ventricular fibrillation that, however, may not necessarily be lethal, within the next 3–4 years.[14] The risk of cardiac arrest/VF was recently estimated at 2.4 per 1000 person-years (95% confidence interval, 1.3–3.9), but no deaths were reported in this registry of 2169 patients over an 8-year follow-up.[9]

Main methods of risk stratification are exercise testing to reveal potential disappearance of preexcitation, and recording of a shortest preexcited RR interval (SPERRI) during AF. A SPERRI <250 ms, or an effective refractory

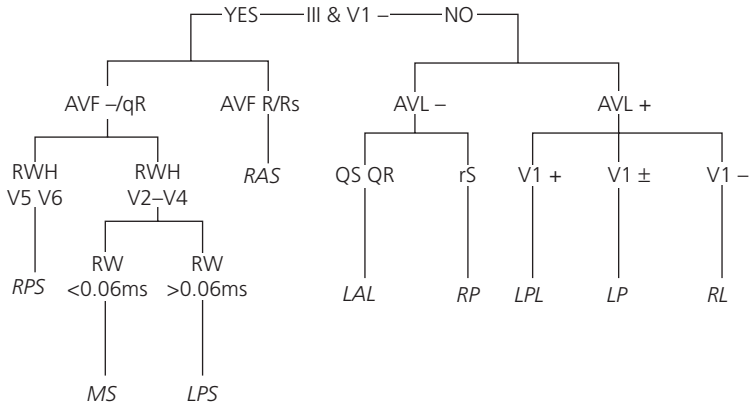

Figure 55.4 The St George's algorithm for localization of accessory pathways. YES, QRS complex negative in both lead III and lead V1; +, positive QRS complex; –: negative QRS complex; ±, equiphasic QRS complex; LAL, left anterolateral; LP, left posterior; LPL, left posterolateral; LPS, left posteroseptal; MS, midseptal; RAS, right anteroseptal; RP, right posterior; RPS, right posteroseptal; RL, right lateral; RW, R wave width in V_1; RWH, the highest R wave recorded in precordial leads.

Xie B, *et al*. Localization of accessory pathways from the 12-lead electrocardiogram using a new algorithm. *Am J Cardiol*. 1994;**74**:161–5 with permission from Elsevier.

period of the pathway <240 ms indicates high risk.[15–17] Additional risk factors are induction of AVRT degenerating to AF, antegrade refractory period of the pathway at electrophysiology study of <240 ms, young age, and multiple accessory pathways.[9–11,14] Isoproterenol challenge during electrophysiology study to overcome the effects of sedation on autonomic tone increases the antegrade conduction capacity of the pathway, and may also reveal high-risk.[18] The indications for catheter ablation of an overt AP in an asymptomatic patient are still controversial (especially in children), and each case should be addressed individually.[19–21]

Therapy

In acute episodes of narrow QRS tachycardia that do not respond to Valsalva manoeuvres, intravenous adenosine is the treatment of choice. Alternatively, a single dose of oral diltiazem (120 mg) and a beta blocker (i.e. propranolol 80 mg) may be tried.[22] In wide QRS tachycardia, adenosine

Table 55.1 ACC/AHA/ESC 2003 GL on SVT. Recommendations for long-term therapy of accessory pathway-mediated arrhythmias

WPW syndrome (pre-excitation and symptomatic arrhythmias), well tolerated	Catheter ablation	I-B
	Flecainide, propafenone, sotalol, amiodarone, beta blockers	IIa-C
	Verapamil, diltiazem, digoxin	III-C
WPW syndrome (with AF and rapid-conduction or poorly tolerated AVRT)	Catheter ablation	I-B
AVRT, poorly tolerated (no pre-excitation)	Catheter ablation	I-B
	Flecainide, propafenone, sotalol, amiodarone	IIa-C
	Beta blockers	IIb-C
	Verapamil, diltiazem, digoxin	III-C
Single or infrequent AVRT episode(s) (no pre-excitation)	None	I-C
	Vagal manoeuvres	I-B
	Pill-in-the-pocket- verapamil, diltiazem, beta blockers	I-B

(*Continued*)

Table 55.1 Continued

	Catheter ablation	IIa-B
	Sotalol, amiodarone	IIb-B
	Flecainide, propafenone	IIb-C
	Digoxin	III-C
Pre-excitation, asymptomatic	None	I-C
	Catheter ablation	IIa-B

ACC/AHA /ESC 2003 guidelines for the management of patients with supraventricular arrhythmias: executive summary. *Eur Heart J*. 2003;**24**:1857–97, with permission from Oxford University Press.

Table 55.2 ESC GL on VA and SCD. Management of patients with Wolff-Parkinson-White syndrome

Ablation in patients with WPW syndrome resuscitated from sudden cardiac arrest due to AF and rapid conduction over the accessory pathway causing VF.	I-B
Ablation in patients with WPW syndrome who are symptomatic and/or who have accessory pathways with refractory periods ≤240 ms in duration.	IIa-B

PACES/HRS 2012 expert consensus statement on the management of the asymptomatic young patient with a Wolff-Parkinson-White (WPW, ventricular preexcitation) electrocardiographic pattern. *Heart Rhythm*. 2012;**9**:1006–24 with permission from Elsevier.

Table 55.3 WPW syndrome and AF and pre-excitation syndromes

ESC 2010 GL on AF. AF in WPW syndrome	
Catheter ablation of an overt AP in patients with AF to prevent SCD.	I-A
Immediate referral to an experienced ablation centre of patients who survived SCD and have evidence of overt AP conduction.	I-C
Catheter ablation for patients with high-risk professions (e.g. pilots, public transport drivers) and overt, but asymptomatic, AP conduction on the surface ECG.	I-B
Catheter ablation in patients at high risk of developing AF in the presence of an overt, but asymptomatic, AP on the surface ECG.	I-B
Catheter ablation of the AP in asymptomatic patients with evidence of an overt AP, only after a full explanation and careful counselling.	IIa-B

ESC 2010 Guidelines for the management of atrial fibrillation. *Eur Heart J*. 2010;**31**:2369–429 with permission from Oxford University Press.

Table 55.4 ACC/AHA/HRS 2015 GL on SVT. Manifest or concealed accessory pathways*

Acute treatment	
Vagal maneuvers for orthodromic AVRT	I-B-R
Adenosine for orthodromic AVRT	I-B-R
Synchronized cardioversion in hemodynamically unstable patients with AVRT if vagal maneuvers or adenosine are ineffective or not feasible	I-B-NR
Synchronized cardioversion in hemodynamically stable patients with AVRT when pharmacological therapy is ineffective or contraindicated	I-B-NR
Synchronized cardioversion in hemodynamically unstable, pre-excited AF	I-B-NR
Ibutilide or IV procainamide in hemodynamically stable, pre-excited AF	I-C-LD
IV diltiazem, or verapamil for orthodromic AVRT in the absence of pre-ecxitation on the resting ECG during SR	IIa-B-R
IV beta blockers for orthodromic AVRT in the absence of pre-ecxitation on the resting ECG during SR	IIa-C-LD
IV beta blockers, diltiazem, or verapamil for orthodromic AVRT and pre-excitation on the resting ECG and no response to other therapies	IIb-B-R
IV digoxin, IV amiodarone, IV or oral beta blockers, diltiazem, and verapamil are potentially harmful in patients with pre-excited AF	III-C-LD

(*Continued*)

Table 55.4 Continued

Ongoing management	
Catheter ablation of the accessory pathway in AVRT and/or pre-excited AF	I-B-NR
Beta blockers, diltiazem, or verapamil for AVRT without pre-excitation on the resting ECG	I-C-LD
Flecainide or propafenone in patients without structural heart disease or ischemic heart disease, AVRT and/or pre-excited AF, and not candidates for catheter ablation	IIa-B-R
Dofetilide or sotalol for AVRT and/or pre-excited AF in patients not candidates for catheter ablation	IIb-B-R
Amiodarone in AVRT and/or pre-excited AF, not candidates for catheter ablation and beta blockers, diltiazem, flecainide, propafenone, and verapamil ineffective or contraindicated	IIb-C-LD
Beta blockers, diltiazem, or verapamil for orthodromic AVRT, pre-excitation on the resting ECG, and not candidates for catheter ablation	IIb-C-LD
Digoxin for orthodromic AVRT, no pre-excitation on the resting ECG, and not candidates for catheter ablation	IIb-C-LD
Digoxin potentially harmful for AVRT, and pre-excitation on the resting ECG	III-C-LD (Harm)

*Similar recommendation on AF in WPW have been given by the AHA/ACC/HRS 2014 GL on AF.
AHA/ACC/HRS 2014 Guideline for the management of patients with atrial fibrillation. *J Am Coll Cardiol*. 2014;**64**:2246–80 with permission from Elsevier.

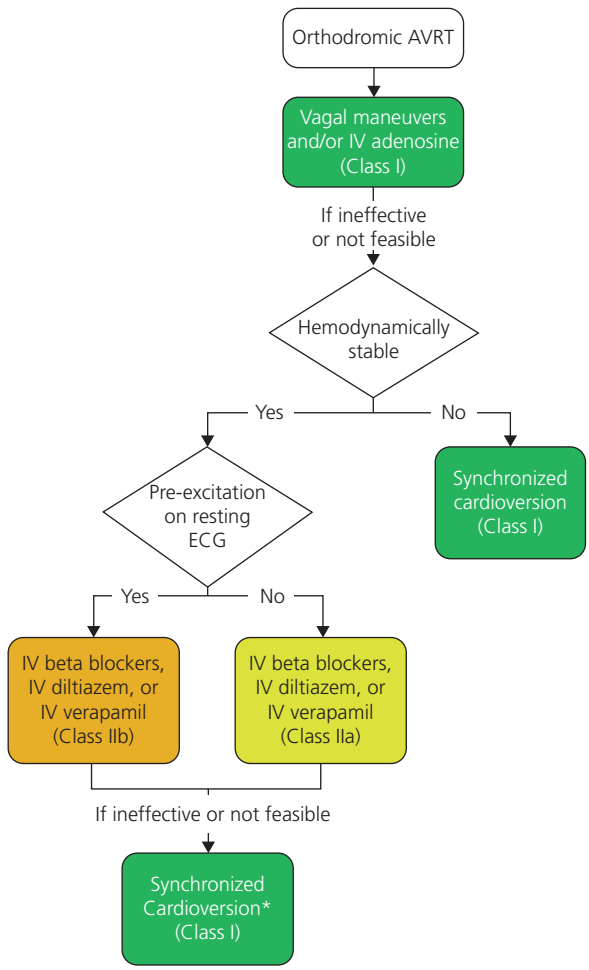

Figure 55.5 ACC/AHA.HRS 2015 GL on SVT. Acute treatment of orthodromic AVRT.

Drugs listed alphabetically.
*For rhythms that break or recur spontaneously, synchronized cardioversion is not appropriate.
ACC/AHA/HRS 2015 Guideline for the management of adult patients with supraventricular tachycardia. *J Am Coll Cardiol*. 2015;doi:10.1016/j.jacc.2015.08.856 with permission from Elsevier.

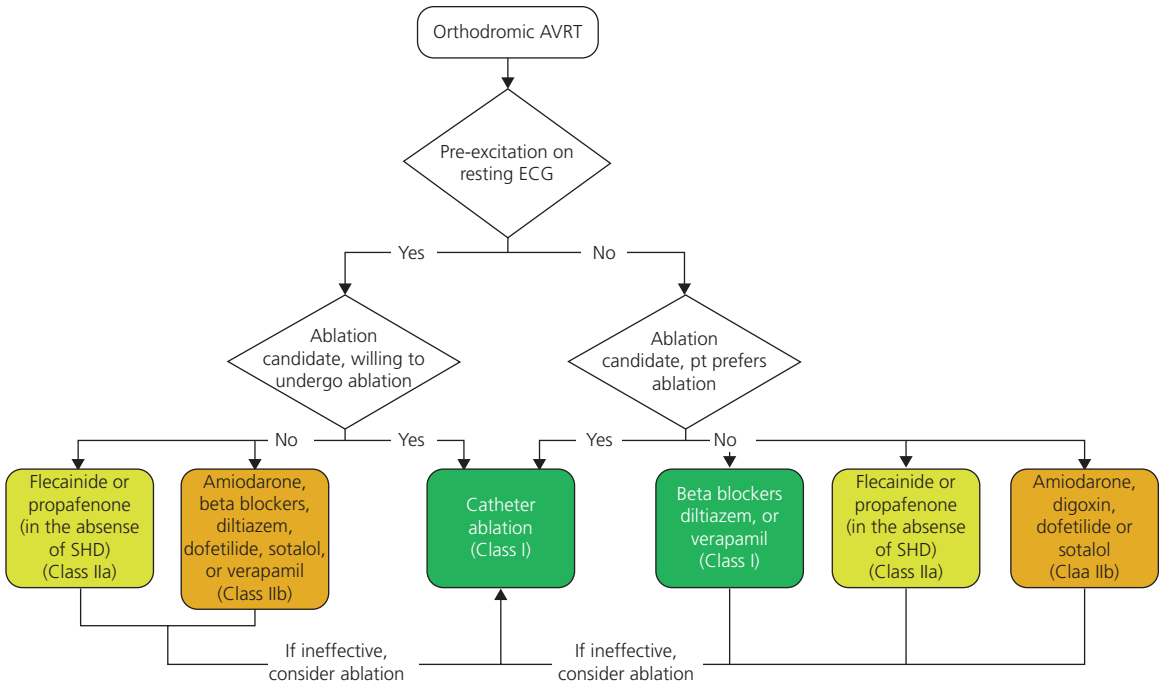

Figure 55.6 ACC/AHA.HRS 2015 GL on SVT. Ongoing management of orthodromic AVRT.

Drugs listed alphabetically.
SHD: structural heart disease (including ischaemic heart disease).
ACC/AHA/HRS 2015 Guideline for the management of adult patients with supraventricular tachycardia. *J Am Coll Cardiol*. 2015;doi:10.1016/j.jacc.2015.08.856 with permission from Elsevier.

Table 55.5 ACC/AHA/HRS 2015 GL on SVT

Asymptomatic patients with pre-excitation	
Low risk of rapid conduction in:	
Abrupt loss of conduction over a manifest pathway during exercise testing in sinus rhythm	I-B-NR
Intermittent loss of pre-excitation during ECG or ambulatory monitoring	I-C-LD
EP study for risk stratification	IIa-B-NR
Catheter ablation of the accessory pathway if EP study identifies high risk, including rapidly conducting pre-excited AF	IIa-B-NR
Catheter ablation of the accessory pathway if the presence of pre-excitation precludes specific employment (such as with pilots)	IIa-B-NR
Observation without further evaluation or treatment	IIa-B-NR
Risk stratification of symptomatic patients with manifest accessory pathways	
Low risk of rapid conduction in:	
Abrupt loss of conduction over the pathway during exercise testing in sinus rhythm	I-B-NR
Intermittent loss of pre-excitation during ECG or ambulatory Monitoring	I-C-LD
EP study for risk stratification	I-B-NR

ACC/AHA/HRS 2015 Guideline for the management of adult patients with supraventricular tachycardia. *J Am Coll Cardiol*. 2015;doi:10.1016/j.jacc.2015.08.856 with permission from Elsevier.

may also be given, but with caution, because it may produce AF with a rapid ventricular rate through a fast pathway. IV ibutilide, flecainide, or procainamide may be given. For long-term suppression beta blockers, propafenone or flecainide (in the absence of CAD) may be given, with a success rate <70%. Catheter ablation is the treatment of choice in symptomatic or high risk patients with WPW syndrome. Success rate is 95%, and complications such as tamponade or AV block (septal pathways) <1%. A mortality 0–0.2% was usually reported,[23,24] but in recent trials perioperative mortality is 0%.[25,26] Recommendations for therapy are presented in Tables 55.1 to 55.4 and Figures 55.5 and 55.6. Additional recommendations for the risk stratification of asymptomatic and symptomatic patients with pre-excitation are presented in Table 55.5.

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Chapter 56

Ventricular arrhythmias

Definitions and classification

Definitions

Ventricular tachycardia (VT) is usually defined as tachycardia (rate >100 beats/min) with three, or more, consecutive beats that originate from the ventricles, independent of atrial or AV nodal conduction.[1,2]

Accelerated idioventricular rhythm denotes a ventricular rhythm <100 beats/min.

Sustained ventricular tachycardia lasts >30 s (unless requiring termination because of haemodynamic collapse) whereas **non-sustained tachycardia** terminates spontaneously within 30 s.

Monomorphic ventricular tachycardia has only one morphology during each episode (Figure 56.1).

Multiple monomorphic ventricular tachycardia has more than one morphology at different times.

Pleomorphic ventricular tachycardia has more than one morphologically distinct QRS complex occurring during the same episode of VT, but the QRS is not continuously changing. In patients with implantable defibrillators (ICD), pleomorphic VT, as well as multiple morphologies, indicate increased risk.[3]

In **polymorphic** ventricular tachycardia, there is a constant change in QRS configuration, indicating a changing ventricular activation sequence, at a heart rate <333 bpm (cycle length >180 ms). Rapid polymorphic ventricular tachycardia cannot be easily distinguished from ventricular fibrillation.

Bidirectional ventricular tachycardia is a rare form of tachycardia with two alternating morphologies, usually right bundle branch block with alternating left and right axis deviation. Typically occurs in digitalis intoxication, catecholaminergic polymorphic ventricular tachycardia, and several other conditions that predispose cardiac myocytes to delayed after-depolarizations (DADs) and triggered activity.[4]

Incessant VT denotes haemodynamically stable VT lasting hours.

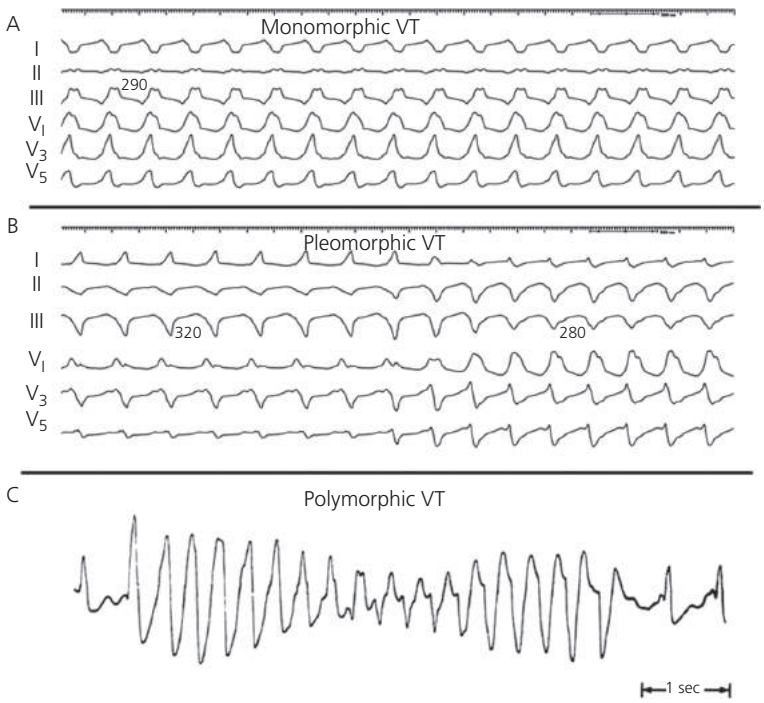


Figure 56.1 Types of VT.

EHRA/HRS Expert consensus on catheter ablation of ventricular arrythmias. *Europace*. 2009;**11**:771–817 with permission from Oxford University Press.

VT storm indicates very frequent episodes of VT, more than three episodes in 24 h, monomorphic or polymorphic, requiring cardioversion.[5]

Torsades de pointes are a form of polymorphic ventricular tachycardia with characteristic beat-by-beat changes (twisting around the baseline) in the QRS complex.

Ventricular flutter indicates a monomorphic, regular ventricular arrhythmia (cycle length variability ≤30 ms), with no isoelectric interval between QRS complexes.

Ventricular fibrillation is rapid, usually more than 333 bpm (cycle length ≤180 ms), grossly irregular ventricular rhythm with marked variability in QRS cycle length, morphology, and amplitude. **Fine VF** is low amplitude VF that can be perceived as asystole.

Pathophysiology

Electrophysiology

Ventricular tachycardia may be focal or macro-reentrant.

Focal VT has a point source of earliest ventricular activation, with a spread of activation away in all directions from that site. The mechanism can be triggered activity, automaticity, microreentry, or focal endocardial breakthrough from an epicardial reentry circuit.

Triggered activity due to early after-depolarizations is implicated in the initiation of polymorphic tachycardias in the **long QT syndromes** (see Chapter 58). Triggered activity due to delayed after-depolarizations is the mechanism of **idiopathic outflow tract tachycardias**.[6] Delayed after-depolarizations are caused by intracellular calcium overload by factors, such as increases in heart rate, beta-adrenergic stimulation, and digitalis, with subsequent activation of the Na/Ca exchanger (see also Chapter 50). Beta-adrenergic effects are mediated through a cAMP-induced increase in intracellular calcium and are antagonized by adenosine, which reduces cAMP. Termination of idiopathic ventricular outflow tract tachycardias by an intravenous bolus of adenosine or infusion of calcium channel blockers or by vagotonic manoeuvres is consistent with triggered activity as the likely mechanism for some of these tachycardias. These tachycardias can be difficult to induce at electrophysiology testing; rapid burst pacing and/or isoproterenol infusion is often required.

Automaticity that is provoked by adrenergic stimulation (not triggered) or disease processes that diminish cell-to-cell coupling may less commonly cause focal VT.[1] This type of VT may become incessant under stress or during isoproterenol administration but cannot be initiated or terminated by programmed electrical stimulation; it can sometimes be suppressed by calcium channel blockers or beta blockers. Automaticity from damaged Purkinje fibres has been suggested as a mechanism for catecholamine-sensitive, focal origin VT.[7] Automaticity can also occur in partially depolarized myocytes, as has been shown for VTs during the early phase of myocardial infarction as well as in some patients with ventricular scars.[1] Automatic premature beats may, in addition, initiate reentrant VTs.

Macro-reentry refers to reentry circuits that can be defined over several centimetres and are due to myocardial scars secondary to a myocardial infarction or other disease process. Reentry around a myocardial scar (scar-related reentry), characterized by regions of slow conduction and anatomical or functional unidirectional conduction block at some point in the reentry path, is the cause of the majority of monomorphic VT seen in patients with heart disease.[7] Myocardial scar is identified from low-voltage regions on ventricular voltage maps, areas with fractionated electrograms, unexcitability during pace mapping, evidence of scar on myocardial imaging, or from an area of known surgical incision. Prior MI is the most common cause, but scar-related VT also occurs in cardiomyopathies and after cardiac surgery for congenital heart disease or valve replacement. Evidence supporting reentry includes initiation and termination by programmed stimulation (although this does not exclude triggered activity), demonstrable entrainment or resetting with fusion, and continuous electrical activity that cannot be dissociated from VT by extrastimuli.

Following MI, there is ion channel remodelling and regional reductions in I_{Na} and I_{Ca} within the scar, reduced coupling between myocytes by increased collagen and alterations in gap junction distribution and function, and intervening patchy fibrosis resulting in a zigzag pattern of transverse conduction. Thus, scar remodelling contributes to the formation of channels and regions where conduction time is prolonged, facilitating reentry. Unidirectional conduction block may occur after a properly timed extra-beat; it is probably mostly functional, rather than fixed, and is present only during tachycardia when the refractory period of the tissue exceeds the tachycardia cycle length or maintained by collision of excitation waves. Functional conduction block can occur in a figure-of-eight type of reentry circuits. Many reentry circuits contain a protected isthmus or channel of variable length, isolated by arcs of conduction block (Figure 56.2).[8] Critical isthmus sites (not necessarily corresponding to voltage map channels identified by electroanatomical mapping)[9,10] defined by concealed entrainment, i.e. no change of QRS morphology, S-QRS interval <70% of the VT cycle length (ideally equal to the electrogram to QRS during VT), and a post-pacing interval—VT cycle length difference ≤30 ms (ideally equal to the VT cycle length), or pacing mapping with paced QRS morphology similar to that during VT and S-QRS interval >40 ms, or local abnormal ventricular activities by pacing, are typically located within the scar with bipolar electrogram voltage <0.5 mV (usually cut-off points of 0.05 mV denote dense scar and 0.5 mV low-voltage regions presumed to indicate more subtle degrees of fibrosis). (See also chronic therapy of VT.) Circuit exit sites, defined by local activation coincident with

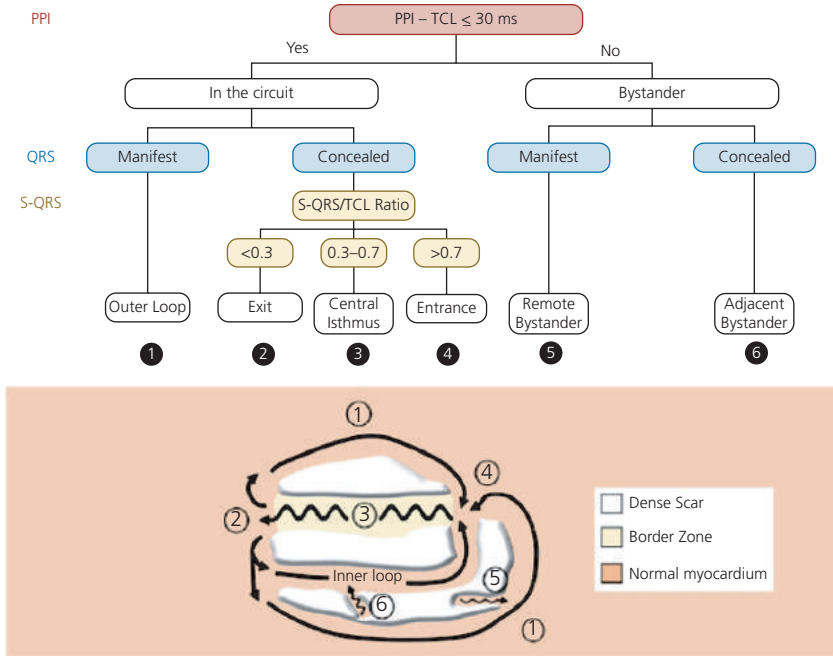


Figure 56.2 A schematic drawing of the components of the ventricular tachycardia circuit. The main components include entrance, central isthmus, and exit sites. Characteristics of entrainment mapping according to the site of pacing are summarized in the algorithm (PPI, post-pacing interval; TCL, tachycardia cycle length; S-QRS, stimulus to QRS interval).

Reproduced from Tanawuttiwat T, *et al*. The role of catheter ablation in the management of ventricular tachycardia, *Eur Heart J*. 2016;**37**:594–609 with permission from Oxford University Press.

the onset of the QRS, are observed in the infarct border zone as described by voltage mapping. Multiple VT morphologies are usually inducible in the same patient, often related to multiple reentry circuits. The majority of reentrant circuits are located in the subendocardium, but subepicardial or intramyocardial reentry may also occur.

Macro-reentry through the bundle branches occurs in patients with slowed conduction through the His-Purkinje system, and is usually associated with severe left ventricular (LV) dysfunction due to dilated cardiomyopathy, valvular heart disease, and, less often, ischaemic heart disease. The necessary condition for bundle branch reentry seems to be prolonged conduction in the His-Purkinje system, and this is reflected in the HV interval which is prolonged during sinus rhythm and prolonged, or equal to the baseline sinus rhythm, during VT. The circuit involves the right and left brunch bundles, with antegrade conduction occurring most of the times through the RB. The His bundle is activated as a bystander, and the HV interval is equal to, or greater than, that during sinus rhythm. HH interval variation usually precedes any VV interval variation in contrast to what happens in microreentrant ventricular tachycardia with retrograde activation of the His bundle.

Left ventricular, fascicular, verapamil-sensitive VT occurs in patients without structural heart disease. The mechanism is reentry that appears to involve a portion of the LV Purkinje fibres, most often in the region of the left posterior fascicle, giving rise to a characteristic right bundle branch block (RBBB) superior axis QRS configuration and a QRS duration that is only slightly prolonged.[11,12]

Ventricular fibrillation

The mechanism of VF remains elusive, and both reentrant (caused by multiple wavelets, mother rotor, or a combination of both) and focal mechanisms (rapidly firing focus initiated by triggered activity or automaticity) have been implicated.[13] Rapid pacing-induced VF generally is attributed to reentrant mechanisms. Ischaemia, drugs, and genetic defects that prolong repolarization and alter intracellular calcium promote polymorphic ventricular arrhythmias degenerating to VF. In certain cases, focal mechanisms may be involved in VF initiation and maintenance.

Presentation

The clinical presentation of ventricular arrhythmias depends on the haemodynamic disturbance they produce.

Rapid tachycardias, long-lasting tachycardias, poor left ventricular function, and atrioventricular dissociation tend to contribute to haemodynamic collapse which may present as **presyncope**, **syncope**, or **sudden death**. When cardiac output and blood pressure are maintained and when the episodes are short-lived, the arrhythmia may present as recurrent palpitations, breathlessness, or chest pain. Occasionally, patients are completely **asymptomatic** during tachycardia. A history of ischaemic heart disease or congestive heart failure in men older than 35 years suggests that a wide QRS tachycardia is probably ventricular in origin.[14]

Physical examination

Low blood pressure, heart failure, and cardiogenic shock may be present as signs of haemodynamic distress.

Atrioventricular dissociation (apparent by a changeable pulse pressure or by Doppler assessment of flow in the ascending aorta).[15]

Irregular cannon waves in the jugular venous pulse.

Variable first heart sound may be seen if retrograde ventriculoatrial block is present.

None of these signs will be present if there is retrograde ventriculoatrial conduction which is present in 20–30% of cases. In this situation, atrial systole coincident with ventricular systole may produce **regular cannon waves**.

ECG morphologies

With **monomorphic VT**, the ECG displays a wide QRS (>120 ms) tachycardia. Narrow QRS may be seen in fascicular VT, bundle branch reentry VT, and septal myocardial VT due to their origin within, or in close proximity to, the His-Purkinje network. Prior MI, idiopathic VT, and cardiomyopathies (more often dilated and ARVD) are the most common causes.

Polymorphic VT may be seen in ischaemic heart disease with or without heart failure, cardiomyopathies, inherited channelopathies, such as Brugada syndrome and catecholaminergic polymorphic VT, and congenital or acquired (drug-associated) long QT syndrome.

Marked QT interval prolongation and the morphologically distinctive **torsades de pointes** occur in three common settings: in congenital LQTS, in drug-associated QTS, and in patients with advanced conduction system disease that has progressed to heart block.

Polymorphic VT storm in a patient with coronary disease is strongly suggestive of acute myocardial ischaemia; pauses may occur prior to polymorphic VT, even in the absence of QT prolongation. Usually, severe underlying heart disease is present. More rarely, VT storm can occur (e.g. in Brugada syndrome, LQTS, catecholaminergic VT, or in drug overdose) in patients who have a structurally normal heart.

Differential diagnosis of wide QRS tachycardia

The differential diagnosis is between supraventricular tachycardia (AVRT or AVNRT) with aberrant (bundle branch block) conduction, AVNRT with a bystander accessory pathway, antidromic (pre-excited) AVRT, fast atrial fibrillation conducted over an accessory pathway, and electrolyte-induced QRS widening (Table 50.2 of Chapter 50).

Several morphologic criteria have been described and the 12-lead electrocardiogram may provide an accurate diagnosis of monomorphic VT in most but not all circumstances (Table 56.1 and Figures 56.3 to 56.5).[16–19] However, most of the existing morphologic criteria favouring ventricular tachycardia have been noted to be present in a substantial number of patients with intraventricular conduction defect during sinus rhythm.[20] Theoretically it is very difficult to differentiate between VT and antidromic SVT (5–10% of all SVTs).

The following features are easily assessed:

Atrioventricular dissociation may be seen as independent atrial activity, especially in lead II, or as 2:1 or 3:1 retrograde block with a P wave following every second or third QRS complex. Intermittent capture of the ventricles by conduction from the independent atrial activity will produce fusion beats (slightly premature with a shape intermediate between sinus and tachycardia morphologies) due to a depolarization of the ventricles, partially by the tachycardia beat and partially by the sinus beat, or capture beats (premature beats with a morphology of conducted beats) due to complete depolarization of the ventricles by the sinus beat. However, because ventricular tachycardia may show 1:1 retrograde conduction to the atrium, the presence of atrioventricular association cannot exclude the diagnosis of ventricular tachycardia.

Concordant negativity in all chest leads is also suggestive of VT.

A QRS complex >140 ms in RBBB-like tachycardia or **>160 ms in LBBB-like** morphology in the absence of antiarrhythmic drugs, with regular RR intervals and with a left axis or an axis between −90 and +180, especially in the presence of a narrow, normal axis QRS during sinus rhythm, is suggestive of VT.

If an RS complex is present in one or more precordial leads, the longest **RS interval (beginning of the R wave to the deepest part of the S wave) >100 ms** is highly specific for ventricular tachycardia (Figure 56.3).[16]

In lead **aVR**: presence of an initial R wave, or width of an initial r or q wave >40 ms, or notching on the initial downstroke of a predominantly negative QRS complex suggest VT. If none of these criteria is present, then a v(i)/v(t) ≤1 (Figure 56.4) suggests VT.[19]

An **R wave peak time (RWPT) ≥50 ms** in lead II (from the isoelectric line to the point of first change in polarity) suggests VT (Figure 56.5).[18] The high accuracy of this criterion, however, was not verified in its first large external application.[21]

A **triphasic RSR'** with R′> R and the S wave extending beyond the baseline in lead V_1 in tachycardias with RBBB morphology favours the diagnosis of supraventricular tachycardia (SVT).

A **monophasic R >30 ms or >60 ms** to nadir S, or **notched S with LBBB** morphology favours the diagnosis of SVT.

Table 56.1 Diagnosis of VT

Brugada *et al*. algorithm

Absence of RS in all precordial leads?

Yes: VT

No: RS interval (beginning of the R wave to the deepest part of the S wave) > 100 ms in any precordial lead?

Yes: VT

No: AV dissociation?

Yes: VT

No: apply the following conventional criteria:

LBBB morphology

V_1 or V_2 Monophasic R>30 ms or >60 ms to nadir S, or notched S: VT

RBBB morphology

V_1 Monophasic R: suggests VT

V_1 or V_6 Triphasic QRS: suggests SVT

Vereckei *et al*. algorithm

aVR

Initial R wave?

Yes: VT

No: Initial r or q wave > 40 ms?

Yes: VT

No: Notch on the descending limb of a negative onset and predominantly negative QRS?

Yes: VT

No: $v_i/v_t \leq 1$?

Yes: VT

No: SVT

v_i/v_t is the ventricular activation velocity ratio by measuring the vertical excursion in millivolts recorded on the ECG during the initial (v_i) and terminal (v_t) 40 ms of the QRS complex.

Pava *et al*. algorithm

Lead II

R-wave peak time (RWPT) ≥ 50 ms

Yes: VT

No: SVT

When the tachycardia has been terminated, further information can be gained from the 12-lead ECG in sinus rhythm. If bundle branch block is present, but with a different morphology or axis to that during tachycardia, the tachycardia is likely to be ventricular in origin. If delta waves are present and they have the same polarity as the QRS complexes of tachycardia, the diagnosis is most probably that of Wolff–Parkinson–White syndrome with antidromic AVRT or atrial fibrillation. An irregular, wide QRS tachycardia with ventricular rates faster than 200 bpm, especially in the younger patient with no previous history of ischaemic heart disease, should always raise the question of pre-excited atrial fibrillation.

Adenosine, given in rapid IV doses up to 0.25 mg/kg, will terminate or reveal most supraventricular tachycardias. Adenosine does not affect most ventricular tachycardias, with the exception of some forms associated with apparently normal hearts, and can, therefore, be used as a diagnostic agent. Verapamil should not be used in this way because of the considerable incidence of life-threatening hypotension which is associated with its administration in ventricular tachycardia.

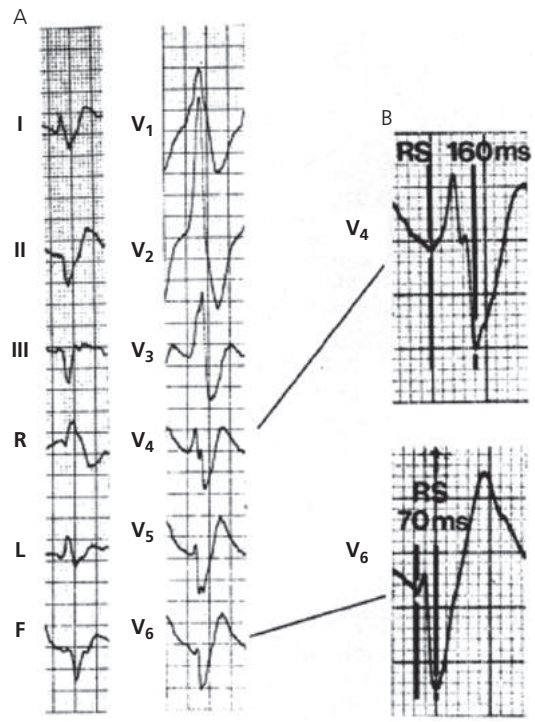


Figure 56.3 RS duration for the Brugada algorithm. The RS interval (enlarged in the right panel) measures 160 ms in lead V_6, and 70 ms in lead V6. Thus, the longest RS interval is ≥100 ms and diagnostic of ventricular tachycardia.

Brugada P, *et al*. A new approach to the differential diagnosis of a regular tachycardia with a wide QRS complex. *Circulation*. 1991;**83**:1649 with permission from Wolters Kluwer.

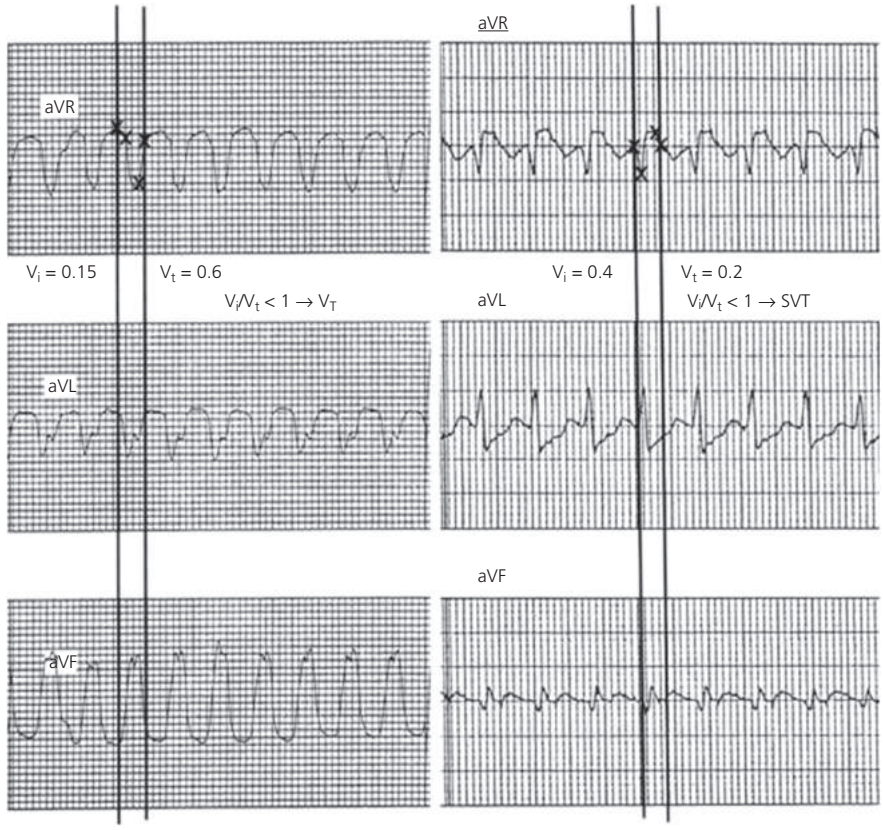


Figure 56.4 Calculation of V_i/v_t in the Vereckei *et al*. algorithm. In both panels, the crossing points of the *vertical lines* with the QRS contour in lead aVR show the onset and end of the QRS complex in lead aVR. The crossing points and initial and terminal 40 ms of the chosen QRS complex are marked by *small crosses*. **Left:** During the initial 40 ms of the QRS, the impulse travelled vertically 0.15 mV; therefore, $v_i = 0.15$. During the terminal 40 ms of the QRS, the impulse travelled vertically 0.6 mV; therefore, $v_t = 0.6$. Thus, $v_i/v_t < 1$ yields a diagnosis of ventricular tachycardia (VT). **Right:** $v_i = 0.4$ and $v_t = 0.2$, determined in the same way as in the left panel; thus, $v_i/v_t > 1$ suggests a diagnosis of supraventricular tachycardia (SVT).

Vereckei A, *et al*. New algorithm using only lead a VR for differential diagnosis of wide QRS complex tachycardia. *Heart Rhythm*. 2008;**5**:89–98 with permission from Elsevier.

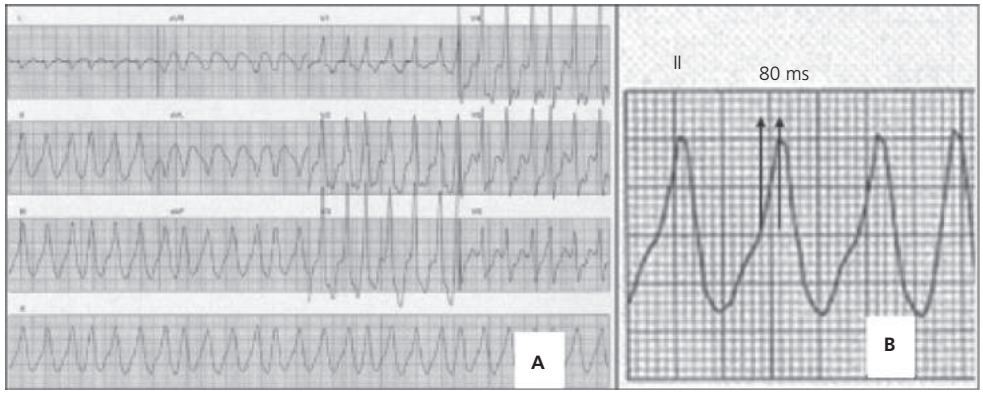


Figure 56.5 The R-wave peak time (RWPT) in lead II.

A: Twelve-lead ECG from a patient with ventricular tachycardia. B: Magnified lead II from panel A. R-wave peak time (RWPT), measured from the isoelectric line to the point of first change in polarity, was >50 ms (80 ms).

Pava LF, *et al*. R-wave peak time at DII: a new criterion for differentiating between wide complex QRS tachycardias. *Heart Rhythm*. 2008;**7**:922–6 with permission from Elsevier.

Acute therapy of ventricular arrhythmias

Cardiac arrest

Recent evidence indicates that the incidence of ventricular fibrillation or pulseless ventricular tachycardia as the first recorded rhythm in out-of-hospital cardiac arrest has declined to less than 30% in the past several decades.[22–24] Pulseless electrical activity (electromechanical dissociation) and asystole are proportionally more frequent with an incidence of 19–23%, while the remaining patients (approximately 50%) have asystole.[25] Survival rate is 30% for VT/VF arrests, but <10% for pulseless electrical activity. Most patients (80%) with a cardiac arrest have demonstrable coronary artery disease, but less than half of all of them seem to have suffered an acute myocardial infarction.[26] The use of thrombolysis during advanced life support for out-of-hospital cardiac arrest did not improve outcome, but early coronary angiography with immediate PCI in patients resuscitated from a shockable rhythm may improve survival.[27] VT/VF accounts for 67% of cardiac arrests in post-MI patients.[28]

A rapid response time is the major determinant of survival, and extracorporeal membrane oxygenation plus intra-arrest PCI of acutely occluded coronary arteries are associated with improved outcomes in patients unresponsive to conventional CPR.[29] Certain resuscitated comatose patients without ST-segment elevation may also be suitable for coronary angiography.[30] Figures 56.6 and 56.7 present 2010 AHA and 2015 ESC Guidelines for CPR and Emergency Care.[1,31]

Important therapeutic points are:

The basic life support (BLS) sequence of steps 'A-B-C' (Airway, Breathing, Chest compressions) has been changed to **'C-A-B' (Chest compressions, Airway, Breathing)** for adults and paediatric patients.

A universal **compression-ventilation ratio of 30:2** performed by lone rescuers for victims of all ages.

For most adults with out-of-hospital cardiac arrest, bystander CPR with chest compression only (**hands-only CPR**) appears to achieve outcomes similar or even better to those of conventional CPR (compressions with rescue breathing).[32,33] The predicted steep decline in arterial oxygen saturation does not occur until many minutes after the start of resuscitation, and the volume of oxygen in the lungs is relatively big when arrest occurs suddenly. In addition, initial reperfusion with hypoxaemic blood may result in fewer injurious oxygen free radicals and less reperfusion injury. Thus, continuous chest compression without active ventilation avoids risks associated with mouth-to-mouth contact, and is recommended when CPR is performed by a bystanding layperson. Recently, a study that analysed two randomized clinical trials of 2500 cardiac arrest events involving dispatcher-assisted CPR instruction, demonstrated that chest compression alone was associated with even an better 5-year prognosis in comparison with standard CPR (compression plus rescue breathing). Survival with continuous chest compression is better among patients whose arrests were due to cardiac causes and among patients whose initial cardiac rhythm was ventricular tachycardia or fibrillation, rather than asystole or electromechanical dissociation.

Chest compressions should be of adequate rate (at least **100/minute**) and of adequate depth of at least 2 inches (**5 cm**) in adults. Recent data, however, have found that maximum survival was in the depth interval of 40.3–55.3 mm (peak 45.6 mm).[34]

Precordial thumb (delivers 5–10 J of mechanical energy) is rarely of benefit, and may be associated with rhythm deterioration.[35]

Induction of **therapeutic hypothermia (32–34°C)** for 12–24 hours after resuscitation from a ventricular tachycardia or ventricular fibrillation arrest has been shown to improve survival and neurological recovery.[36] Actually, a targeted temperature of 36°C confers similar results with 33°C.[37]

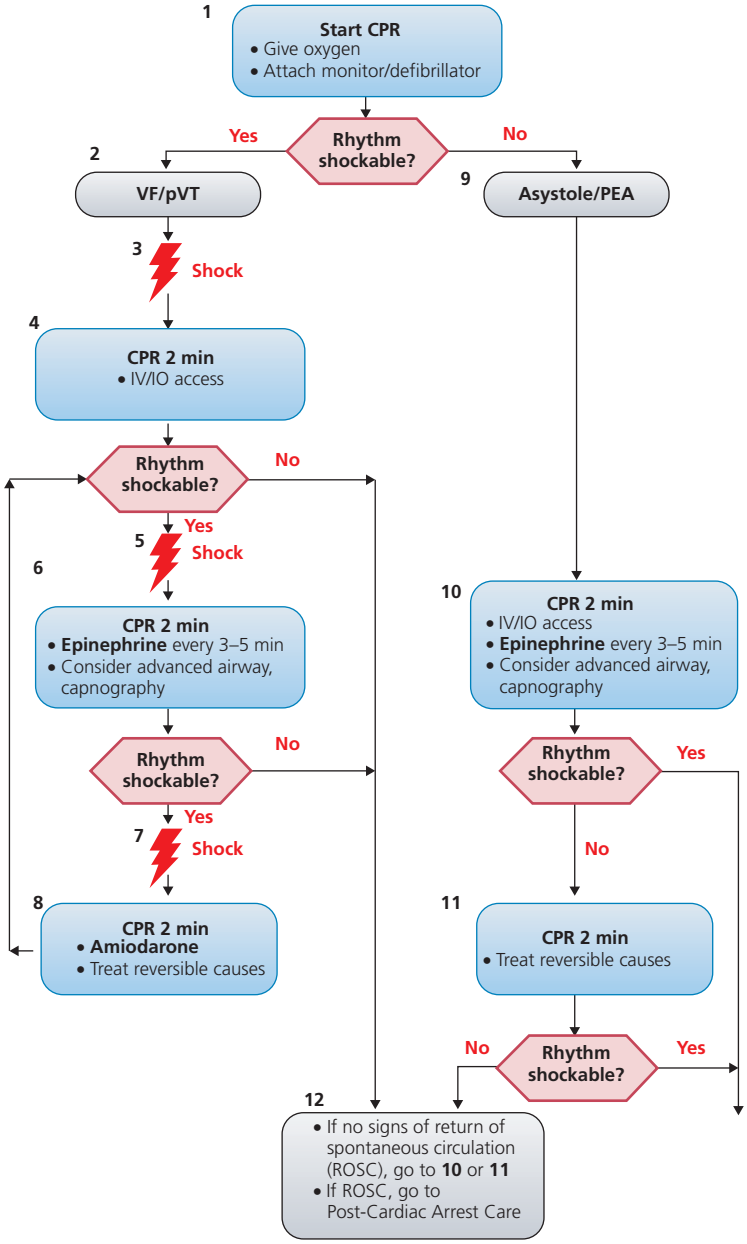
Atropine is no longer recommended for routine use in the management of pulseless electrical activity/asystole. Neither amiodarone nor lidocaine resulted in significantly higher rate of survival or favourable neurologic outcome compared to placebo in patients with out-of-hospital cardiac arrest (ROC trial). However, there was a suggestion for a significantly higher survival rate in the subgroup of patients with bystander-witnessed arrest (ROC trial).[38]

Epinephrine is recommended although its impact on survival and neurological outcomes is controversial.[39,40] In patients with non-shockable cardiac arrest, earlier administration of epinephrine may be associated with a higher survival.[41]

Immediate **coronary angiography** is indicated in comatose cardiac arrest survivors even in the absence of ST-elevation, since the post-resuscitation ECG is rather unreliable.[42]

Monomorphic VT, polymorphic VT, torsade de pointes, incessant VT, and VT storm

Acute management is presented in Table 56.2. The value of lidocaine is now refuted while adenosine may be used in monomorphic VT, especially when the diagnosis of VT is not certain. The prognostic value of an electrical storm is rather debatable, most probably depending on the underlying heart condition.[5,43,44] Catheter ablation may be useful for the short-term management of VT storm.[45]



- Push hard (at least 2 inches [5 cm]) and fast (100–120/min) and allow complete chest recoil
- Minimize interruptions in compressions
- Avoid excessive ventilation
- Rotate compressor every 2 minutes, or sooner if fatigued
- If no advanced airway, 30:2 compression-ventilation ratio
- Quantitative waveform capnography
  - If $PETCO_2$ <10 mm Hg, attempt to improve CPR quality
- Intra-arterial pressure
  - If relaxation phase (diastolic) pressure <20 mm Hg, attempt to improve CPR quality

- **Biphasic:** Manufacturer recommendation (eg, initial dose of 120–200 J); if unknown, use maximum available. Second and subsequent doses should be equivalent, and higher doses may be considered.
- **Monophasic:** 360 J

- **Epinephrine IV/IO dose:** 1 mg every 3–5 minutes
- **Amiodarone IV/IO dose:** First dose: 300 mg bolus. Second dose: 150 mg.

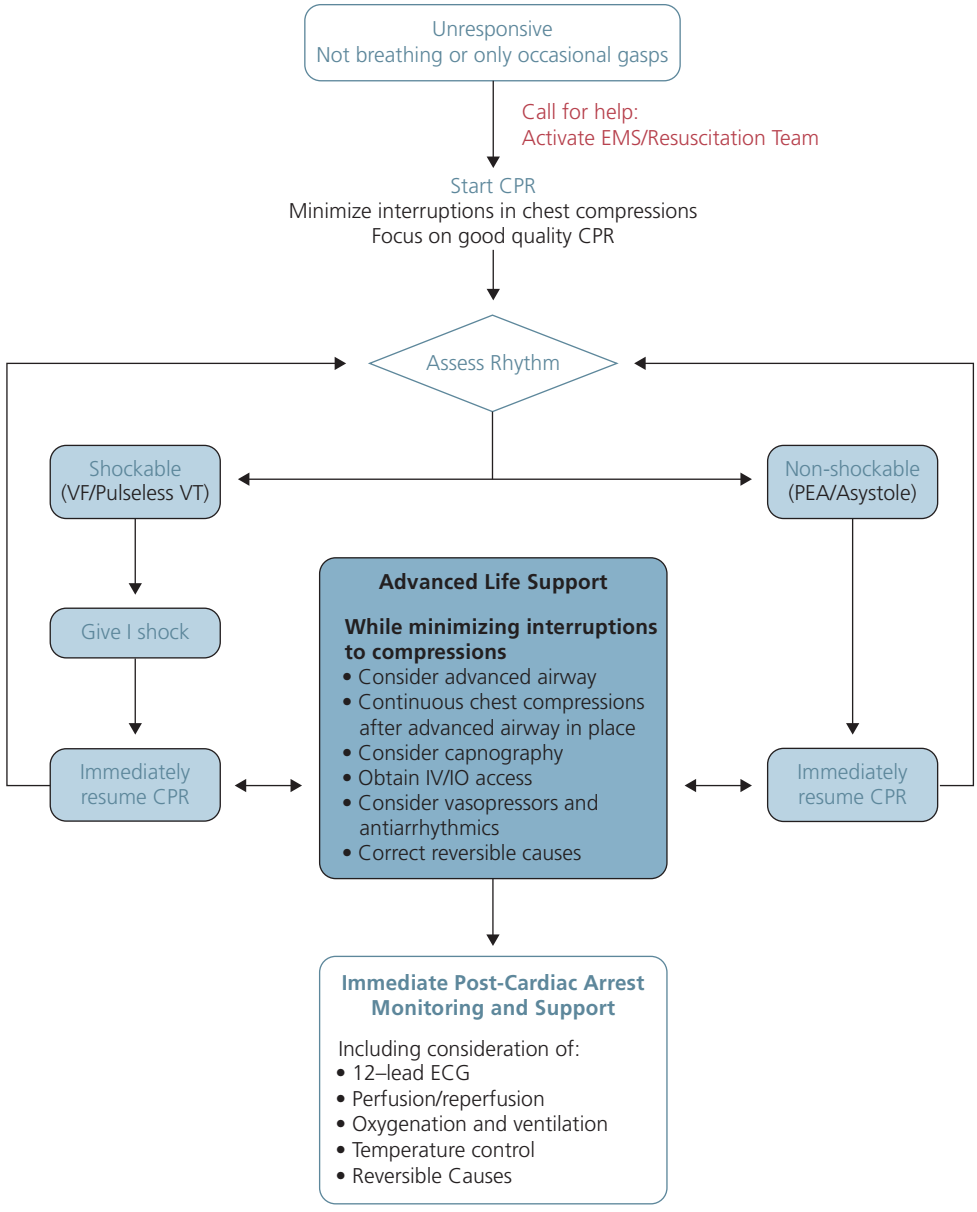
- Endotracheal intubation or supraglottic advanced airway
- Waveform capnography or capnometry to confirm and monitor ET tube placement
- Once advanced airway in place, give 1 breath every 6 seconds (10 breaths/min) with continuous chest compressions

- Pulse and blood pressure
- Abrupt sustained increase in $PETCO_2$ (typically ≥40 mm Hg)
- Spontaneous arterial pressure waves with intra-arterial monitoring

- **H**ypovolaemia
- **H**ypoxia
- **H**ydrogen ion (acidosis)
- **H**ypo-/hyperkalaemia
- **H**ypothermia
- **T**ension pneumothorax
- **T**amponade, cardiac
- **T**oxins
- **T**hrombosis, pulmonary
- **T**hrombosis, coronary

Figure 56.6 2010 AHA guidelines for CPR and emergency care.

2015 American Heart Association Guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2015;**132**[suppl 2]:S444–64 with permission from Wolters Kluwer.



CPR = cardiopulmonary resuscitation; ECG = electrocardiogram; EMS = emergency medical services; i.v. = intravenous; i.o. = intraosseous; PEA = pulseless electrical activity; VF = ventricular fibrillation; VT = ventricular tachycardia.

Figure 56.7 ESC 2015 GL on VA and SCD. Universal cardiac arrest algorithm.

ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J.* 2015; **36**:2793–867 with permission from Oxford University Press.

Table 56.2 Acute management of ventricular arrhythmias

ACC/AHA/ESC 2006 GL on VA	
Sustained monomorphic ventricular tachycardia	
Wide QRS tachycardia should be presumed to be VT if the diagnosis is unclear.	I-C
DC cardioversion with appropriate sedation in sustained monomorphic VT with haemodynamic compromise.	I-C
IV procainamide (or ajmaline in some European countries) for stable sustained monomorphic VT.	IIa-B
IV amiodarone in sustained monomorphic VT that is haemodynamically unstable, refractory to conversion with countershock, or recurrent despite procainamide or other agents.	IIa-C
Pacing termination of sustained monomorphic VT refractory to cardioversion or frequently recurrent despite antiarrhythmic medication.	IIa-C
IV lidocaine for stable sustained monomorphic VT specifically associated with acute myocardial ischaemia or infarction.	IIb-C
Calcium channel blockers, such as verapamil and diltiazem, in wide QRS complex tachycardia of unknown origin, especially in patients with a history of myocardial dysfunction.	III-C
Repetitive monomorphic ventricular tachycardia	
IV amiodarone, beta blockers, and IV procainamide (or sotalol or ajmaline in Europe) for repetitive monomorphic VT in the context of coronary disease and idiopathic VT.	IIa-C
Polymorphic VT	
DC cardioversion with appropriate sedation for sustained polymorphic VT with haemodynamic compromise.	I-B
IV beta blockers for recurrent polymorphic VT, especially if ischaemia is suspected or cannot be excluded.	I-B
IV loading with amiodarone for recurrent polymorphic VT in the absence of congenital or acquired LQTS.	I-C
Urgent angiography with a view to revascularization for patients with polymorphic VT when myocardial ischaemia cannot be excluded.	I-C
IV lidocaine for treatment of polymorphic VT specifically associated with acute myocardial ischaemia or infarction.	IIb-C
Torsades de pointes	
Withdrawal of offending drugs and correction of electrolyte abnormalities.	I-A
Acute and long-term pacing for torsades de pointes due to heart block and symptomatic bradycardia.	I-A
IV magnesium sulfate for LQTS and few episodes of torsades de pointes. Magnesium is not likely to be effective in patients with a normal QT interval.	IIa-B
Acute and long-term pacing for recurrent pause-dependent torsades de pointes.	IIa-B
Beta blockade combined with pacing as acute therapy for patients with torsades de pointes and sinus bradycardia.	IIa-C
Isoproterenol as temporary treatment in recurrent pause-dependent torsades de pointes without congenital LQTS.	IIa-B
Potassium repletion to 4.5–5 mmol/L for torsades de pointes.	IIb-B
IV lidocaine or oral mexiletine in LQT3 and torsades de pointes.	IIb-C
Incessant ventricular tachycardia	
Revascularization and beta blockade followed by IV procainamide or amiodarone for recurrent or incessant polymorphic VT due to acute myocardial ischaemia.	I-C
IV amiodarone or procainamide followed by VT ablation in frequently recurring or incessant monomorphic VT.	IIa-B
IV amiodarone and intravenous beta blockers, separately or together, in VT storm.	IIb-C
Overdrive pacing or general anaesthesia for frequently recurring or incessant VT.	IIb-C
Spinal cord modulation for frequently recurring or incessant VT.	IIb-C
ESC 2015 GL on VA and SCD	
Cardioversion or defibrillation and acute treatment of sustained ventricular arrhythmias	
Direct current cardioversion in sustained VT and haemodynamic instability.	I-C
IV flecainide or a conventional beta-blocker, verapamil or amiodarone in sustained VT without haemodynamic instability and in absence of structural heart disease (e.g. idiopathic RVOT)	IIb-C

ACC/AHA/ESC 2006 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Circulation*. 2006;**114**:e385–e484 with permission from Wolters Kluwer.
ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015; **36**:2793–867 with permission from Oxford University Press.

Risk stratification

Resting 12-lead ECG

ECG during tachycardia is essential for differential diagnosis (Figure 56.8). **ECG during sinus rhythm** after interruption of tachycardia may reveal signs of ischaemic heart disease, conduction defects, electrolyte disturbances, and syndromes of inherited arrhythmias (Brugada syndrome, ARVD, long QT syndrome) (Table 56.3). QRS duration >120 ms, ST–T abnormalities, and QT >440 ms or <400 ms have all been associated with increased mortality.[46]

Laboratory tests

Complete blood count, cardiac enzymes, serum electrolytes (including magnesium), creatinine, BUN, and liver and thyroid function tests should be checked.[47] Additional specific tests, such as iron studies and HIV, should also be obtained when clinically indicated.

Transthoracic echocardiography

Transthoracic echocardiography may detect signs of cardiomyopathy, ARVC and other structural abnormalities, and impaired LV function. There has been overwhelming evidence that, in patients with heart disease in general, left ventricular ejection fraction is the major determinant of cardiac and total mortality. The results of several studies, including the SCD-HeFT and MACAS, have also established the importance of **LVEF** as the most critical prognostic factor in patients with ischaemic or non-ischaemic LV dysfunction and NSVT.[48,49] However, analysis of arrhythmic death in patients enrolled in the MUSTT has shown that patients whose only factor is EF ≤30% have a predicted 2-year arrhythmic death risk ≤5% and the risk of sudden death in patients with coronary disease may depend on multiple variables in addition to LVEF.[50]

Exercise testing

Apart from demonstration of ischaemia, exercise testing may also be helpful in patients with long QT syndrome, exercise-triggered RVOT tachycardia, and catecholaminergic polymorphic VT (Table 56.3). NSVT induced by treadmill exercise testing, aimed at evaluating presumed long QT syndrome, suggests catecholaminergic polymorphic VT, rather than long QT syndrome.[51] Although life-threatening arrhythmias may occur in up to 2% of individuals subjected to the test, exercise is recommended since it is better to expose arrhythmias under controlled circumstances.

Other tests for myocardial ischaemia

Functional tests, such as myocardial perfusion and stress echocardiography, are required to demonstrate myocardial ischaemia. Acute myocardial ischaemia is an established cause of polymorphic ventricular rhythms,[52] preceding 35 to 80% of deaths due to a ventricular tachyarrhythmia.[26] The association of monomorphic ventricular tachycardia, a substrate-dependent arrhythmia, with acute ischaemia is less well characterized, but ischaemia may induce monomorphic ventricular tachycardia in the presence of a myocardial scar.[53]

Coronary angiography

It is mandatory in any patient with a life-threatening ventricular arrhythmia or aborted sudden death.[1]

Cardiac magnetic resonance

CMR imaging with delayed hyperenhancement has been used for detecting an arrhythmogenic substrate in patients with underlying LV dysfunction.[54] In this respect, CMR is also useful in ARVC/D (see Cardiomyopathies), sarcoidosis, and other infiltrative myopathies[55] and has also been shown to help in risk stratification of hypertrophic cardiomyopathy.[56]

Ambulatory electrocardiography

Holter monitoring is valuable for detecting NSVT (Table 56.4). Although previous studies have detected NSVT as a predictor of arrhythmic mortality, in the era of reperfusion and beta blockers, NSVT does not carry independent predictive power in identifying patients with ischaemic or dilated cardiomyopathy at risk of sudden cardiac death, particularly in multivariate analyses when confounders, such as LVEF, are taken into account.[57–59] In non-ST elevation acute coronary syndrome, NSVT occurring beyond 48 hours after admission indicates an increased risk of sudden death.[60] In patients with HCM and, most probably, in patients with inherited channelopathies, detection of NSVT on Holter predicts arrhythmia episodes.[61] The use of Holter for evaluation of treatment is limited since the suppression of frequent ventricular ectopy or NSVT by class IC antiarrhythmic drugs or amiodarone does not imply a favourable diagnosis. (CAST and CAST II and CHF-STAT).[62–64]

T wave alternans

T wave alternans are thought to reflect dispersion of repolarization and have been shown to predict future arrhythmic events better than SAECG and QRS duration.[65] In patients with reduced LV function (LVEF <40%) and NSVT, microvolt T wave alternans has also predicted unstable ventricular tachyarrhythmias better than electrophysiology testing and LVEF <30%.[66] However, although TWA predicted higher total mortality in a MADIT II-like population, the risk of tachyarrhythmic events did not differ according to TWA results.[67] The ABCD (Alternans Before Cardioverter-Defibrillator) study was the first trial to use micro-TWA to guide prophylactic ICD insertion in patients with LVEF <40% and NSVT. Risk stratification strategies using non-invasive TWA versus invasive EPS were comparable at 1 year, with very low positive

and very high negative predictive values, and complementary when applied in combination.[68] Thus, strategies employing TWA, EPS, or both might identify subsets of patients least likely to benefit from ICD insertion. Data from patients with ICD have also suggested that variability of TWA is greater before spontaneous VT/VF recordings.[69]

Assessment of autonomic tone

Heart rate variability (HRV) has been identified as an independent risk factor for arrhythmic mortality in post-myocardial infarction patients.[70] Depressed baroreflex sensitivity has also been independently associated with an increased cardiac mortality and sudden death after MI and with a higher predictive power than heart rate variability.[71] However, in the beta-blocking era, the common arrhythmia risk variables, particularly the autonomic and standard ECG markers, such as QRS duration and QT dispersion, have limited predictive power in identifying patients at risk of sudden cardiac death.[72] In patients with non-ischaemic cardiomyopathy, results on the value of heart rate variability have been conflicting.[49,73] Heart rate turbulence and deceleration capacity have also been studied as non-invasive measures of cardiac autonomic regulation.[74]

Signal-averaged electrocardiography

Although, in survivors of myocardial infarction, an abnormal SAECG has been associated with increased risk of arrhythmic and total mortality, its value for risk stratification purposes is not established, especially in patients treated with thrombolysis or beta blockers.[75] In patients presenting with unexplained syncope, the presence of late potentials is a good predictor of induction of sustained ventricular tachycardia.[76] However, its positive predictive value in this setting is low (<30%), as opposed to high negative predictive value (90%). Thus, a negative SAECG might obviate the need for further investigations when the suspicion of a ventricular arrhythmia is low, but, in the case of a high suspicion of ventricular arrhythmia, a negative SAECG is not sufficient evidence for exclusion of non-sustained or sustained ventricular tachycardia as the cause of syncope. In patients with DCM, SAECG does not predict sudden death,[49] but, in arrhythmogenic right ventricular dysplasia, SAECG can identify those with more extensive disease and a propensity for inducible ventricular tachycardia at programmed electrical stimulation (PES) and is now considered a minor diagnostic criterion (see Cardiomyopathies).

Electrophysiology testing

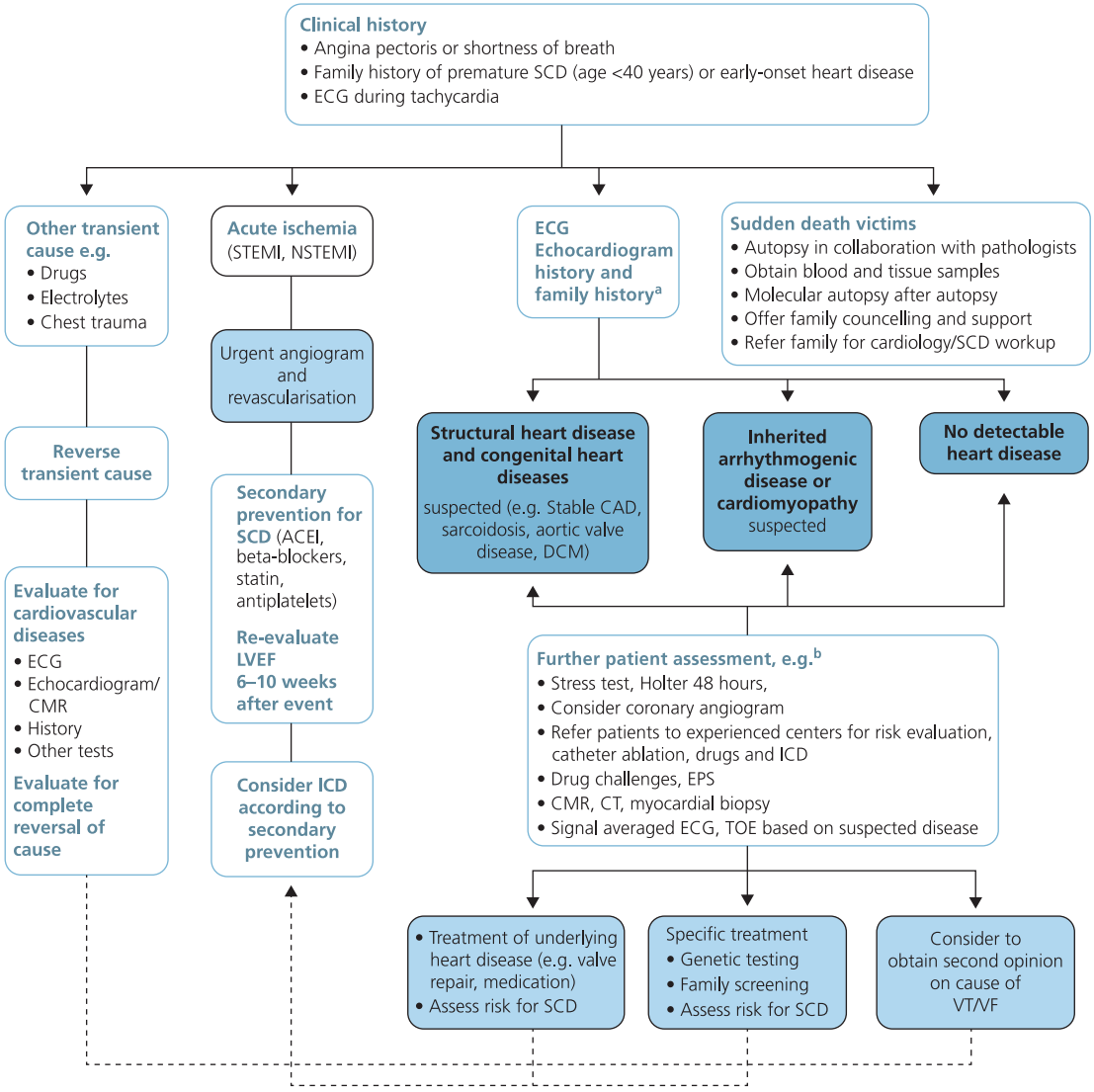
Electrophysiology testing may be required for establishment of initial diagnosis in patients presenting with non-sustained ventricular rhythms (Table 56.3). For EP testing in syncope, see also Chapter 67 on syncope. Indications include the need for differential diagnosis from SVT with aberration, AF in the context of an accessory pathway or other forms of aberration, drug testing for the diagnosis of the Brugada syndrome, and programmed electrical stimulation for induction of VT.

Induction of sustained arrhythmia by (PES) still retains a predictive power in ischaemic patients with impaired LV function. In ischaemic patients with NSVT, the induction of sustained ventricular tachycardia is associated with a 2- to 3-fold increased risk of arrhythmia-related death.[77] In patients with reduced LVEF (<40%) and NSVT, inducibility of sustained monomorphic ventricular tachycardia at baseline PES is associated with a 2-year actuarial risk of sudden death or cardiac arrest of 50% compared to a 6% risk in patients without inducible ventricular tachycardia.[78] Analysis of patients enrolled in the MUSTT, as well as of those in the registry, revealed that non-inducible patients have a significantly lower risk of cardiac arrest or sudden death compared to inducible patients at 2 and 5 years (12% vs 24% and 18% vs 32%, respectively).[79] Still, however, as these results indicate, patients with non-inducible sustained VT are not free of risk of sudden death. The MUSTT Investigators have further analysed the relation of ejection fraction and inducible ventricular tachyarrhythmias to mode of death in 1791 patients enrolled in MUSTT who did not receive antiarrhythmic therapy. Total and arrhythmic mortality were higher in patients with an ejection fraction <30% than in those whose ejection fractions were 30% to 40%. The relative contribution of arrhythmic events to total mortality was significantly higher in patients with inducible tachyarrhythmia and among patients with an ejection fraction ≥30%. This study, therefore, suggested that the major utility of electrophysiological testing may be restricted to patients having an **ejection fraction between 30% and 40%**.[80] The prognostic significance of VT inducibile by three extrastimuli is similar to that of VT induced by one or two extrastimuli or by burst pacing.[81] These results should be considered in the context of evidence from analysis of stored ICD data that have shown little association between spontaneous and induced ventricular arrhythmias.[82] The remodelling process after MI is ongoing with a resultant low correlation between induced and clinically occurring VT in the long term.[83] Furthermore, in early studies, the use of beta blockers was suboptimal. There has been some recent evidence that programmed stimulation performed as early as 3 days after MI in patients with LVEF ≤40% induces VT in up to 1/3 of patients, and may identify patients at high risk for spontaneous tachyarrhythmia and sudden cardiac death.[84] Fast VT/ventricular flutter with a CL 200–230 ms (but not VF with CL <200 ms) is the arrhythmia mainly induced and confers similar prognostic significance as VT with CL >230.[84] Revascularized patients with ST-segment-elevation myocardial infarction with LVEF ≤30% or ≤35% with New York Heart Association class II/III heart failure, but no inducible ventricular tachycardia approximately 4 days after PCI, have a favourable long-term prognosis even without ICD.[85]

In the ischaemic patient with relatively preserved left ventricular function (LVEF >40%), the role of PES is not established. Inducible monomorphic VT, however, indicates consideration of catheter ablation and, if needed,

ICD while inducibility of VF may be a non-specific sign, especially if three extra stimuli are used.[86] However, further investigations for ischaemia, cardiomyopathies, or inherited channelopathies may be appropriate. The prognostic usefulness of programmed stimulation in patients with non-ischaemic dilated cardiomyopathy, including those with NSVT, remains controversial.[87,88] There has been some evidence that inducibility of ventricular arrhythmias,[89] and especially polymorphic VT or VF,[90] indicates increased likelihood of subsequent ICD therapies and might be considered as a useful risk stratifier.

Inducible sustained monomorphic or polymorphic VT is an independent risk factor for subsequent events in patients with repaired tetralogy of Fallot[91] and sarcoidosis.[92]



ACEI = angiotensin-converting enzyme inhibitors; CAD = coronary artery disease; CMR = cardiac magnetic resonance; CT = computed tomography; DCM = dilated cardiomyopathy; ECG = electrocardiogram; EPS = electrophysiological study; GL -guidelines; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; NSTEMI = non-ST-segment elevation myocardial infarction; SCD = sudden cardiac death; STEMI = ST-segment elevation myocardial infarction; TOE = transoesophageal echocardiography; VF = ventricular fibrillation; VT = ventricular tachycardia.
[a]Clinical history of chest pain, dyspnoea, and symptoms associated with certain cardiac conditions and family tree.
[b]The need for furhter tests and evaluations will be guided by the initial assessment and by suspected cardiovascular diseases.

Figure 56.8 ESC 2015 GL on VA and SCD. Diagnostic workup in patients presenting with sustained ventricular tachycardia or ventricular fibrillation.

ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015; **36**:2793–867 with permission from Oxford University Press.

Table 56.3 Investigations in patients with ventricular arrhythmias

ACC/AHA/ESC 2006 GL on VA	
Exercise testing	
Adult patients who have an intermediate or greater probability of having CHD by age, gender, and symptoms to provoke ischaemic changes or ventricular arrhythmias.	I-B
Exercise testing, regardless of age, in known or suspected exercise-induced ventricular arrhythmias, including catecholaminergic VT.	I-B
To evaluate response to medical or ablation therapy in known exercise-induced ventricular arrhythmias.	IIa-B
In low probability of CHD by age, gender, and symptoms.	IIb-C
Isolated premature ventricular complexes (PVCs) in middle-aged or older patients without other evidence.	IIb-C
Ambulatory electrocardiography	
To clarify the diagnosis by detecting arrhythmias, QT interval changes, T wave alternans (TWA), or ST changes, to evaluate risk, or to judge therapy.	I-A
When symptoms are sporadic, to establish whether or not they are caused by transient arrhythmias.	I-B
Implantable recorders in sporadic symptoms suspected to be related to arrhythmias, such as syncope when a symptom-rhythm correlation cannot be established by conventional diagnostic techniques.	I-B
Electrocardiographic techniques and measurements	
TWA to improve the diagnosis and risk stratification of patients with ventricular arrhythmias or who are at risk for developing life-threatening ventricular arrhythmias.	IIa-A
Signal-averaged ECG (SAECG), heart rate variability (HRV), baroflex sensitivity, and heart rate turbulence.	IIb-B
Left ventricular function and imaging	
Patients suspected of having structural heart disease.	I-B
Patients with dilated, hypertrophic, or RV cardiomyopathies, AMI survivors, or relatives of patients with inherited disorders associated with sudden cardiac death.	I-B
Exercise testing with an imaging modality (echocardiography or nuclear perfusion [single photon emission computed tomography (SPECT)]) to detect silent ischaemia in intermediate probability of CHD by age, symptoms, and gender and less reliable ECG assessment because of digoxin use, LVH, greater than 1 mm ST segment depression at rest, WPW syndrome, or LBBB.	I-B
Pharmacological stress testing with an imaging modality (echocardiography or myocardial perfusion SPECT) to detect silent ischaemia in intermediate probability of CHD by age, symptoms, and gender and physical inability to perform a symptom-limited exercise test.	I-B
MRI, cardiac computed tomography (CT), or radionuclide angiography when echocardiography does not provide accurate assessment of LV and RV function and/or evaluation of structural changes.	IIa-B
Coronary angiography in patients with life-threatening ventricular arrhythmias or in survivors of SCD, who have an intermediate or greater probability of having CHD by age, symptoms, and gender.	IIa-C
LV imaging can be useful in patients undergoing biventricular pacing.	IIa-C
Electrophysiological testing in patients with coronary heart disease	
Patients with remote MI and symptoms suggestive of ventricular tachyarrhythmias, including palpitations, presyncope, and syncope.	I-B
Patients with CHD to guide and assess the efficacy of VT ablation.	I-B
Patients with CHD for the diagnostic evaluation of wide QRS complex tachycardias of unclear mechanism.	I-C
Risk stratification in patients with remote MI, NSVT, and LVEF equal to ≤40%.	IIa-B
Electrophysiological testing in patients with syncope	
Patients with syncope of unknown cause with impaired LV function or structural heart disease.	I-B
Bradyarrhythmias or tachyarrhythmias are suspected, but non-invasive diagnostic studies are not conclusive.	IIa-B
EHRA/HRS/APHRS 2014 consensus statement on VA	
Non-sustained ventricular arrhythmias	
Resting 12-lead electrocardiogram (ECG) and a transthoracic echocardiogram in all patients. Especially in patients in whom the arrhythmia morphology suggests such a specific aetiology, assess valvular and right heart morphology and function.	IIa-B
Repeat 12-lead ECGs whenever an inherited arrhythmia syndrome with varying electrocardiographic manifestations or a transient condition (e.g. coronary spasm) is suspected.	IIa-C
In selected patients, and especially in those with sustained arrhythmias, a second imaging modality (e.g. a magnetic resonance study, stress testing with perfusion scanning, or echocardiography).	Ia-B

(*Continued*)

Table 56.3 Continued

A test for myocardial ischaemia when the clinical presentation and/or the type of arrhythmia suggests the presence of coronary artery disease.	IIa-C
The risk of cardiac events is often dictated by an underlying heart disease rather than the arrhythmia. Therefore, optimal treatment of underlying cardiovascular diseases.	I-A
Prolonged ECG monitoring by Holter ECG, prolonged ECG event monitoring, or implantable loop recorders when documentation of further potentially longer arrhythmias would change management.	IIa-C
In patients with incompletely characterized arrhythmias with wide QRS complexes, both supraventricular and VAs should be considered in developing a care plan.	IIa-C
Sustained Monomorphic VT	
A 12-lead ECG should be recorded during sustained VTs	I-B
For patients with no evidence of structural heart disease	
(a) cardiac MRI	IIb-B
(b) signal-averaged ECG	IIb-C
(c) exercise testing	IIb-B
Inbasive EPS for patients with a wide QRS complex tachycardia and uncertain diagnosis	IIa-C
Sustained Polymorphic VT/VF	
Investigate for structural heart disease, inherited arrhythmia syndromes, early repolarization, coronary artery spasm, and pro-arrhythmic effects of medications using:	
a. Twelve-lead ECG during the arrhythmia and SR	I-C
b. Echocardiography.	I-b
c. Coronary arteriography.	I-b
ESC 2015 GL on VA and SCD	
Non-invasive evaluation of patients with suspected or known ventricular	
Resting 12-lead ECG	
Resting 12-lead ECG in all patients.	I-A
ECG monitoring	
Ambulatory ECG to detect and diagnose arrhythmias. Twelve-lead ambulatory to evaluate QT-interval changes or ST changes.	I-A
Cardiac event recorders when symptoms are sporadic	I-B
Implantable loop recorders when symptoms, e.g. syncope, are sporadic and suspected to be related to arrhythmias and when a symptom–rhythm correlation cannot be established by conventional diagnostic techniques.	I-B
SA-ECG to improve the diagnosis of ARVC in patients with VAs or in those who are at risk of developing life-threatening VAs.	I-B
Exercise stress testing	
In adult patients who have an intermediate or greater probability of having CAD by age and symptoms, to provoke ischaemic changes or VA.	I-B
Exercise stress testing in patients with known or suspected exercise-induced VA, including CPVT, to achieve a diagnosis and define prognosis.	I-B
Exercise stress testing in evaluating response to medical or ablation therapy in known exercise-induced VA.	IIa-C
Imaging	
Echocardiography for assessment of LV function and detection of structural heart disease	I-B
Echocardiography for assessment of LV and RV function in high risk of developing serious VAs or SCD, such as in dilated, hypertrophic or RV cardiomyopathies, survivors of acute myocardial infarction or relatives of patients with inherited disorders associated with SCD.	I-B
Exercise testing plus imaging (exercise stress echocardiography test or nuclear perfusion, SPECT) to detect silent ischaemia in patients who have an intermediate probability of having CAD by age or symptoms and in whom an ECG is less reliable (digoxin use, LV hypertrophy >1-mm ST-segment depression at rest, WPW syndrome, or LBBB).	I-B
Pharmacological stress testing plus imaging modality to detect silent ischaemia in patients who have an intermediate probability of having CAD by age or symptoms and are physically unable to perform a symptom-limited exercise test.	I–B
CMR or CT s when echocardiography does not provide accurate assessment of LV and RV function and/or evaluation of structural changes.	IIa–B

(*Continued*)

Table 56.3 Continued

Invasive evaluation of patients with suspected or known ventricular arrhythmias	
Coronary angiography	
In patients with life-threatening VAs or in survivors of SCD, who have an intermediate or greater probability of having CAD by age and symptoms.	IIa-C
Electrophysiological study	
In patients with remote myocardial infarction with symptoms suggestive of ventricular tachyarrhythmias, including palpitations, presyncope and syncope.	I-B
In patients with syncope when bradyarrhythmias or tachyarrhythmias are suspected, based on symptoms (e.g. palpitations) or the results of non-invasive assessment, especially in patients with structural heart disease.	I-C
For the differential diagnosis of ARVC and benign RVOT tachycardia or sarcoidosis.	IIb-B

ARVC, arrhythmogenic right ventricular cardiomyopathy; CAD, coronary artery disease; CMR, cardiac magnetic resonance; CPVT, catecholaminergic polymorphic ventricular tachycardia; CT, computed tomography; RVOT, right ventricular outflow tract; SA-ECG, signal-averaged ECG; SCD, sudden cardiac death; SPECT, single-photon emission computed tomography; VA, ventricular arrhythmia; WPW, Wolff–Parkinson–White.

ACC/AHA/ESC 2006 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Circulation*. 2006;**114**:e385–e484 with permission from Wolters Kluwer.

EHRA/HRS/APHRS expert consensus on ventricular arrhythmias. *Europace*. 2014;16:1257–83 with permission from Oxford University Press.

ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015; **36**:2793–867 with permission from Oxford University Press.

Long-term therapy

It depends on the underlying substrate and mechanism of arrhythmia, and details are provided in the next section. General principles are:

- Management of any identifiable underlying disorder (i.e. heart failure, significant ischaemia, etc.) is essential. **Beta blockers, ACEIs, ARBs**, and **statins** have been shown in many studies to reduce mortality and sudden cardiac death.[93] **Antiplatelet therapy** in the SOLVD trial was also associated with reduced incidence of sudden cardiac death.[94] Although there has been evidence that omega-3 fatty acids may reduce life-threatening arrhythmic events, results have not been consistent.[95,96] Fatty acid supplementation currently has a Class IIb-B recommendation. Statins should be used in all patients with CAD. They do not reduce the risk of VTs or cardiac arrest but result in a 11% reduction in the risk of SCD, presumably by preventing coronary events.[97]
- **Smoking** is strongly discouraged, and abstinence from **alcohol** is recommended in cases where there is a suspected correlation between alcohol intake and ventricular arrhythmias.
- Correction of **hypokalaemia** and **hypomagnesaemia** are useful. Intravenous magnesium prolongs sinus node recovery time, reduces automaticity, and homogenizes transmural ventricular repolarization. It has been reported to be useful in preventing atrial fibrillation and ventricular arrhythmias after cardiac and thoracic surgery; in reducing the ventricular response in acute-onset atrial fibrillation, including for patients with Wolff–Parkinson–White syndrome; in the treatment of digoxin-induced supraventricular and ventricular arrhythmias, multifocal atrial tachycardia, and polymorphic ventricular tachycardia or ventricular fibrillation from drug overdoses. Intravenous magnesium is, however, not useful in monomorphic ventricular tachycardia and shock-resistant ventricular fibrillation.[98,99]
- With the exception of beta blockers, no currently available antiarrhythmic agent (Table 56.4) has been shown in randomized clinical trials to reduce mortality in patients with ventricular arrhythmias or to prevent sudden cardiac death in patients prone to arrhythmias.[100,101] Implantable cardioverter-defibrillators (ICD) remain the only means to reduce mortality in patients prone to life-threatening ventricular arrhythmias (primary prevention) or with clinical life-threatening ventricular arrhythmias (secondary prevention). General indications for ICD are presented in Tables 56.5 and 56.6.[1,102] Additional indications in patients with heart failure, post-MI, cardiomyopathies and genetic channelopathies are discussed in the relevant chapters.

Summarizing recommendations by ACCF/AHA/HRS 2012 GL on Device Therapy, ACCF/AHA 2013 GL on STEMI, ACCF/AHA 2013 GL on heart failure, and ESC 2015 on VA and SCD, an ICD is indicated in:

- Survivors of cardiac arrest due to VF or haemodynamically unstable sustained VT
- Structural heart disease and spontaneous sustained VT
- Syncope of undetermined origin with haemodynamically significant sustained VT or VF induced at electrophysiological study

- Ischaemic (>40 days post-MI) or dilated cardiomyopathy, and LVEF ≤35%, and NYHA II/III
- Ischaemic (>40 days post-MI) cardiomyopathy, and LVEF ≤30%, and NYHA I
- Post-MI (>48 h), sustained VT/VF, not due to transient or reversible ischaemia, re-infarction, or metabolic abnormalities
- Post-MI (>40 days), LVEF <40%, NSVT, and inducible VF/VT
- Sustained VT and normal ventricular function, cardiomyopathies and risk factors for sudden death, and genetic channelopathies with syncope.

Other indications in specific clinical settings are discussed under clinical forms of VT. Table 56.7 presents recommendations of the HRS/ACC/AHA consensus statement for the use of ICD for clinical scenarios that are not well represented in clinical trials and, therefore, no hard evidence exists.[103] For optimum ICD programming, see Chapter 69.

- **Amiodarone with beta blockers** may be considered in patients who do not meet the criteria for an ICD. This combination is preferred to sotalol due to its proarrhythmic potential.[104] The ESC 2015 GL on VA and SCD consider amiodarone in patients with VF/VT and an indication for ICD, when an ICD is not available, contraindicated for concurrent medical reasons, or refused by the patient (IIb-C). However, data on the effect of amiodarone on mortality are controversial (see below). In patients with ICD, **sotalol** may be used for reduction of the number of shocks in the absence of severely depressed LV function.[105] **Celivarone**, a non-iodinated analogue of amiodarone, has also been promising in preventing ICD interventions.[106]
- **Catheter ablation** is indicated in bundle branch reentry and idiopathic VT. In other forms of VT, such as frequent monomorphic VT or VT storm in ischaemic patients who already have an ICD, ablation (endocardial or epicardial)[107–111] may also reduce the number of ICD shocks (Table 56.8). In ischaemic patients, all inducible VT are ablated in 38–72% of them, with a procedure-related mortality of 0.5% and 12–50% recurrence rate within the following year. In a recent mult-centre cohort, non-inducibility after VT ablation indicated reduced mortality compared to persistent inducibility, but the long-term survival of these patients was poor (<25% at 5 years).[111] In non-ischaemic patients, acute success in eliminating inducible VT is 55–89%, with VT recurrence of 16–63% and with the outcome depending on the underlying heart disease.[112] Long-term outcome is worse in non-ischaemic than ischaemic cardiomyopathy.[113] Compared with patients with non-ischaemic dilated cardiomyopathy, patients with arrhythmogenic RV cardiomyopathy had better outcomes and patients with sarcoidosis had worse outcomes.[112]

Table 56.4 ESC 2015 GL on VA and SCD. Anti-arrhythmic drugs for the treatment of ventricular arrhythmias

Anti-arrhythmic drugs (Vaughan Williams class)	Oral dose (mg/day)[a]	Common or important adverse effects	Indications	Cardiac contraindications and warnings
Amiodarone (III)	200–400	Pulmonary fibrosis, hypothyroidism and hyperthyroidism, neuropathies, corneal deposits, photosensitivity, skin discolouration, hepatotoxicity sinus bradycardia, QT prolongation, and occasional TdP.	VT, VF	Conditions and concomitant treatments associated with QT interval prolongation; inherited LQTS; sinus bradycardia (except In cardiac arrest): sinus node disease (unless a pacemaker is present); severe AV conduction disturbances (unless a pacemaker is present); decompensated HF or cardiomyopathy.
Beta-blocker (II)	Various	Bronchospasm, hypotension, sinus bradycardia, AV block, fatigue, depression sexual disturbances.	PVC, VT, LQTS, CPVT	Severe sinus bradycardia and sinus node disease (unless a pacemaker is present); AV conduction disturbances (unless a pacemaker is present); acute phase of myocardial infarction (avoid if bradycardia, hypotension, LV failure): decompensated HF; Prinzmetal angina.
Disopyramide (IA)	250–750	Negative In trope, QRS prolongation, AV block, pro-arrhythmia (atrial flutter, monomorphic VT, occasional TdP), anticholinergic effects.	VT, PVC	Severe sinus node disease (unless a pacemaker is present): severe AV conduction disturbances (unless a pacemaker Is present); severe intraventricular conduction disturbances; previous myocardial infarction; CAD; HF; reduced LVEF; hypotension.

(*Continued*)

Table 56.4 Continued

Anti-arrhythmic drugs (Vaughan Williams class)	Oral dose (mg/day)[a]	Common or important adverse effects	Indications	Cardiac contraindications and warnings
Flecainide (IC)	200–400	Negative Inotrope, QRS widening, AV block, sinus bradycardia pro-arrhythmia (atrial flutter, monomorphic VT, occasional TdB). Increased incidence of death after myocardial infarction.	PVC, VT	Sinus node dysfunction (unless a pacemaker is present; AF/flutter (without the concomitant use of AV-blocking agents); severe AV conduction disturbances (unless a pacemaker is present): severe intraventricular conduction disturbances; previous myocardial infarction CAD; HF; reduced LVEF; hemodynamically significant valvular heart disease; Brugada syndrome; inherited LQTS (other than LQTS3); concomitant treatments associated with QT-interval prolongation.
Mexiletine (IB)	450–900	Tremor, dysarthria, dizziness gastrointestinal disturbance, hypotension, sinus bradycardia.	VT, LQT3	Sinus node dysfunction (unless a pacemaker is present): severe AV conduction disturbances (unless a pacemaker is present); severe HF; reduced LVEF; inherited LQTS (other than LQTS3); concomitant treatments associated with QT-interval prolongation.
Procainamide (IA)	1000–4000	Rash, myalgia. vasculitis hypotension, lupus. agranulocytosis, bradycardia, QT prolongation, TdP.	VT	Severe sinus node disease (unless a pacemaker is present): severe AV conduction disturbances (unless a pacemaker is present); severe intraventricular conduction disturbances; previous myocardial infarction; CAD; HF; reduced LVEF; hypotension; reduced Brugada syndrome.
Propafenone (IC)	450–900	Negative inotrope, gastrointestinal disturbance, QRS prolongation, AV block, sinus bradycardia pro-arrhythmia (atrial flutter monomorphic VT, occasional TdP).	PVC, VT	Severe sinus bradycardia and sinus node dysfunction (unless a pacemaker is present): AF/flutter (without the concomitant use of AV-blocking agents); severe AV-conduction disturbances (unless a pacemaker is present); severe intraventricular conduction disturbances: previous myocardial infarcoon; CAD; HF; reduced LVEF; haemodynamically significant valvular heart disease; Brugada syndrome; inherited LQTS (other than LQTS3); concomitant treatments associated with QT interval prolongation.
Quinidine	600–1600	Nausea, diarrhea, auditory and visual disturbance, confusion, hypotension, thrombocytopenia haemolytic anaemia, anaphylaxis, QRS and QT prolongation, TdP.	VT, VF, SQTS, Brugada syndrome	Severe sinus node (unless a pacemaker is present); AV-conduction disturbances (unless a pacemaker is present); severe intraventricular conduction disturbances; previous myocardial infarcoon; CAD; HF; reduced LVEF; hypotension; inherited Long QT syndrome; concomitant treatments associated with QT interval prolongation.
Ranolazine (IB)	750–2000	Dizziness nausea, constipation, hypotension, gastrointestinal disturbance, headache, rash, sinus bradycardia, QT prolongation.	LQTS3[b]	Severe sinus bradycardia and sinus node disease; severe HF; inherited Long QT Syndrome (other than LQTS3); concomitant treatments associated with QT moral prolongation.
Sotalol (III)	160–320	As for other beta-blockers and TdP.	VT (ARVC)[c]	Severe sinus bradycardia and sinus node disease (unless a pacemaker is present); AV conduction disturbances (unless a pacemaker is present); severe HF; Prinzmati's angina; inherited LQTS; concomitant treatments associated with QT interval prolongation.

(*Continued*)

Table 56.4 Continued

Anti-arrhythmic drugs (Vaughan Williams class)	Oral dose (mg/day)[a]	Common or important adverse effects	Indications	Cardiac contraindications and warnings
Verapamil (IV)	120-480	Negative inotrope (especially in patients with reduced LVEF), rash, gastrointestinal disturbance, hypotension, sinus bradycardia AV block, VT.	LV fascicular tachycardia	Severe sinus bradycardia and sinus node disease (unless a pacemaker is present); severe AV conduction disturbances (unless a pacemaker is present); acute phase of myocardial infarction) (avoid if bradycardia, hypotension. left ventricular failure); HF; significantly reduced LVEF; atrial flutter or fibrillation associated with accessory conducting pathways (e.g. WPW syndrome).

AF, atrial fibrillation; ARVC, arrhythmogenic right ventricular cardiomyopathy; AV, atrio-ventricular; CAD, coronary artery disease; HF, heart failure; LQTS3, long QT syndrome type 3; PVC, premature ventricular complex; SQTS, short QT syndrome; TdP, Torsade de Pointes; WPW, Wolff–Parkinson–White.
a: Adult drug doses are quoted in this table.
b: Ranolazine is only approved for the treatment of chronic stable angina. Note that other doses may apply in special conditions.
c: Sotalol has been indicated for ARVC but its use has been questioned.
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Table 56.5 Indication for ICD*

ACCF/AHA/HRS 2012 GL on device therapy	
Cardiac arrest due to VF or unstable VT and no reversible cause	I-A
Structural heart disease and spontaneous sustained VT (stable or unstable)	I-B
Syncope of undetermined origin with inducible haemodynamically significant sustained VT at EPS	I-B
Ischaemic (>40 days post-MI) or non-ischaemic cardiomyopathy, LVEF ≤35%, NYHA II/III	I-A
Ischaemic cardiomyopathy, >40 days post-MI, LVEF ≤30%, NYHA I	I-A
Non-sustained VT due to prior MI, LVEF <40% and inducible VF or sustained VT at EPS	I-B
Unexplained syncope, significant LV dysfunction, and non-ischaemic cardiomyopathy	IIa-C
Sustained VT and normal or near-normal LV function	IIa-C
HCM and one or more risk factors for SCD	IIa-C
ARVD/C and one or more risk factors for SCD	IIa-C
LQTS and syncope and/or sustained VT on beta blockers	IIa-B
Non hospitalized patients awaiting transplantation	IIa-C
Brugada syndrome and syncope or documented VT	IIa-C
CPVT and syncope and/or sustained VT on beta blockers	IIa-C
Cardiac sarcoidosis, giant cell myocarditis, or Chagas disease	IIa-C
Non-ischaemic cardiomyopathy, LVEF ≤35%, NYHA I	IIb-C
LQTS and risk factors for sudden death	IIb-B
Syncope and advanced structural heart disease	IIb-C
Familial cardiomyopathy associated with sudden death	IIb-C
LV noncompaction	IIb-C
ICD therapy is not indicated for patients who do not have a reasonable expectation of survival with an acceptable functional status for at least 1 year, even if they meet ICD implantation criteria specified in the Class I, IIa, and IIb recommendations above	III-C
Incessant VT or VF	III-C
Significant psychiatric illnesses that may be aggravated by implantation or preclude follow-up	III-C
NYHA IV patients with drug-refractory congestive heart failure who are not candidates for cardiac transplantation or CRT-D	III-C
Syncope of undetermined cause without inducible ventricular tachyarrhythmias and without structural heart disease	III-C
VF or VT amenable to surgical or catheter ablation (eg, atrial arrhythmias associated with the Wolff-Parkinson-White syndrome, RVOT or LVOT VT, idiopathic VT, or fascicular VT in the absence of structural heart disease).	III-C
Ventricular tachyarrhythmias due to a completely reversible disorder in the absence of structural heart disease (eg, electrolyte imbalance, drugs, or trauma)	III-B

(*Continued*)

Table 56.5 Continued

ACCF/AHA 2013 GL on STEMI	
ICD before discharge in patients who develop sustained VT/VF more than 48 hours after STEMI, provided the arrhythmia is not due to transient or reversible ischemia, reinfarction, or metabolic abnormalities	I-B
ESC 2015 GL on VA and SCD	
Documented VF or haemodynamically not tolerated VT, in the absence of reversible causes or within 48 h after myocardial infarction,	I-A
Symptomatic HF (NYHA class II–III) and LVEF ≤35% after ≥3 months of optimal medical therapy :	
– Ischaemic aetiology (at least 6 weeks after myocardial infarction).	I-A
– Non-ischaemic aetiology.	I-B
Recurrent sustained VT (not within 48 h after myocardial infarction) in patients with a normal LVEF	IIa-C
Patients who are listed for heart transplant.	IIa-C
ICD implantation or temporary wearable defibrillator <40 days after myocardial infarction in selected patients (incomplete revascularization (inability to treat culprit or non-culprit lesions), pre-existing LVEF dysfunction, occurrence of arrhythmias >48 h after the onset of ACS, polymorphic VT or VF).	IIb-C

* For patients who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status >1 y.
ACCF/AHA/HRS 2012 Focused Update Incorporated Into the ACCF/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2013;**61**: e6–e75 with permission for Elsevier.
ACCF/AHA 2013 Guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2013;**61**:e78–e140 with permission from Elsevier.
ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015; **36**:2793–867 with permission from Oxford University Press.

Table 56.6 ESC 2015 GL on VA and SCD

Psychosocial management after ICD implantation	
Assessment of psychological status and treatment of distress in patients with recurrent inappropriate shocks.	I-C
Discussion of quality-of-life issues before ICD implantation and during disease progression in all patients.	I-C
Subcutaneous implantable cardioverter defibrillator	
As an alternative to transvenous defibrillators in patients with an indication for an ICD when pacing therapy for bradycardia support, cardiac resynchronization or antitachycardia pacing is not needed.	IIa-C
As a useful alternative to the transvenous ICD system when venous access is difficult, after the removal of a transvenous ICD for infections or in young patients with a long-term need for ICD therapy.	IIb-C
Wearable cardioverter defibrillator	
Adult patients with poor LV systolic function who are at risk of sudden arrhythmic death for a limited period, but are not candidates for an implantable defibrillator (e.g. bridge to transplant, bridge to transvenous implant, peripartum cardiomyopathy, active myocarditis and arrhythmias in the early post-myocardial infarction phase).	IIb-C

ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015; **36**:2793–867 with permission from Oxford University Press.

Table 56.7 HRS/ACC/AHA 2014 expert consensus statement on the use of ICD in patients not represented in clinical trials

ICD implantation within 40 days of myocardial infarction
ICD recommended
Sustained or haemodynamically significant VT not due to ischaemia or injury (amenable to revascularization) >48h post-MI and the patient not candidate for ablation
NYHA II/III and LVEF ≤35% with LV recovery uncertain, and pacing indicated
NYHA I and LVEF ≤30% with LV recovery uncertain, and pacing indicated
ICD can be useful
Sustained or haemodynamically significant VT not due to ischaemia or injury (amenable to revascularization) >48h post-MI and the patient a candidate for ablation
Syncope thought to be due to VT and no evidence of ischaemia
ICD implantation within 90 days of revascularization
ICD recommended
Sustained or haemodynamically significant VT prior to revascularization, and abnormal LV function or incomplete revascularization.
NYHA II/III and LVEF ≤35% with LV recovery uncertain, and pacing indicated
NYHA I and LVEF ≤30% with LV recovery uncertain, and pacing indicated

(*Continued*)

Table 56.7 Continued

ICD can be useful
Sustained or haemodynamically significant VT after revascularization, and that can be treated with ablation
Sustained or haemodynamically significant VT prior to revascularization, and not due to ischaemia or injury.
Syncope thought to be due to VT and no evidence of ischaemia
NYHA II/III and LVEF ≤35% with LV recovery uncertain, and pacing not indicated
NYHA I and LVEF ≤30% with LV recovery uncertain, and pacing not indicated
ICD implantation less than 9 months after diagnosis of nonischaemic cardiomyopathy
ICD recommended
Sustained or haemodynamically significant VT
NYHA II/III and LVEF ≤35% with LV recovery unlikely
ICD can be useful
Syncope thought to be due to VT and no evidence of ischaemia
Patient on transplant list or LVAD
Nonischaemic cardiomyopathy 3-9 months, and LVEF ≤35% with LV recovery unlikely

HRS/ACC/AHA Expert consensus statement on the use of implantable cardioverter defibrillator therapy in patients who are not included or not well represented in clinical trials. *J Am Coll Cardiol*. 2014;**64**:1143–77 with permission from Elsevier.

Table 56.8 Specific therapies

EHRA/HRS/APHRS2014 consensus statement on ventricular arrhythmias	
Sustained monomorphic VT (SMVT)	
ICD for patients with structural heart disease and SMVT	I-A
For structural heart disease and recurrent SMVT, specific treatment with AADs (amiodarone, mexiletine, or sotalol), catheter ablation, and/or antitachycardia pacing (ATP) from an ICD, in addition to an ICD. Treatment of the underlying disease or ischaemia will in most cases not be sufficient to prevent monomorphic VT recurrences.	IIa-B
For patients with an ICD as primary prophylaxis, programming to a long VT detection interval and a high VF detection rate	II a-A
Sustained polymorphic VT/VF	
Specific antiarrhythmic therapies, e.g. quinidine in patients with idiopathic VF, sodium channel blocker therapy in patients with long QT syndrome III, intensive autonomic inhibition in patients with catecholaminergic VTs, or quinidine in BrS, in close cooperation with a specialist in these diseases to reduce the risk of recurrence as an adjunct to-and rarely as an alternative to defibrillator therapy in survivors of polymorphic VAs.	IIa-B
For VT/VF storm, correct reversible factors such as electrolyte abnormalities, pro-arrhythmic drugs, ischaemia, and decompensated chronic heart failure	I-C
Suppression of VT/VF storm with beta-adrenergic blockers, amiodarone, and/or lidocaine	IIa-C
For unstable patients with VT/VF storm in whom pharmacological suppression has not been effective, neuraxial modulation, mechanical ventilation, catheter ablation, and/or anaesthesia	IIb-C
Catheter ablation of VTs or a triggering focus of VF in patients with VT/VF storm when adequate experience is available	IIa-C
For VT/VF storm and significant structural heart disease, implantation of a LV assist device (LVAD) or heart transplant evaluation early after the initial event.	IIa-C
ESC 2015 GL on VA and SCD	
Catheter ablation for the treatment of sustained monomorphic ventricular tachycardia	
Urgent catheter ablation in scar-related heart disease presenting with incessant VT or electrical storm.	I-B
Ischaemic heart disease and recurrent ICD shocks due to sustained VT.	I-B
After a first episode of sustained VT in patients with ischaemic heart disease and an ICD.	IIa-B
Surgical ablation of ventricular tachycardia	
Surgical ablation guided by preoperative and intraoperative electrophysiological mapping performed at an experienced centre in patients with VT refractory to anti-arrhythmic drug therapy after failure of catheter ablation by experienced electrophysiologists.	I-B
Surgical ablation at the time of cardiac surgery (bypass or valve surgery) in clinically documented VT or VF after failure of catheter ablation.	IIb-C

EHRA/HRS/APHRA 2014 Expert consensus on ventricular arrhythmias. *Heart Rhythm*. 2014;**11**:e116–96 with permission from Elsevier.
ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015; **36**:2793–867 with permission from Oxford University Press.

Clinical forms of ventricular arrhythmias

Premature ventricular beats and non-sustained VT in normal subjects

In asymptomatic, apparently healthy persons, Holter recordings in older studies have revealed a frequency of NSVT, ranging from 0 to 3%, but the condition gets more frequent with age. The prognostic significance of PVCs and NSVT in normal subjects has been controversial.[114] Several studies have indicated that a higher frequency of PVCs is associated with a decrease in LVEF and an increase in mortality,[115–117] and this effect appears to be additive when atrial premature beats (APCs) occur concurrently (ARIC study).[116] However, in an analysis of NHANES III data, no significant association of VPCs with total mortality was detected.[118] APCs, however, were associated with total and cardiovascular mortality. When detected during exercise, and especially at recovery, NSVT indicates increased cardiovascular mortality within the next decades.[119,120] In trained athletes, NSVT commonly occurs during ambulatory Holter electrocardiography,[121,122] and is most probably benign when suppressed by exercise. NSVT in athletes without structural heart disease is considered part of the 'athlete's heart syndrome' and has no adverse prognostic significance, provided conditions, such as hypertrophic cardiomyopathy, early repolarization syndrome (J wave and/or QRS slurring), and other genetic channelopathies, are excluded (see Arrhythmias in athletes).

Therapy

Specific antiarrhythmic drug therapy is not indicated for PVCs or NSVT (Tables 56.9 and 56.10 and Figure 56.9). In symptomatic cases, beta 1 selective blockers may be given. Catheter ablation may also be tried in drug-resistant, frequent monomorphic VPBs. In patients with frequent VPBs originating from the RVOT, catheter ablation is more efficacious than drug therapy, especially when there is a QS morphology in lead I.[123]

Idiopathic VT

Idiopathic VT indicates VT that occurs in the absence of clinically apparent structural heart disease. Approximately two-thirds of idiopathic VT originate in the RV and the rest in the LV (Figure 56.10).

Ventricular outflow tract tachycardias

Idiopathic ventricular outflow arrhythmias usually present in the form of **repetitive uniform PVCs, repetitive monomorphic NSVT** (that usually disappears as the heart rate increases with exercise) and **paroxysmal sustained monomorphic VT** (that is usually exercise-provoked). They mainly (approximately 80%) arise in the right ventricular outflow tract (RVOT), and rarely below it, and 10–15% from the LVOT and are, most probably, due to triggered activity secondary to cAMP-mediated delayed after-depolarizations.[6] Defects of connexins (proteins involved in cell-to-cell connections) may also be responsible.[124] Inducibility of sustained monomorphic VT (adenosine-sensitive) is possible with concomitant administration of isoprenaline in <50% of the cases of outflow tract tachycardias.

Right ventricular outflow tract (RVOT) tachycardias produce a LBBB pattern with inferior axis and R/S transition at or beyond V_3. R/S transmission beyond V_4 and notching in the inferior leads indicates a free wall, rather than septal site, of origin, and a positive R wave in lead I posterior, rather than anterior, septal and free wall sites.[125]

Left ventricular outflow tract (LVOT) tachycardias may produce a RBBB morphology with inferior axis and R/S transition at V_1 or V_2 due to the more posterior location of LVOT compared to RVOT.[126] If the R/S transition is in V_3, the tachycardia may originate from either the RVOT (usually) or the LVOT. A V_2 transition ratio ≥0.60 predicts LVOT origin.[127] The transition ratio represents percentage R wave during VT divided by percentage R wave during SR, $[R/(R+S)_{VT}$ divided by $[R/(R+S)]_{SR}$, and is calculated by measuring R wave amplitude (highest point to isoelectric line) and S wave (lowest point to isoelectric line) durations in mV during VT and SR.

Ventricular outflow tract tachycardias originating above the semilunar valves usually arise at the coronary cusps.[128] They have a variable QRS morphology, depending on the site of origin: tachycardias originating in the **left coronary cusp** have a QRS morphology consistent with an M or a W pattern in lead V_1; tachycardias originating in the **right coronary cusp** or the **left ventricular side of the septum** may have an LBBB pattern; and tachycardias arising from the commissure between the left and right cusps display a QS morphology in lead V_1, with notching on the downward deflection and precordial transition in V_3. LBBB morphology with an R wave in V_1 and large R waves in the inferior leads suggests the pulmonary artery as site of origin. Catheter ablation is the treatment of choice. Rarely (<10%), there can also be an **epicardial** site of origin (prominent r in V_1, delayed QRS onset to maximal deflection interval).[129]

Fascicular tachycardias

Idiopathic left ventricular tachycardias may also be due to reentry within the Purkinje network; they are verapamil-(but not adenosine-) sensitive and may originate within one of the fascicles of the left bundle branch. Usually, the posterior fascicle is involved, resulting in a tachycardia with RBBB and left axis deviation (90%), but cases with

Table 56.9 Specific management of NSVT

Clinical setting	Investigations	Therapy
Idiopathic NSVT	EP testing differentiates from ARVC	Beta blockers, calcium channel blockers; RF ablation if inducible sustained VT, progressively reduced LVEF, or symptoms
Arrhythmogenic ventricular cardiomyopathy	Value of EP testing not established NSVT indicates intermediate arrhythmic risk (<2% per year)	Not established. Perhaps amiodarone or sotalol; ICD frequently considered
Hypertension, valve disease	No need for specific management	Optimal antihypertensive therapy, including beta blockers
Non-STE ACS, NSVT >48 h after admission	Meticulous ischaemia testing	Revascularization and optimal medical therapy[1]
Acute MI, NSVT >24 h till pre-discharge	Routine for acute MI	Revascularization and optimal medical therapy
Previous MI with LVEF = 31–40%	Ischaemia testing, EP testing[2]	Revascularization and optimal medical therapy. If EP-inducible monomorphic VT or VF[3]: ICD[4]
Previous MI with LVEF ≤30% or LVEF ≤35% and NYHA II/III	Ischaemia testing. No EP needed[2]	Revascularization and optimal medical therapy ICD[4]
Asymptomatic CAD with EF >40%	Ischaemia testing	Revascularization and optimal medical therapy. No need for specific NSVT therapy
Syncope in CAD with EF >40%	Ischaemia testing, EP testing[2]	Revascularization and optimal medical therapy. If EP-inducible monomorphic VT or VF[3]: ICD
Non-ischaemic dilated cardiomyopathy	Value of EP testing not established	Optimal CCF therapy (medical and CRT if indicated). Ablation for bundle branch reentry. ICD for syncope or LVEF ≤30–35% and NYHA II/III
Hypertrophic cardiomyopathy	Evaluate additional risk factors:	Beta blockers, ICD, especially with frequent and prolonged (>10 beats) episodes of NSVT
	- Previous cardiac arrest	
	- Unexplained syncope	
	- Massive LV hypertrophy (≥30 mm)	
	- Hypotensive or attenuated blood pressure response to upright exercise	
Congenital heart disease (usually repaired Fallot)	EP testing	Predictive value of NSVT not established. Consider corrective surgery. If VT inducible: ablation and ICD
Long QT syndrome	Genotype analysis useful	Beta blockers, ICD if syncope despite beta blockers
Catecholaminergic polymorphic VT	Value of EP testing not established	Beta blockers and perhaps calcium channel blockers. ICD if cardiac arrest
Brugada syndrome	Value of EP testing disputed	Possibly quinidine (more data needed). ICD if cardiac arrest

[1] Optimal medical therapy for NSVT in the setting of coronary artery disease is defined as administration of beta blockers (essential, unless absolutely contraindicated), aspirin, statins, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.
[2] If conditions remain the same after indicated revascularization.
[3] Prognostic significance of inducible monomorphic VT induced by three extrastimuli is similar to that of VT induced by one or two extrastimuli. Monomorphic VT, as opposed to VF, usually does not respond to revascularization. VF induced by three extrastimuli may represent a non-specific response.
[4] ICD is recommended if indications exist at least 40 days after MI.
EP, electrophysiology study; ARVC, arrhythmogenic right ventricular cardiomyopathy; non-STE ACS, non-ST elevation acute coronary syndrome (non-STEMI or unstable angina); MI, myocardial infarction; LVEF, left ventricular ejection fraction; ICD, implantable cardioverter-defibrillator; CAD, coronary artery disease; CCF, congestive cardiac failure; CRT, cardiac resynchronization therapy.
Katritsis D, *et al*., Non-sustained ventricular tachycardia. *J Am Coll Cardiol*. 2012;**60**:1993–2004 with permission from Elsevier.

Table 56.10 EHRA/HRS/APHRS 2014 Consensus statement on ventricular arrhythmias

Recommendations on non-sustained VAs	
Infrequent ventricular ectopic beats, couplets, and triplets without other signs of an underlying structural heart disease or an inherited arrhythmia syndrome should be considered as a normal variant in asymptomatic patients.	IIa-C
Invasive electrophysiological study in significant structural heart disease and non-sustained VAs especially if accompanied by unexplained symptoms such as syncope, near-syncope, or sustained palpitations	IIa-C
No treatment other than reassurance for patients without structural heart disease or inherited arrhythmia and asymptomatic or mildly symptomatic PVCs.	I-C
Beta-blocker in survivors of a myocardial infarction and other patients with reduced LV function and non-sustained VAs	I-A
Beta-blockers in symptomatic patients with non-sustained VAs.	IIb-C
A non-dihydropyridine calcium channel antagonist as an alternative to beta-blocker in patients without structural heart disease.	IIb-C
In symptomatic non-sustained VAs on an adequately dosed beta-blocker or a non-dihydropyridine calcium channel antagonist, treatment with an antiarrhythmic drug (AAD; amiodarone, flecainide, mexiletine, propafenone, sotalol) to improve symptoms	IIb-C
Flecainide and propafenone are not recommended to suppress PVCs in patients with reduced LV function (unless caused by ventricular ectopy itself), myocardial ischaemia, or myocardial scar.	III-A
Sotalol should be used with caution in patients with chronic kidney disease and should be avoided in patients with a prolonged QT interval at baseline or with excessive prolongation of QT interval >0.50 s upon therapy initiation.	I-B
Amiodarone appears to be less overall pro-arrhythmic in patients with heart failure and may be preferred to other membrane-active AADs unless an ICD has been implanted.	IIb-C
Catheter ablation for symptoms or LV dysfunction with frequent non-sustained VAs (e.g. >PVC 10 000 per 24 h) in patients with significant symptoms or LV dysfunction without another detectable cause.	IIa-B
Amiodarone, sotalol, and/or other beta-blockers as pharmacological adjuncts to reduce ICD shocks and to suppress symptomatic NSVT in patients who are unsuitable for ICD therapy	IIb-B

EHRA /HRS /APHRS 2014 expert consensus on ventricular arrhythmias. *Europace*. 2014;**16**:1257–83, with permission from Oxford University Press.

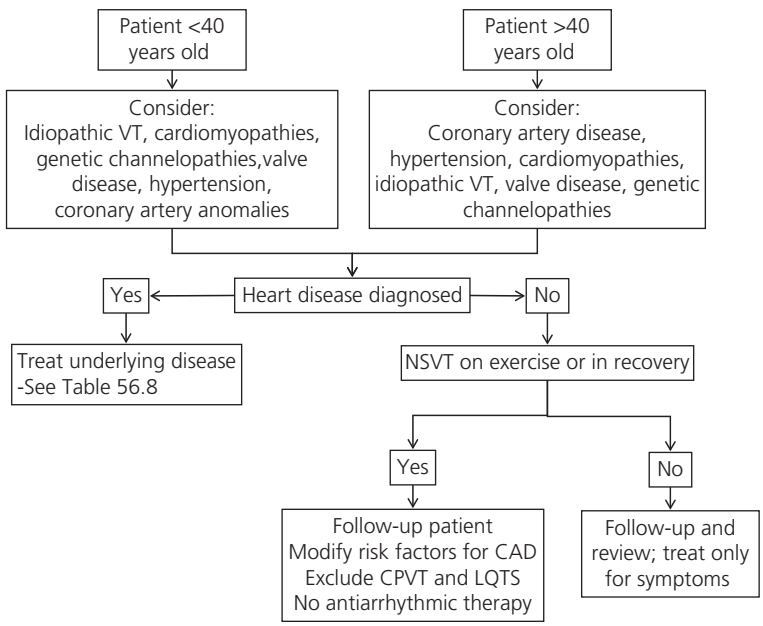

Figure 56.9 Clinical approach to the patient with NSVT.

CAD, coronary artery disease; CPVT, catecholaminergic polymorphic ventricular tachycardia; LQTS, long QT syndromes.
Katritsis D, et al., Non-sustained ventricular tachycardia. *J Am Coll Cardiol*. 2012;**60**:1993–2004 with permission from Elsevier.

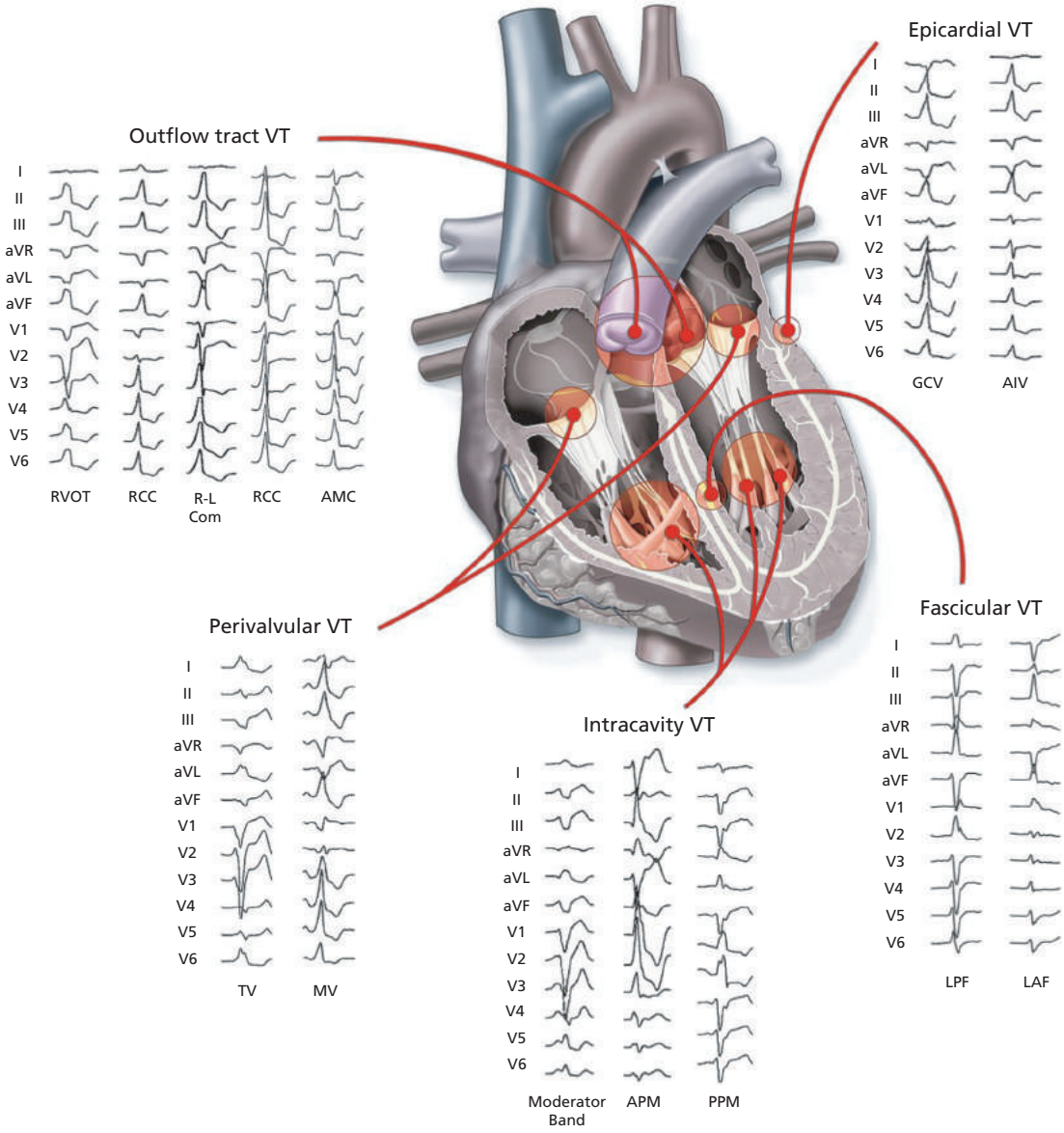

Figure 56.10 Twelve-lead electrocardiogram morphology of different sites of origin in idiopathic ventricular tachycardia (RVOT, right ventricular outflow tract; RCC, right coronary cusp; R–L com, right–left coronary cusp commissure; AMC, aortomitral continuity; TV, tricuspid annulus; MV, mitral annulus; APM, anterior PAP; PPM, posterior PAP; LPF, left posterior fascicle; LAF, left anterior fascicle; GCV, greater cardiac vein; AIV, anterior inter-ventricular vein).

Reproduced from Tanawuttiwat T, *et al*. The role of catheter ablation in the management of ventricular tachycardia, *Eur Heart J*. 2016;**37**:594–609 with permission from Oxford University Press.

inferior axis due to anterior or high septal fascicular origin may also occur.[11,130]

Other sites of origin

Tachycardias may also originate in the **AV annuli**, either in the tricuspid (LBBB pattern) or the mitral annulus (RBBB pattern or RS in V_1 and monophasic R or RS in V_2–V_6).[131] Tachycardias from the **papillary muscles** have a focal (no reentrant) mechanism not involving the Purkinje network but, usually, the posterior papillary muscle, and present with RBBB morphology. Tachycardias may also originate around the **His bundle** or in the **intraventricular septum** (LBBB with inferior axis).[132]

Prognosis and therapy

NSVT originating from the RVOT may occasionally cause syncope, although the risk of death is very low. However, malignant ventricular arrhythmias and sudden death may occur in patients with RVOT ectopic activity.[133–135] Short cycle length during NSVT, especially a second cycle length of NSVT <317 ms, and a history of syncope have been proposed as predictors of coexistence of VF or polymorphic VT.[136,137]

Differentiation from ARVC/D (see Cardiomyopathies) is crucial, especially since, rarely, idiopathic VT may arise in the RV body, and subjects with RVOT VT, as well as with LVOT VT, may have subtle structural and functional abnormalities as detected by magnetic resonance imaging.[138] QRS duration in lead I of >120 ms, earliest onset QRS in lead V_1, QRS notching, and a transition of V_5 or later predict the presence of ARVC/D (Figure 56.11).[139] The developed electrocardiographic scoring system to distinguish between idiopathic and ARVC/D VT[140] is presented in Table 39.3 of Chapter 39 on ARVC/D.

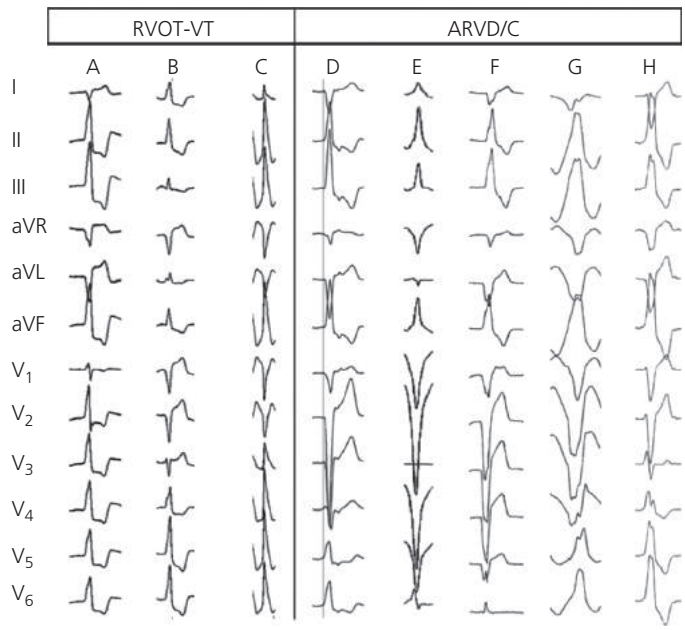

Figure 56.11 Differentiation between RVOT VT and ARVD/C. Twelve-lead electrocardiograms from patients with right ventricular outflow tract tachycardia (RVOT VT) (A to C) and arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) (D to H), showing characteristic features. (A) RVOT VT from an anterior septal location, showing precordial transition at V_2 and narrow QRS duration in lead I (78 ms). (B) RVOT VT originating superior to His bundle region, showing precordial transition at V_4, positive R wave in aVL, and narrow QRS in lead I (86 ms). (C) RVOT VT from a posterior septal location, showing precordial transition at V_3 and narrow QRS duration in lead I (118 ms). (D) ARVD/C ventricular tachycardia (VT), showing late precordial transition V_5, wide QRS duration in lead I (124 ms), and earliest onset QRS in V_1 (vertical line). (E) ARVD/C VT shows very late precordial transition in V_6 and wide QRS duration in lead I (126 ms). (F) ARVD/C VT shows very late precordial transition V_6 and wide QRS duration in lead I (150 ms). (G) ARVD/C VT shows late precordial transition in V_5, wide QRS duration in lead I (160 ms), and notching of the QRS (II, III, aVF, V_4 to V_6). (H) ARVD/C VT shows wide QRS duration in lead I (128 ms) and notching of the QRS (II, III, aVF, V_4 to V_6).

Hoffmayer KS, *et al*. Electrocardiographic comparison of ventricular arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy and right ventricular outflow tract tachycardia. *J Am Coll Cardiol*. 2011;**58**:831–8 with permission from Elsevier.

Catheter ablation is the treatment of choice for idiopathic VT, with success rates exceeding 80% for RVOT VT, and fascicular tachycardias (Table 56.11). Catheter ablation of tachycardias from the papillary muscles may be difficult due to the contraction of the muscle, whereas success rates are lower with epicardial or intraseptal sites. There is no associated mortality, but there is a 1.7% risk of tamponade or pericardial effusion.[141,142] Calcium channel blockers and beta blockers may also be considered.

Idiopathic VF

Idiopathic VF is diagnosed by exclusion of apparent causes, although a latent cardiomyopathy or channelopathy cannot be excluded. Several mutations of ion channels coding and other genes have been associated with idiopathic ventricular fibrillation (see Chapter 57). ICD is recommended in survivors (Table 56.12).

Short-coupled torsade de pointes is a rare variant of polymorphic VT of unknown aetiology. It is characterized by an extremely short-coupled interval of the first premature ventricular contraction (<300 ms) initiating the tachycardia.[143] This predominantly affects young patients who often present with unclear syncope and a positive family history for SCD. In most cases torsade deteriorates into VF and an ICD is recommended for survivors with a definitive diagnosis (Table 56.13).

Ischaemic heart disease

Non-ST elevation acute coronary syndromes

Non-sustained VT is detected in 18–25% of patients 2 to 9 days after admission, and even short episodes of VT, lasting 4–7 beats, are independently associated with the risk of SCD over the subsequent year, especially when associated with myocardial ischaemia.[60] Earlier episodes within 48 hours after admission do not carry the same risk. In the EARLY ACS trial, the cumulative incidence of sustained VT/VF is 1.5%, with 60% of them occurring >48 h after enrolment.[144] Both early and late sustained VT/VF

Table 56.11 Treatment of idiopathic ventricular tachycardia

ACC/AHA/ESC 2006 GL on VA. Idiopathic ventricular tachycardia	
Catheter ablation in patients with structurally normal hearts with symptomatic, drug-refractory VT arising from the RV or LV or in those who are drug-intolerant or who do not desire long-term drug therapy.	I-C
EP testing in patients with structurally normal hearts with palpitations or suspected outflow tract VT.	IIa-B
Beta blockers and/or calcium channel blockers (and/or IC agents in RVOT VT) in patients with structurally normal hearts with symptomatic VT arising from the RV.	IIa-C
ICD implantation for sustained VT in patients with normal or near-normal ventricular function.	IIa-C
ESC 2015 GL on VA and SCD	
Treatment of outflow tract ventricular tachycardia	
Catheter ablation of RVOT VT/PVC in symptomatic patients and/or in patients with a failure of anti-arrhythmic drug therapy (e.g.beta-blocker) or in patients with a decline in LV function due to RVOT-PVC burden.	I-B
Treatment with sodium channel blockers (class IC agents) in LVOT/aortic cusp/epicardial VT/PVC symptomatic patients.	I-C
Catheter ablation of symptomatic LVOT/aortic cusp/ epicardial VT/PVC after failure of one or more sodium channel blockers (class IC agents) or in patients not wishing long-term anti-arrhythmic drug therapy	IIa-B
Treatment to prevent recurrence of idiopathic ventricular tachycardia	
Idiopathic left VT	
Catheter ablation	I-B
Beta-blockers, verapamil or sodium channel blockers (class IC agents)	I-C
Papillary muscle tachycardia	
Beta-blockers, verapamil or sodium channel blockers (class IC agents)	I-C
Catheter ablation under echo guidance	IIa-B
Mitral and tricuspid annular tachycardia	
Beta-blockers, verapamil or sodium channel blockers (class IC agents)	I-C
Catheter ablation	IIa-B

ACC/AHA/ESC 2006 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Circulation*. 2006;**114**:e385–e484 with permission from Wolters Kluwer.
ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015; **36**:2793–867 with permission from Oxford University Press.

Table 56.12 ESC 2015 GL on VA and SCD. Treatment of idiopathic ventricular fibrillation

ICD in survivors of idiopathic VF	I-B
Catheter ablation by experienced operatotrs of PVCs triggering recurrent VF leading to ICD interventions	I-B
Catheter ablation by experienced operatotrs of PVCs leading to electrical storm	I-B

ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015; 36:2793–867 with permission from Oxford University Press.

are associated with increased risk of death, even after adjustment for revascularization and LV function.[144] In the MERLIN-TIMI 36 trial, the presence of myocardial ischaemia or VT alone, as detected on 7-day continuous electrocardiographic monitoring, and particularly in combination, is independently associated with poor cardiovascular outcomes.[145] Appropriate revascularization as well as monitoring beyond 48 h are probably indicated in this setting.

Acute myocardial infarction

NSVT occurs in up to 75% of reperfused patients and, during the first 13[146] to 24 hours,[147] does not carry a prognostic significance. In-hospital NSVT following this period indicates increased in-hospital mortality. However, in patients who had a prior myocardial infarction treated with reperfusion and beta blockers, NSVT is not an independent predictor of long-term mortality when other covariates, such as left ventricular ejection fraction, are taken into account.[114]

Accelerated idioventricular rhythm, which characteristically follows myocardial infarction, tends to remain stable and usually does not give rise to ventricular fibrillation and does not require antiarrhythmic treatment.

Ventricular fibrillation during the acute phase (up to 48 h) indicates a higher in-hospital mortality, but survivors do not have adverse prognosis.[148]

Sustained monomorphic VT indicates a pre-existing scar.

Table 56.13 ESC 2015 GL on VA and SCD. Treatment of short-coupled torsade de pointes

ICD in conclusive diagnosis of short-coupled TdP	I-B
IV verapamil to acutely suppress/prevent an electrical storm or recurrent ICD discharges	IIa-B
Catheter ablation for long-term suppression/prevention of an electrical storm or recurrent ICD discharges	IIa-B

ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015; **36**:2793–867 with permission from Oxford University Press.

Therapy Frequent VPBs and NSVT do not require antiarrhythmic drug therapy in the setting of an acute coronary syndrome. Electrolyte correction and oral beta blockers are useful.

Chronic IHD

Compared with the pre-reperfusion era, late ventricular tachyarrhythmias are now less common, but they are still documented in approximately 20% of patients with recent MI (more than 7 days) and EF <0.40 within the next 2 years.[57]

NSVT after discharge following MI, in the era of reperfusion and use of beta blockers, is not an independent predictor of mortality, especially after ejection fraction is taken into account.[114] It may carry an adverse prognostic significance in patients with LVEF >35%.[149]

Monomorphic VT is usually due to scar-related reentry, and its incidence has been reduced from 3% to 1–2% in the reperfusion era. The QRS morphology during tachycardia may show either RBBB (origin of VT in the LV) or LBBB pattern (RV or septal origin) or may even be non-specific. Both RBBB and LBBB patterns can be seen in the same patient when the infarct scar involves the interventricular septum. Axis depends on the site of origin (apical origin has a superior axis while basal origin results in inferior axis) or may be 'undetermined'. Several algorithms have been published for identification of the exit site of post-infarction VT from the 12-lead ECG (Figure 56.12).[150,151]

Polymorphic VT or VF may be due to acute ischaemia (acute coronary syndrome or spasm) or in the context of scar-related VT that degenerates into VF (Figure 56.9).[52,152]

Therapy Monomorphic VT usually does not respond to revascularization.[153] Polymorphic VT or VF may, or may not, respond to revascularization (Table 56.7), and reassessment by means of LVEF and EPS if LVEF >35% is indicated 3 months after revascularization.[154,155] New-onset ventricular arrhythmias, especially VF occurring after the first 48 h of cardiac surgery, are associated with increased long-term mortality, especially in older patients with reduced LV function.[156] Flecainide[63] and sotalol[104] increase mortality whereas amiodarone shows a trend towards reducing arrhythmia episodes but without significantly affecting total mortality (EMIAT and CAMIAT studies)[157,158] or even showing a trend towards increasing it.[159] Therefore, no antiarrhythmic drug is suitable for primary prevention of cardiac death, with the exception of beta blockers which have been shown, in several studies, to reduce total and cardiac mortality in post-infarction patients, at least during the first year post-MI.[160] The ACC/AHA 2013 GL on STEMI as well as the ESC 2015 GL on VA and SCD recommend ICD implantation in patients who develop sustained VT/VF more than 48 hours after STEMI, provided the arrhythmia is not due to transient or reversible ischaemia, reinfarction, or metabolic abnormalities.[161] In addition, if

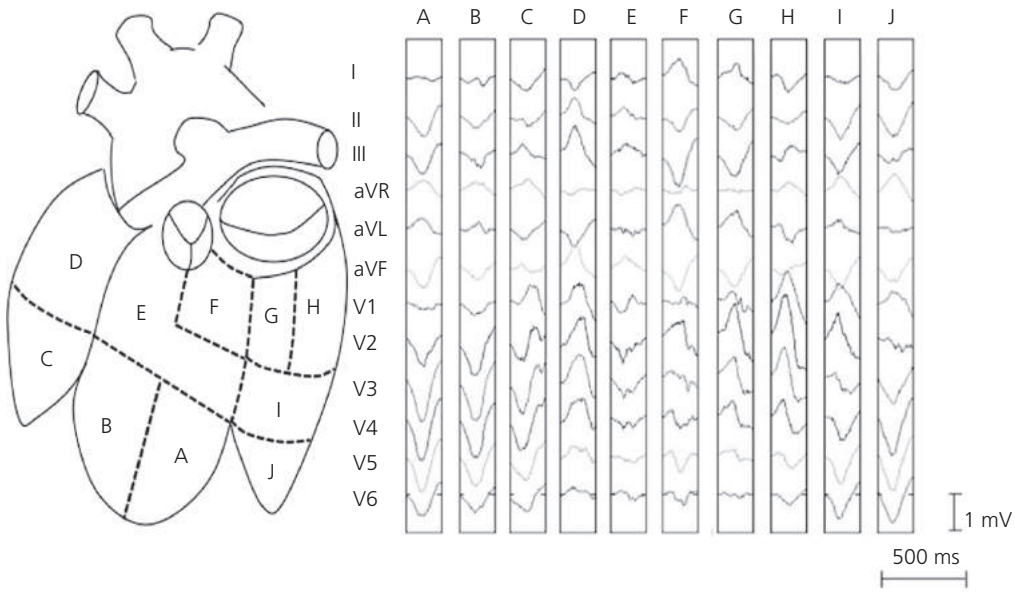

Figure 56.12 Localization of origin of post-infarct VT from the 12-lead ECG. Cardiac sections (left panel) and corresponding ECGs (right panel).

Yokokawa M, et al. Automated analysis of the 12-lead electrocardiogram to identify the exit site of postinfarction ventricular tachycardia. *Heart Rhythm*. 2012;**9**:330–4.

new-onset VF occurs >48 h after cardiac surgery and no reversible cause can be found, ICD implantation may be considered earlier.[156]

Certain patients with NSVT, in the context of reduced LV function, need an ICD. In the MADIT study[162] on 196 patients with prior MI, EF ≤35%, a documented episode of NSVT, and inducible and non-suppressible sustained VT, ICD yielded a 54% reduction in total mortality compared to conventional (mainly amiodarone) therapy during a mean 27-month follow-up. The MUSTT enrolled 704 patients with coronary artery disease, asymptomatic NSVT, EF ≤40%, and inducible sustained VT. The risk of cardiac arrest or death from arrhythmia among patients who received treatment with ICD was significantly lower than that among patients who did not receive ICDs (relative risk, 0.24; 95% confidence interval, 0.13–0.45; p <0.001).[163] Subsequently, in the MADIT II on 1232 post-infarction patients with markedly depressed LV function (LVEF ≤30%), ICD resulted in 26% reduction of mortality over an 8-year follow-up, regardless of the presence or absence of other risk stratifiers, including NSVT.[164]

In patients **without ventricular arrhythmias** ICDs should be considered at least 40 days after MI in order to achieve reduction of total mortality (DINAMIT and IRIS studies)[165,166] and ≥3 months from a coronary revascularization procedure.[167] According to most published data, patients with a recent myocardial infarction do not benefit from ICD, especially when they have LVEF <25% and/or wide QRS,[168] but this is debatable.[169] Both DINAMIT and IRIS had excluded patients with sustained ventricular arrhythmias during this period, and sudden cardiac death was reduced, despite no effect on overall mortality in the DINAMIT trial.[165] There is a substantial (10%) risk of arrhythmias within the first month following MI.[170] There has also been some evidence for a benefit of early ICD implantation if sustained monomorphic VT (CL ≥200 ms, lasting more than 10 s) is induced at electrophysiology study 9 days post-MI,[171] whereas non-inducibility carries a good prognosis even in LVEF <30–35%.[85] Current guidelines recommend that patients with an initially reduced LVEF who are possible candidates for ICD therapy should undergo reevaluation of LVEF ≥40 days after discharge.[161] During this period, 1.6% of them may have VT/VF, and the use of a wearable cardioverter-defibrillator might be considered.[172]

Other indications for **ICD implantation** in post-MI patients are presented in Table 56.5 (see also Chapter 29 on STEMI and Chapter 32 on HF). In summary, ICD is indicated in patients who present with monomorphic VT or VF and for patients with IHD (>40 days after MI and 90 days after revascularization) and:

- LVEF <30% and NYHA I, or
- LVEF <35% and NYHA II or III, or

- LVEF <40% in the context of NSVT and inducible VT at EPS.

In addition, ICD is recommended in:

- Sustained VT/VF, >48 h after MI, and not due to a treatable cause.

There have been concerns about the efficacy of ICD in women and the elderly (see Chapter 69).[173]

Catheter ablation is also useful by means of reducing ICD discharges and can be now accomplished with electroanatomical mapping during sinus rhythm, even in unmappable tachycardias, with a mortality of 0.4–3%.[108–110] CMR may also be helpful in guiding ablation.[174] Usually, an endocardial approach is necessary, and epicardial ablation is rarely indicated,[175] but recurrences in post-MI patients are common. Epicardial VT usually have delayed onset of ventricular activation, with a pseudodelta >34 ms and an RS >121 ms.[176] Alternatively, beta blockers and amiodarone may prevent ICD shocks and are more effective than sotalol in this respect but with a higher rate of complications.[105]

Heart failure

In patients with heart failure and LVEF <30–40%, the reported prevalence of NSVT is 30–80%.[114] Although the GESICA-GEMA investigators identified NSVT as an independent predictor of total mortality in patients with heart failure (35–40% IHD) and LVEF ≤35%,[177] in the CHF-STAT (70–75% IHD), after adjusting other variables and especially for LVEF, NSVT was not an independent predictor of sudden death or total mortality in patients with heart failure and LVEF <35–50%.[178] Similar results were published by the PROMISE investigators.[179] Only during the recovery period after exercise, frequent ventricular ectopy has been found to carry an adverse prognostic significance in patients with heart failure.[180] However, in a recent analysis of ICD interrogation data in the SCD-HeFT population, long runs of rapid rate NSVT were associated with subsequent appropriate ICD shocks and an increase in mortality.[181]

Optimal medical therapy (ACEI/ARBs, beta blockers and mineralocorticoid receptor antagonists) is essential to reduce mortality in heart failure with a relatively preserved EF of 35–40% (ESC 2015 GL on VA and SCD, I-A).

In patients with heart failure and LVEF <35%, the GESICA study (516 patients of whom 75% with DCM) found **amiodarone** beneficial by means of reducing mortality and hospital admissions.[182] However, the much larger SCD-HeFT (2521 patients, 52% ischaemic) indicated substantial benefit only from ICD therapy in patients with low EF (≤35%) and NYHA classes II and III. ICD therapy was associated with a decreased risk of death of 23% and an absolute decrease in mortality of 7.2 percentage points after 5 years in the overall population.[48] Dronedarone is detrimental in heart failure patients.[183] There has been some evidence (MADIT-CRT) that ventricular resynchronization may reduce episodes of VT or VF in patients who respond to it whereas non-responders may have a higher event rate.[184] LVEF values and QRS duration do not appear to directly modify the survival benefit of ICD in patients with baseline LVEF <35%.[168] Changes in LVEF with medical therapy are inversely associated with all-cause mortality and appropriate shocks for ventricular tachyarrhythmias. In patients whose follow-up LVEF improved to >35%, the risk of an appropriate shock remains but is markedly decreased.[185] Amiodarone may be used to reduce appropriate shocks (Table 56.14).

Table 56.14 ESC 2015 GL on VA and SCD. Ventricular arrhythmias in reduced LVEF, with or without heart failure

Premature ventricular complexes (PVC)	
Frequent symptomatic PVC or NSVT:	
– Amiodarone	IIa-B
– Catheter ablation	IIa-B
Catheter ablation in LV dysfunction associated with PVCs.	IIa-B
Treatment of sustained recurrent monomorphic ventricular tachycardia	
Optimization of heart failure medication	I-C
Amiodarone in patients with or without an ICD.	IIa-C
Prevention of recurrences of sustained recurrent monomorphic ventricular tachycardia	
Urgent catheter ablation in specialized or experienced centres in incessant VT or electrical storm resulting in ICD shocks.	I-B
Amiodarone or catheter ablation is recommended recurrent ICD shocks due to sustained VT.	I-B
ICD implantation in patients undergoing catheter ablation whenever they satisfy eligibility criteria for ICD.	I-C
Amiodarone or catheter ablation after a first episode of sustained VT in patients with an ICD.	IIa-B

ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015; **36**:2793–867 with permission from Oxford University Press.

Cardiomyopathies

Dilated cardiomyopathy

Although VT or VF are the most common cause of death in dilated cardiomyopathy (DCM), other causes, such as bradycardia, electromechanical dissociation, and pulmonary embolus account for up to 50% of sudden cardiac death in patients with advanced heart failure. **NSVT** may be detected in 40–50% of patients with DCM, but results on its independent prognostic significance have been conflicting. LVEF and NSVT have been found to be significant predictors of arrhythmic events,[186] but, after medical stabilization with an angiotensin-converting enzyme inhibitor and beta blocker, the number and length of NSVT runs did not increase the risk of major ventricular arrhythmia in patients with LVEF ≤0.35, as opposed to those with LVEF >0.35.[187] In the Marburg Cardiomyopathy Study,[49] on univariate analysis, non-sustained VT and frequent ventricular premature beats showed a significant association with a higher arrhythmia risk, but, on multivariate analysis, only LVEF was found to be a significant predictor of major arrhythmic events. The combination of LVEF ≤30% and NSVT denoted an 8-fold higher risk for subsequent arrhythmic events, compared to LVEF ≤30% and no NSVT. Signal-averaged ECG, baroreflex sensitivity, heart rate variability, and T wave alternans were not helpful for arrhythmia risk stratification.

The arrhythmic risk stratification of patients with non-ischaemic cardiomyopathy still remains unsatisfactory.[188] The value of EP testing is debatable and is no longer recommended in this setting. However, it may be useful in inducing a monomorphic VT that could be amenable to catheter ablation and as a risk stratifier since inducibility of ventricular arrhythmias,[89] and especially polymorphic VT or VF,[90] indicates increased likelihood of subsequent ICD therapies. In approximately one-third of the cases of idiopathic dilated cardiomyopathy, and probably in a small percentage of ischaemic patients, VT is due to ***bundle branch reentry***. Bundle branch reentrant tachycardia may also occur in patients with intraventricular conduction defects as well as in the absence of any myocardial or valvular abnormality.[189] Although these tachycardias are usually unstable, the 12-lead ECG, when obtainable, may show either LBBB or RBBB pattern, depending on the orientation of activation of the bundle branches, and the H-V interval during tachycardia is usually, but not invariably, equal to or greater than the H-V interval measured during sinus rhythm.[190] The majority of VT in non-ischaemic cardiomyopathy arises near the **s**uperior and lateral perivalvular aortic and mitral regions, and many of them are epicardial in origin. Criteria for epicardial VTs are a q wave in lead 1, but not in inferior leads, and delayed onset and decline of the ventricular activation in precordial leads.[191] The use of contrast-enhanced CMR helps to identify an endocardial vs. epicardial origin.[174]

Catheter ablation is the treatment of choice in bundle branch reentry (ESC 2015 GL on VA and SCD, I-C). The role of **ICD** for primary prevention in DCM is controversial. There was significant reduction of sudden death and a trend for reduced mortality with ICD in patients with non-ischaemic heart failure and non-sustained VT (DEFINITE),[192] but these results were not reproduced in the AMIOVIRT study,[193] that failed to detect any difference between amiodarone and ICD in patients with DCM and NSVT, or the CAT study,[194] that reported no difference between ICD and controls in DCM. The value of amiodarone is controversial. Current indications for ICD are provided in Table 56.5 and Chapter 32 on heart failure.

Hypertrophic cardiomyopathy

In hypertrophic cardiomyopathy, 20–30% of patients may have **NSVT**.[114] Frequent and prolonged (>10 beats) episodes of non-sustained VT on Holter, as opposed to rare, brief episodes, indicate an increased risk of sudden death in HCM, especially in young patients (<30 years).[61,195] Mortality rate is approximately 1% annually, with events usually occurring without warning, largely in asymptomatic or mildly symptomatic young patients, with no difference according to gender.[196] Risk stratification and indications for ICD are discussed in Chapter 37. Amiodarone has no longer a role.

Arrhythmogenic right ventricular cardiomyopathy

Diagnosis and treatment of this condition are discussed in Chapter 39. The main problem is with ARVC/D-associated VT that presents with inferior axis; in this case, the differential diagnosis with idiopathic VT is of clinical importance. Asymptomatic patients with ARVC/D and NSVT have a trend for an increased arrhythmic risk and a rate of appropriate ICD intervention of 3.7% per year.[197] Syncope predicts life-threatening ventricular arrhythmia, and EPS has low predictive accuracy for future arrhythmic events.[197]

Other cardiomyopathies

The association between infiltrative cardiomyopathies and ventricular arrhythmias and sudden death is well documented. Specific conditions are discussed in Chapter 38 on cardiomyopathies. Complex ventricular arrhythmias are common in **amyloidosis** (57% of patients have PVCs and 18% NSVT) and carry prognostic significance.[198] Cardiac **sarcoidosis** may present with non-sustained polymorphic or monomorphic VT that usually responds to steroids. Usually VT is either Purkinje-related (QRS <170 ms), or scar-related and may respond to catheter ablation.[199] Spontaneous development or EPS induction of sustained monomorphic VT is an ominous sign, and ICD

may be indicated.[92] Patients with **Chagas' cardiomyopathy**, presenting with either sustained VT or NSVT, have a major risk for mortality in the presence of moderate LV systolic dysfunction (LVEF <40%).[200]

Congenital heart disease

Conditions that have been associated with the greatest risks of late sudden death are tetralogy of Fallot, D- and L-transposition of the great arteries, aortic stenosis, and functional single ventricle or significant systemic or single ventricular dysfunction. Periodic Holter monitoring is indicated in these patients, and electrophysiologic assessment is indicated in the presence of unexplained syncope.[201] Recommendations for the management of patients with congenital heart disease are presented in Table 56.15 .

Valvular disease

In patients with valvular disease, the incidence of non-sustained ventricular tachycardia is considerable (up to 25% in aortic stenosis and in significant mitral regurgitation) and appears to be a marker of underlying left ventricular pathology.[202] In mitral valve prolapse, although complex ventricular arrhythmias have been detected in patients who underwent Holter monitoring before sudden death, multivariate analysis failed to identify ventricular arrhythmias (as opposed to NYHA class, AF, and LVEF) as an independent predictor of sudden death.[203,204] However, frequent complex ventricular ectopy from the LV outflow tract in female patients with ECG repolarization abnormalities on inferior leads, and CMR-detected fibrosis of thepapillary muscles, indicate an increased risk for sudden death (see Chapter 18).[205,206] Recommendations for management are provided in Table 56.16 and the relevant chapters on valve disease.

Hypertension

In patients with arterial hypertension, non-sustained ventricular tachycardia is correlated to the degree of cardiac hypertrophy and subendocardial fibrosis.[207] Approximately 12–28% of patients with hypertension and left ventricular hypertrophy present with non-sustained ventricular tachycardia as opposed to 8% of patients with hypertension alone.[208]

Table 56.15 Ventricular arrhythmias in congenital heart disease

EHRA/HRS/APHRS 2014 consensus statement on VA	
Recommendations on VAs in congenital heart disease	
Electrophysiological testing in adults with unexplained syncope and 'high-risk' CHD substrates associated with primary VAs or poorly tolerated atrial tachyarrhythmias, such as tetralogy of Fallot, transposition of the great arteries with atrial switch surgery, or significant systemic or single ventricular dysfunction.	I-C
In patients with ICD and recurrent monomorphic VT, VT storm, or multiple appropriate shocks, additional therapy including ATP, treatment with antiarrhythmic agents, and/or catheter ablation as adjunctive therapy in an adequately trained centre.	I-C
In patients who require surgical haemodynamic interventions, pre-operative electrophysiological testing and intra-operative ablation when adequate expertise is available.	IIa-C
Asymptomatic patients with good ventricular function, normal or near-normal ventricular haemodynamics and low-risk subtypes of CHD may be followed without advanced therapy and invasive evaluation despite the presence of moderately frequent and/or complex ventricular ectopy.	IIb-C
Catheter ablation for patients with CHD who have newly recognized or progressive ventricular dysfunction and a high burden of monomorphic ventricular ectopy.	IIb-C
PACES/HRS 2014 consensus statement on arrhythmias in ACHD	
Indications for ablation in adult patients with congenital heart disease	
As adjunctive therapy to an ICD in adults with CHD and recurrent monomorphic VT, a VT storm, or multiple appropriate shocks that are not manageable by device reprogramming or drug therapy.	I-C
As an alternative to drug therapy for symptomatic sustained monomorphic VT in patients with ICDs.	IIa-B
Catheter ablation for post-operative CHD and non-sustained or haemodynamically poorly tolerated VT by means of an empiric anatomic approach.	IIb-C
Frequent ventricular ectopy associated with deteriorating ventricular function.	IIb-C
Not indicated for asymptomatic relatively infrequent ventricular ectopy and stable ventricular function.	III-C
Not appropriate prophylactic therapy in patients deemed to be at increased risk for sudden cardiac death.	III-C

(Continued)

Table 56.15 Continued

Arrhythmia surgery in adults with CHD undergoing open cardiac surgery	
Concomitant ventricular arrhythmia surgery	
Surgical ventricular tachycardia ablation guided by electrophysiologic mapping for sustained monomorphic VT.	IIa-B
Surgical ventricular tachycardia ablation guided by electrophysiologic mapping for inducible sustained monomorphic VT with an identified critical isthmus and no clinical sustained VT.	IIb-C
Ventricular arrhythmia surgery for rapid ventricular tachycardia not mapped preoperatively but mapped intraoperatively.	IIb-C
Prophylactic ventricular arrhythmia surgery	
Prophylactic arrhythmia surgery not indicated in increased risk of surgical mortality from ventricular dysfunction or major co-morbidities, when prolongation of cardiopulmonary bypass or cross-clamp times due to arrhythmia surgery might negatively impact outcomes.	III-C
Empiric ventricular arrhythmia surgery is not indicated without clinical or inducible sustained ventricular tachyarrhythmia.	III-C
PACES/HRS 2014 consensus statement on arrhythmias in ACHD	
ICD therapy in adults with CHD	
Survivors of cardiac arrest due to VF or hemodynamically unstable VT and no reversible etiology	I-B
Spontaneous sustained VT	I-B
Catheter ablation for sustained VT as an alternative or adjunct to ICD	I-C
Systemic LVEF ≤ 35%, biventricular physiology, and NYHA II or III	I-B
Tetralogy of Fallot and multiple risk factors for sudden cardiac death, such as left ventricular systolic or diastolic dysfunction, nonsustained VT, QRS duration ≥180 ms, extensive right ventricular scarring, or inducible sustained VT	IIa-B
Single or systemic right ventricular EF < 35%, particularly in the presence of complex ventricular arrhythmias, unexplained syncope, NYHA IIor III QRS duration ≥140 ms,or severe systemic AV valve regurgitation	IIb-C
Systemic LVEF ≤ 35%, and NYHA I	IIb-C
Syncope of unknown origin with hemodynamically significant sustained VT/VF inducible at electrophysiologic study	IIb-B
Nonhospitalized adults awaiting heart transplantation	IIb-C
Syncope and moderate or complex CHD and a high clinical suspicion of ventricular arrhythmia when ivasive and noninvasive investigations have failed to define a cause	IIb-C
Life expectancy with an acceptable functional status <1 year	III-C
Incessant VT/VF	III-C
Significant psychiatric illness that may be aggravated by ICD	III-C
NYHA IV and not candidates for cardiac transplantation or CRT	III-C
Eisenmerger syndrome	III-B
Endocardial leads are avoided in adults with CHD and intracardiac shunts. Risk assessment regarding hemodynamic circumstances, concomitant anticoagulation, shunt closure prior to endocardial lead placement, or alternative approaches for lead access should be individualized	III-B
AHA 2015 statement on ACHD	
Arrhythmias and device implantation	
In the patient with sustained VT or cardiac arrest, hemodynamic catheterization, coronary angiography and electrophysiological testing, to identify the need for possible surgical intervention such as valve replacement, which may allow intraoperative VT ablation	I-C
ICD implantation for cardiac arrest survivors and patients with sustained VT discovered on electrophysiological study	I-C
ESC 2015 GL on VA and SCD	
Prevention of sudden cardiac death and management of ventricular arrhythmias in patients with CHD	
ICD in survivors of an aborted cardiac arrest after excluding reversible causes.	I-B
ICD inpatients with symptomatic sustained VT who have undergone haemodynamic and electrophysiological evaluation.	I-B
Catheter ablation as additional therapy or an alternative to ICD in patients with CHD who have recurrent monomorphic VT or appropriate ICD therapies that are not manageable by device reprogramming or drug therapy.	I-C
ICD in a systemic LVEF <35%, biventricular physiology, symptomatic HF ,and NYHA II/III.	I-C
ICD in syncope of unknown origin in the presence of either advanced ventricular dysfunction or inducible sustained VT or VF.	IIa-B

(Continued)

Table 56.15 Continued

ICD in tetralogy of Fallot and multiple risk factors for SCD, including LV dysfunction, non-sustained VT, QRS duration >180 ms or inducible sustained VT.	IIa-B
Catheter ablation as an alternative to drug therapy for symptomatic sustained monomorphic VT in patients with ICD.	IIa-B
ICD with advanced single or systemic RV dysfunction in the presence of other risk factors such as non-sustained VT, NYHA functional class II or III or severe systemic AV valve regurgitation.	IIb-B
PVS for risk stratification in tetralogy of Fallot and one or more risk factors among LV dysfunction, non-sustained VT and QRS duration >180 ms.	IIb-B
PVS in non-sustained VT to determine the risk of sustained VT.	IIb-C
Surgical ablation guided by electrophysiological mapping in patients undergoing cardiac surgery, and clinical sustained VT with inducible sustained monomorphic VT and an identified critical isthmus.	IIb-C
Catheter ablation or prophylactic anti-arrhythmic therapy is not recommended for asymptomatic infrequent PVC in patients with CHD and stable ventricular function.	III-C
PVS is not recommended to stratify the risk in the absence of other risk factors or symptoms.	III-B

ACHD, adult congenital heart disease; PVS, programmed ventricular stimulation; PVC, premature ventricular complex.
EHRA/HRS/APHRA 2014 Expert consensus on ventricular arrhythmias. *Heart Rhythm*. 2014;**11**:e116–96 with permission from Elsevier.
PACES /HRS Expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease. *Heart Rhythm*. 2014;**11**:e102–65 with permission from Elsevier.
AHA 2015 Statement on congenital heart disease in the older adult. *Circulation*. 2015;**131**:1884–1931 with permission from Wolters Kluwer.
ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015; **36**:2793–867 with permission from Oxford University Press.

Table 56.16 Valvular heart disease

ACC/AHA/ESC 2006 GL on VA	
Patients with ventricular arrhythmias should be evaluated and treated following current recommendations for each disorder.	I-C
The effectiveness of mitral valve repair or replacement to reduce the risk of SCD in patients with mitral valve prolapse, severe mitral regurgitation, and serious ventricular arrhythmias is not well established.	IIb-C
ESC 2015 GL on VA and SCD	
ICD in patients with valvular heart disease who, after surgical repair, satisfy the criteria for primary and secondary prevention of SCD.	I-C
Surgical treatment of acute aortic regurgitation due to endocarditis associated with sustained VT, unless otherwise contraindicated.	I-C
An EPS with standby catheter ablation should be considered in patients who develop VT following valvular surgery in order to identify and cure bundle branch re-entry VT.	IIa-C

ACC/AHA/ESC 2006 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Circulation*. 2006;**114**:e385–e484 with permission from Wolters Kluwer.
ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015; **36**:2793–867 with permission from Oxford University Press.

Other conditions

Acute myocarditis may be complicated by conduction disturbances or ventricular arrhythmias (see Chapter 45). Giant cell myocarditis is a cause of monomorphic or polymorphic VT that is usually sustained and associated with high mortality. Recommendations for patients with **myocarditis**, as well as for **rheumatic heart disease** or **endocarditis**, are presented in Table 56.17.

Cardiovascular causes account for at least 40% of deaths in patients with **end-stage renal failure**, and 20% of these are sudden.[209] Arrhythmias often occur during haemodialysis sessions and for at least 4 to 5 h afterward. During this period, haemodynamic status and fluctuations in electrolytes, especially potassium, magnesium, and calcium, are likely to play a crucial role in triggering events and should be monitored carefully. Risk factors predisposing to ventricular arrhythmias include LVH, hypertension, anaemia, LV dysfunction, and underlying CAD (Table 56.18).

Patients with **neuromuscular disorders** may present with ventricular arrhythmias or conduction defects.[210] Permanent pacemaker insertion may be considered for progressive muscular dystrophies, such as myotonic muscular dystrophy type 1 (Steinert's disease), limb-girdle (Erb's) dystrophy, and Kearns–Sayre syndrome with any degree of AV block (including first-degree AV block) with or without symptoms, because there may be unpredictable progression of AV conduction disease (see Chapter 55). However, patients with myotonic muscular dystrophy type 1, as well as certain lamin A/C (LMNA—a cause of limb-girdle dystrophy) and desmin mutation

Table 56.17 Inflammatory heart disease

ACC/AHA/ESC 2006 GL on VA	
Myocarditis, rheumatic heart disease, or endocarditis	
Temporary pacemaker insertion in patients with symptomatic bradycardia and/or heart block during the acute phase of myocarditis.	I-C
Acute aortic regurgitation associated with VT should be treated surgically, unless otherwise contraindicated	I-C
Acute endocarditis complicated by aortic or annular abscess and AV block should be treated surgically, unless otherwise contraindicated.	I-C
ICD* in patients with life-threatening ventricular arrhythmias who are not in the acute phase of myocarditis.	IIa-C
ICD* in cardiac sarcoidosis, giant cell myocarditis, or Chagas' disease	IIa-C
Antiarrhythmic therapy in patients with symptomatic NSVT or sustained VT during the acute phase of myocarditis.	IIa-C
ICD during the acute phase of myocarditis.	III-C
2015 ESC 2015 GL on VA and SCD	
Management of ventricular arrhythmias in inflammatory heart disease	
Patients with life-threatening, sustained ventricular tachyarrhythmias are referred to specialized centres with the ability to perform haemodynamic monitoring, cardiac catheterization and endomyocardial biopsy and to use mechanical cardio-pulmonary assist devices and specialized arrhythmia therapies.	I-C
Temporary pacing in bradycardia and/or heart block triggering VA during the acute phase of myocarditis/pancarditis.	I-C
Anti-arrhythmic therapy in symptomatic non-sustained or sustained VT during the acute phase of myocarditis.	IIa-C
ICD or pacemaker in inflammatory heart diseases should be considered after resolution of the acute episode.	IIa-C
ICD* in haemodynamically compromising sustained VT occurring after the resolution of acute episodes.	IIa-C
A wearable defibrillator for bridging until full recovery or ICD implantation in patients after inflammatory heart diseases with residual severe LV dysfunction and/or ventricular electrical instability.	IIa-C
ICD* earlier in patients with giant cell myocarditis or sarcoidosis who had haemodynamically compromising sustained VA or aborted cardiac arrest.	IIb-C
Demonstration of persistent myocardial inflammatory infiltrates by immunohistological evidence and/or abnormal localized fibrosis by CMR after acute myocarditis as an additional indicator of increased risk of SCD.	IIb-C

* For patients who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status >1 year.
ACC/AHA/ESC 2006 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Circulation*. 2006;**114**:e385–e484 with permission from Wolters Kluwer.
ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015; **36**:2793–867 with permission from Oxford University Press.

carriers, may also need ICD backup due to malignant ventricular arrhythmias.[211,212] Patients with lamin A/C mutations are prone to ventricular arrhythmias when at least two of the following independent risk factors are present: non-sustained ventricular tachycardia, ejection fraction <45%, male sex, and non-missense mutations.[213]

Table 56.18 ACC/AHA/ESC 2006 GL on VA

End-stage renal failure	
The acute management of ventricular arrhythmias in end-stage renal failure should immediately address haemodynamic status and electrolyte (potassium, magnesium, and calcium) imbalance.	I-C
Life-threatening ventricular arrhythmias, especially in patients awaiting renal transplantation, should be treated conventionally, including the use of ICD* and pacemaker as required.	I-C

* For patients who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status >1 year.
ACC/AHA/ESC 2006 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Circulation*. 2006;**114**:e385–e484 with permission from Wolters Kluwer.

Electrolyte disorders

Rapid hyperkalaemia, hypokalaemia (<3.5 mmol/L), and hypomagnesaemia are all associated with ventricular arrhythmias and SCD in patients with MI or even with structurally normal hearts (some of whom may have underlying channelopathies).[209] Hypomagnesaemia is associated with polymorphic VT or torsades de pointes. Hypokalaemia, with or without hypomagnesaemia, may be responsible for ventricular arrhythmias in subjects with hypertension and congestive cardiac failure treated with thiazide and/or loop diuretics, acute starvation, acute alcohol toxicity/withdrawal, and those with ventricular arrhythmias associated with digoxin and other Vaughan Williams class 1 antiarrhythmic drugs.[214]

Changes in the extracellular ionic concentrations of calcium required to produce EP changes that may contribute to ventricular arrhythmias are not encountered in clinical

practice. Significant *hypocalcaemia* and *hypomagnesaemia* can prolong the QT interval due to prolongation in phase 2 of the action potential and hence a delay in the onset of repolarization. The long QT interval is the result of a long ST segment and the T wave is normal in duration. Occasionally, hyperparathyroidism can cause important **elevations in serum calcium** concentrations. Intracellular fluctuations in calcium concentration influenced by drugs (e.g. digitalis glycosides), exercise (e.g. catecholamines), and reperfusion following myocardial ischaemia can trigger life-threatening arrhythmias. The protective effects of beta blockade in the latter settings may, in part, be due to the inhibition of calcium influx into myocytes.

Recommendations for management are provided in Table 56.18.

Table 56.19 ACC/AHA/ESC 2006 GL on VA

Electrolyte disturbances	
Potassium (and magnesium) salts in treating ventricular arrhythmias secondary to hypokalaemia (or hypomagnesaemia) resulting from diuretic use in patients with structurally normal hearts.	I-B
Maintain serum potassium levels >4.0 mmol/L in any patient with documented life-threatening ventricular arrhythmias and a structurally normal heart.	IIa-C
Maintain serum potassium levels >4.0 mmol/L in patients with acute MI.	IIa-B
Magnesium salts in the management of VT secondary to digoxin toxicity in patients with structurally normal hearts.	IIa-B

ACC/AHA/ESC 2006 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Circulation*. 2006;**114**:e385–e484 with permission from Wolters Kluwer.

Drug-induced arrhythmias

With the exception of beta blockers, all antiarrhythmic drugs are proarrhythmic. In addition, drug interactions may also cause arrhythmia by means of intervening with metabolism and pharmacokinetics, such as inhibition of CYP3A4 that metabolizes certain drugs or impairment of renal function and drug excretion, and by combining drugs of similar proarrhythmic action that is not apparent when each drug is used alone (macrolides with QT-prolonging antiarrhythmics).

Drug-induced long QT syndrome

Marked QT prolongation, often accompanied by the development of torsades de pointes, occurs in ≥1% of patients receiving QT-prolonging antiarrhythmic drugs and, much more rarely, in patients receiving non-cardiac agents with QT-prolonging potential (<0.01 to 0.1%).[215] QTc prolongation is also associated with an increased risk of stroke, independent of traditional risk factors.[216] Fluoroquinolones that are currently on the market, for example, present a very low risk of drug-induced torsades de pointes, with a frequency of this adverse event occurring at a rate of approximately 0.2–2.7 per million prescriptions.[217] Actually, numbers of drug-induced QT prolongation and torsades de pointes may be higher, as an active surveillance in Germany has indicated.[218] Recently, a small absolute increase in cardiovascular deaths, which was most pronounced among patients with a high baseline risk of cardiovascular disease, was detected during 5 days of azithromycin therapy (47–245 additional cardiovascular deaths per million courses),[219] and in March 2013 an FDA warning was published regarding the use of azithromycin for patients who are already at risk for cardiovascular events. However, in a study on Danish young and middle-aged adults, azithromycin use was not associated with an increased risk of death from cardiovascular causes compared to penicillin V.[220] Psychotropic drugs such as clothiapine, haloperidol, prochlorperazine, thioridazine, olanzapine, quetiapine, risperidone, and sulpiride are associated with increased risk of ventricular arrhythmias and sudden cardiac death.[221] Clothiapine, haloperidol, phenothiazines, citalopram, and escitalopram prolong the QT and may increase arrhythmia propensity, especially when administered to patients with hypokalaemia, abnormal T wave morphology, HCV infection, and HIV infection.[222] Amitriptyline is also associated with increased risk for modest QT prolongation, although the absolute magnitude of these effects is modest. Selective serotonin reuptake inhibitors such as sertraline may be associated with less risk.[223] Recently, an algorithm to reduce the risk of malignant arrhythmia in patients to be treated with psychotropic medications was proposed.[224] If the QT-interval or QTc reaches a length >500 ms or increases by >60 ms compared with the baseline, treatment with the particular drug should be ceased or the dose reduced. Hypokalaemia should be avoided and concomitant treatment with more than one drug with the propensity of prolonging the QT interval should be avoided.[224]

While many drugs have been associated with isolated cases of torsades de pointes, Table 56.20 lists those generally recognized as having QT-prolonging potential. An up-to-date list is maintained at http://www.torsades.org and http://www.qtdrugs.org. Patients with classic LQTS mutations, but normal or borderline QTc intervals, are generally much more susceptible to QTc-prolonging medications compared with the general population, yet they may be difficult to detect before drug exposure. Most clinically relevant drug-related QTc prolongation occurs via inhibition of I_{Kr}, a potassium current mediated in humans by the ion channel KCNH2 encoded by the human ether-a-go-go-related gene (HERG), analogous to the genetic LQT2 form of the disease. However, some drugs may also prolong the QT by augmenting the late inward sodium current (INa-L) through the phosphoinositide 3-kinase pathway.[225] Risk amplifiers for QT prolongation include female gender, age, hypokalaemia, hypomagnesaemia, bradycardia, and the

Table 56.20 Drug-induced long QT

Antiarrhythmic drugs
Class I (quinidine, disopyramide, procainamide, ajmaline)
Class III (sotalol, ibutilide, dofetilide)
Psychiatric drugs
Antipsychotic agents (thioridazine, mesoridazine, droperidol, pimozide, chlorpromazine, haloperidol)
Tricyclic antidepressants (citalopram)
Antibiotics
Quinolones*
Macrolides (azithromycin, erythromycin, clarithromycin)
Pentamidine, halofantrine, chloroquine
Other drugs
Cisapride, ketanserin
Coronary vasodilators (bepridil)
Methadone, cocaine
Arsenic

* Sparfloxacin, the most potent, has been withdrawn from the market. Ciprofloxacin is the safest quinolone in this respect.
Among cardiac drugs, indapamide and amiodarone may cause mild QT prolongation.
The antihistamines astemizole and terfenadine have been withdrawn from the market.

presence of underlying structural heart disease, particularly ventricular hypertrophy and congestive heart failure, and concomitant administration of drugs, such as ketoconazole that are inhibitors of the cytochrome P4504A4 (CYP3A4) that metabolizes other drugs that may prolong QT.[215] Most cases of drug-induced TdP occur in the setting of substantial prolongation of the QTc interval, typically to values >500 ms, although QTc alone is a relatively poor predictor of arrhythmic risk in any individual patient.[226] The QT interval remains a predictor, although crude, of torsades de pointes.[227]

In clinical practice, care should be taken when combining class III antiarrhythmic agents with other drugs that prolong the QT. After initiation of a drug associated with TdP, ECG signs indicative of risk for arrhythmia include:[228]

- An increase in QTc from pre-drug baseline of 60 ms
- Marked QTc interval prolongation >500 ms
- T-U wave distortion that becomes more exaggerated in the beat after a pause
- Visible (macroscopic) T wave alternans
- New-onset ventricular ectopy, couplets, and non-sustained polymorphic ventricular tachycardia initiated in the beat after a pause.

A reasonable strategy is to document the QTc interval before and at least every 8–12 h after the initiation, increased dose, or overdose of QT-prolonging drugs. Management is presented in Table 56.21.

Table 56.21 Management of drug-induced long QT syndrome

ACC/AHA/ESC 2006 GL on VA	
Removal of the offending agent in patients with drug-induced LQTS.	I-A
IV magnesium sulfate for patients who take QT-prolonging drugs and present with few episodes of torsades de pointes in which the QT remains long.	IIa-B
Atrial or ventricular pacing or isoproterenol for patients taking QT-prolonging drugs who present with recurrent torsades de pointes.	IIa-B
Potassium ion repletion to 4.5–5 mmol/L for patients who take QT-prolonging drugs and present with few episodes of torsades de pointes in whom the QT remains long.	IIb-C
ESC 2015 GL on VA and SCD	
Management of drug-related pro-arrhythmia	
Withdrawal of offending agents whenever drug-induced arrhythmias are suspected and the presence of other arrhythmogenic substrates has been excluded.	I-B
Prophylactic ICD implantation based on an individual evaluation of the future risk of life-threatening VA, despite a possible correctable cause for VA	IIa-C
Arrhythmic risk in psychiatric patients	
Dosage adjustment or interruption of the offending agent when, after treatment with antipsychotic drugs, the QTc interval reaches a length >500 ms or increases by >60 ms compared with baseline.	I-C
Monitoring of plasma potassium levels to avoid hypokalaemia during treatment with antipsychotic drugs.	I-C
Avoidance of treatment with more than one drug prolonging the QT interval	I-C
Evaluation of the QT interval before initiation of treatment and during titration of dose with antipsychotic drugs	IIa-C

ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. *Circulation*. 2006;**114**:e385–e484 with permission from Wolters Kluwer.
ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015; **36**:2793–867 with permission from Oxford University Press.

Digitalis toxicity

In mild cases, discontinuation of the drug and maintenance of normal potassium levels is enough. Management of severe cases is presented in Table 56.22.

Sodium channel blockers

They delay depolarization and thus slow conduction and prolong the QRS. In the presence of ischaemia or scar, this may result in reentrant arrhythmias. The use of flecainide or encainide in the CAST was associated with a 3.6-fold increase in the risk of fatal arrhythmias in post-MI patients.[62] Genetic factors, such as a SCN5A polymorphism, may play a role in determining susceptibility to these effects. In addition to slowing of conduction velocity, sodium channel blocking drugs may also selectively abbreviate epicardial action potential duration, resulting in a transmural gradient of repolarization, elevation of the ST segment, and reentry.[215] Non-antiarrhythmic agents with sodium channel properties are tricyclic antidepressants, phenytoin, local anaesthetic agents, and drugs used to treat neuropathic pain. Recently, nortriptyline was found to increase the risk for sudden cardiac arrest in the general population, in the presence of genetic and/or non-genetic factors that block the cardiac sodium channel.[229]

5-fluorouracil

5-fluorouracil causes lethal and potentially fatal arrhythmias, irrespective of underlying coronary disease during the acute infusion period, the vast majority occurring during the first administration.[230] Arrhythmias induced by this drug are mostly ischaemic in origin and usually occur in the context of coronary spasm produced by this drug.[231] Cardiac monitoring during the infusion period, especially the first, is recommended for all patients receiving 5-fluorouracil therapy. Symptoms, with or without corresponding ECG changes compatible with cardiac ischaemia, should lead to an immediate discontinuation of the infusion.

Anthracycline (doxorubicin, amrubicin)

Cardiotoxicity is dose-dependent, with intermittent high doses and higher cumulative doses increasing the risk of cardiomyopathy and lethal arrhythmias (see also Chapter 31).[232,233] This form of cardiomyopathy can occur acutely soon after treatment, within a few months of treatment, or many years later. VT, as opposed to AF, is rare.

Recommendations for **transient arrhythmias from reversible causes** are presented in Table 56.23.

Table 56.22 ACC/AHA/ESC 2006 GL on VA

Digitalis toxicity	
Antidigitalis antibody in sustained ventricular arrhythmias, advanced AV block, and/or asystole that are considered due to digitalis toxicity.	I-A
Patients with mild cardiac toxicity (e.g. isolated ectopic beats only) can be managed effectively with recognition, continuous monitoring of cardiac rhythm, withdrawal of digitalis, restoration of normal electrolyte levels (including serum potassium >4 mmol/L), and oxygenation.	IIa-C
Magnesium or pacing for severe toxicity (sustained ventricular arrhythmias, advanced AV block, and/or asystole).	IIa-C
Dialysis for the management of hyperkalaemia for severe toxicity (sustained ventricular arrhythmias; advanced AV block, and/or asystole).	IIb-C
Lidocaine or phenytoin not recommended for severe digitalis toxicity (sustained ventricular arrhythmias, advanced AV block, and/or asystole).	III-C

ACC/AHA/ESC 2006 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Circulation*. 2006;**114**:e385–e484 with permission from Wolters Kluwer

Table 56.23 ACC/AHA/ESC 2006 GL on VA

Transient arrhythmias of reversible cause	
Myocardial revascularization, when appropriate, in patients experiencing cardiac arrest due to VF or polymorphic VT in the setting of acute ischaemia or MI.	I-C
Unless electrolyte abnormalities are proved to be the cause, survivors of cardiac arrest due to VF or polymorphic VT in whom electrolyte abnormalities are discovered, in general, should be evaluated and treated in a manner similar to that of cardiac arrest without electrolyte abnormalities.	I-C
Patients with sustained monomorphic VT should be evaluated and treated in a manner similar to that of patients with VT without electrolyte abnormalities or antiarrhythmic drugs present. Antiarrhythmic drugs or electrolyte abnormalities should not be assumed to be the sole cause of sustained monomorphic VT.	I-B
Patients with polymorphic VT, in association with prolonged QT interval due to antiarrhythmic medications or other drugs, should be advised to avoid exposure to all agents associated with QT prolongation. A list of such drugs can be found on the websites http://www.qtdrugs.org and http://www.torsades.org.	I-B

ACC/AHA/ESC 2006 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Circulation*. 2006;**114**:e385–e484 with permission from Wolters Kluwer.

Ventricular arrhythmias in athletes

Vigorous exertion increases the incidence of acute coronary events in those who did not exercise regularly whereas habitual physical activity reduces the overall risk of myocardial infarction and SCD. A detailed discussion is presented in Chapter 68 on sudden cardiac death. ECG and echocardiographic screening programmes can reduce the incidence of SCD in professional athletes, although differentiation between adaptive LV chamber enlargement from mild forms of cardiomyopathy may be impossible.[234] Electroanatomical mapping-guided endomyocardial biopsy may be useful in identifying athletes with ARVC/D or myocarditis.[235] Many athletes with ICDs can engage in vigorous and competitive sports without physical injury or failure to terminate the arrhythmia despite the occurrence of both inappropriate and appropriate shocks.[236]

Athletes with non-sustained and asymptomatic exercise-induced ventricular arrhythmias may participate in low-intensity competitive sports, provided that no structural heart disease has been demonstrated. Recommendations for disqualification from high-intensity sports have been published.[237] See also Chapter 83 on athlete's heart on Miscellaneous Topics.

Ventricular arrhythmias in pregnancy

VT may be related to elevated catecholamines; post-partum cardiomyopathy should be ruled out, especially if VT occurs during the last 6 weeks or in the early post-partum period.[238] In women with the congenital long QT syndrome, the risk of cardiac arrest is greater during the post-partum period compared with before or during pregnancy.[239] All antiarrhythmic drugs cross the placenta. Selective beta blockers may be used. There are some concerns about low weight for gestational age when used before the 6th week of pregnancy. No association with low weight for gestational age has been found for labetalol (started after the 6th week of gestation) as opposed to atenolol. Sotalol and flecainide are also considered safe, but experience is limited. Amiodarone may be used, but fetal concentration is 20% of maternal concentration and may cause neonatal hypothyroidism (9% of newborns), hyperthyroidism, goitre, and growth retardation. Ideally, all antiarrhythmic drugs should be avoided during the first 8 weeks. In emergencies, immediate cardioversion is safe. IV procainamide, IV sotalol (with normal QT), or IV amiodarone may also be used. The presence of an ICD is not a contraindication for pregnancy. Recommendations of the ESC are presented in Table 56.24. See also Chapters 86 and 87.

Table 56.24 Ventricular arrhythmias in pregnancy

ESC GL on pregnancy 2011	
Implantation of an ICD, if clinically indicated, prior to pregnancy but is also recommended, whenever indicated, during pregnancy.	I-C
For long-term management of the congenital long QT syndrome, β-blocking agents during pregnancy and also postpartum when they have a major benefit.	I-C
Oral metoprolol,[1,2] propranolol,[1,2] or verapamil,[1,3] for long-term management of idiopathic sustained VT.	I-C
Immediate electrical cardioversion of VT for sustained, unstable, and stable VT.	I-C
Sotalol[4] or procainamide for acute conversion of sustained, haemodynamically stable, and monomorphic VT.	IIa-C
Implantation of permanent pacemakers or ICDs (preferably one chamber) should be considered with echocardiographic guidance, especially if the fetus is beyond 8 weeks gestation.	IIa-C
IV amiodaron for acute conversion of sustained, monomorphic, haemodynamically unstable VT, refractory to electrical cardioversion or not responding to other drugs.	IIa-C
Oral sotalol,[4] encainide,[3] propafenone,[3] for long-term management of idiopathic sustained VT if other drugs fail.	IIa-C
Catheter ablation in drug-refractory and poorly tolerated tachycardias.	IIb-C
ESC 2015 GL on VA and SCD	
ICD if an indication emerges during pregnancy.	I-C
β-blocking agents during pregnancy and also post-partum in patients with LQTS or CPVT.	I-C
Oral metoprolol, propranolol or verapamil for long-term management of idiopathic sustained VT.	I-C
Immediate electrical cardioversion for sustained VT, especially if haemodynamically unstable.	I-C
Sotalol or procainamide i.v. for acute conversion of haemodynamically stable monomorphic sustained VT.	Iia-C
Amiodarone i.v. for acute conversion of sustained, monomorphic VT when haemodynamically unstable, refractory to electrical cardioversion or not responding to other drugs.	IIa-C
Catheter ablation for management of drug-refractory and poorly tolerated tachycardias.	IIb-C

1: AV nodal blocking agents should not be used in patients with pre-excitation on resting ECG.
2: Beta-blocking agents should be used with caution in the first trimester.
3: Consider AV nodal blocking agents in conjunction with flecainide and propafenone for certain atrial tachycardias.
4: Class III drugs should not be used in cases with prolonged QTc.
ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**:3147–97, with permission from Oxford University Press.
ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015; http://dx.doi.org/10.1093/eurheartj/ehv316 with permission from Oxford University Press.

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Part X

Genetic channelopathies

Relevant guidelines

HRS/EHRA 2011 Consensus statement on the state of genetic testing

HRS/EHRA Expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Europace*. 2011;**13**:1077–109.

ACCF/AHA/HRS 2012 Guidelines for device-based therapy of cardiac rhythm abnormalities

2012 ACCF/AHA/HRS Focused update incorporated into the ACCF/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2013;**61**:e6–75.

HRS/EHRA/APHRS 2013 Consensus statement on inherited arrhythmia

HRS/EHRA/APHRS Expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Europace*. 2013;**15**:1389–406.

ESC 2015 Guidelines on ventricular arrhythmias and prevention of sudden cardiac death

2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015;**36**:2793–2867.

AHA 2016 scientific statement on early repolarization

Electrocardiographic early repolarization: A scientific statement from the American Heart Association. *Circulation* 2016;Mar 7:[Epub ahead of print].

Chapter 57

Definitions of inherited arrhythmias

Definitions

Inherited arrhythmias comprise a group of disorders with inherited susceptibility to arrhythmias and conduction disturbances due to mutations in genes mainly encoding the Na^+ and K^+ channels and other arrhythmogenic mechanisms, such as those linked to Ca^{++} transport (Table 57.1 and Figure 57.1).[1] The DNA among humans consists of the same nucleotide sequence, but normal variations in small sections of sequence or single nucleotides do exist among individuals (polymorphisms). Single nucleotide substitutions that occur with a measurable frequency (ie >0.5% allelic frequency) among a particular ethnic population are called single-nucleotide polymorphisms, whereas those that occur less frequently are termed mutations. **Loss-of-function mutations** of a particular gene produce different phenotypes from gain-of-function mutations of the same gene; loss-of-function mutations in the gene KCNQ1 encoding for voltage-gated potassium channels that affect the repolarizing current IKs cause long QT syndrome, whereas gain-of-function mutations of the same gene cause a phenotype of short QT syndrome or AF. **Gain-of-function mutations** of gene SCN5A cause long QT syndrome, whereas loss-of-function mutations cause Brugada syndrome, conduction disorders, and a form of dilated cardiomyopathy (Table 57.1). The majority of heritable cardiomyopathies and channelopathies are associated with disease susceptibility genes characterized by incomplete penetrance, i.e. low likelihood that the mutation will cause clinically recognizable disease. Thus, although these disease entities are monogenic, there is variable penetrance, which reflects the contribution by modifier genes, thus resulting in diverse phenotypes.[2] Usually, they are autosomal dominant, rather than autosomal recessive.

Genetic testing has now emerged as a useful clinical tool for the diagnosis and risk stratification of genetic conditions, but distinguishing pathologic mutations from innocent genetic variants is not always straightforward. Currently, genetic testing may establish the diagnosis in LQTS, CPVT, BrS, and HCM and may also facilitate risk stratification in LQTS and HCM.[3] According to the 2011 Consensus Statement of HRS/EHRA, genetic testing is recommended in cases with a sound clinical suspicion for the presence of a channelopathy or a cardiomyopathy when the positive predictive value of a genetic test is high (likelihood of positive result >40% and signal/noise ratio <10).[4] The conventional approach of genetic linkage analysis (Sanger sequencing) has been replaced with the newer approach of Next Generation DNA Sequencing (NGS), that enables rapid analysis of large numbers of genes simultaneously.[5] NGS technology can be used in the form of 'targeted gene panels' in which there is a focus on a set of genes known to be associated with specific disorders, or as whole exome sequencing (WES) which covers almost all protein-coding sequences, or whole-genome sequencing (WGS) that includes nearly all non-coding sequences as well. Targeted gene panels are faster and cheaper. These are exciting advancements, although several questions remain about their clinical applicability and cost-effectiveness.[6–11] A freely available internet resource, GeneTests, provides a searchable database of clinical genetic testing laboratories,

Table 57.1 Known channel mutations in genetic channelopathies.

New mutations are continuously discovered. Most conditions are inherited in an autosomal dominant pattern, although both recessive (JLN, CPVT) and X-linked patterns (BrS) have been described.

Chromosomal locus	Gene	Protein	Current/ Mechanism	Phenotype
11p15.5	*KCNQ1*	*K_v7.1*	*I_{Ks}*	LQTS, JLNS, SQTS, AF
7q35–q36	*KCNH2*	*HERG*	*I_{Kr}*	LQTS, SQTS, AF
3p22	SCN5A	*Na_v1.5*	*I_{Na}*	LQTS, MEPPC, BrS, AF, PCCD, SSS, DCM, LVNC
3p22	*SCN10A*	*Na_v1.8*	*I_{Na}*	BrS, ERS, SSS, PCCD, AF, VT/VF

(*Continued*)

Table 57.1 Continued

Chromosomal locus	Gene	Protein	Current/ Mechanism	Phenotype
4q25–q27	*ANKB*	*Ankyrin B*	I_{Na-K}, I_{Na-Ca}, I_{Na}	LQTS, AF, CPVT
21q22.1–q22.2	*KCNE1*	*MinK*	I_{Ks}	LQTS, JLN, AF
21q22.1	*KCNE2*	*MiRP1*	I_{Kr}	LQTS, AF
17q24.3	*KCNJ2*	*Kir2.1*	I_{K1}	LQTS, potassium-sensitive periodic paralysis, hypoplastic mandible (Andersen–Tawil syndrome), bicuspid AV, SQTS, AF, PCCD, CPVT
12p13.3	*CACNA1C*	*Ca_v1.2*	I_{Ca}	LQTS, syndactyly, septal defects (Timothy syndrome), BrS, SQTS
3p24	*CAV3*	*Caveolin-3*	I_{Na}	LQTS
11q23.3	*SCN4B*	*Navβ4*	I_{Na}	LQTS
7q21–q22	*AKAP9*	*A-kinase anchorin (yotiao)*	I_{Ks}	LQTS
20q11.2	*SNTA1*	*α-1 syntrophin*	I_{Na}	LQTS
11q24.3	*KCNJ5*	*Kir3.4 subunit*	I_{KAch}	LQTS
14q31	*CALM1*	*Calmodulin 1*	*Ca kinetics*	CPVT, LQTS, VF
2p21	*CALM2*	*Calmodulin 2*	*Ca kinetics*	CPVT, LQTS
19q13	*CALM3*	*Calmodulin 3*	*Ca kinetics*	LQTS
10p12.33	*CACNB2b*	*Ca_vbeta2β*	I_{Ca}	SQTS, BrS
7q21–q22	*CACNA2D1*	*$Ca_{va2δ-1}$*	I_{Ca}	SQTS, BrS
13p22.3	*GPD1L dehydrogenase 1-like*	*Glycerol-3-phosphate*	I_{Na}	BrS
19q13	*SCN1B*	*$Na_{vβ1}$*	I_{Na}	BrS, LQTS, PCCD, AF, LVNC
11q13.4	*KCNE3*	*MiRP*	I_{to}, I_{ks}	BrS
11q23.3	*SCN3B*	*Beta subunit*	I_{Na}	BrS
15q24.1	*HCN4*	*HCN4*	I_f	BrS, SSS, AF, LVNC
1p13.3	*KCND3*	*Kv4.3*	I_{to}	BrS
12p11.23	*KCNJ8*	*Kir6.1*	I_{KATP}	BrS, ERS
17p13.1	*MOG1*	*MOG1 (RAN guanine nucleotide release factor 1)*	I_{Na}	BrS
3p21.2–p14.3	*SLMAP*	*SLMAP*	I_{Na}	BrS
Xq22.3	*KCNE5*	*MiRP*	I_{to}	BrS, VF
3q29	*DLG1*	*Synapse-associated 97*	*Junction functions*	BrS
12p12.1	*ABCC9*	*SUR2A*	*IKATP*	BrS
11q23	*SCN2B*	*Beta subunit*	I_{Na}	BrS
12p11	*PKP-2*	*Placophilin-2*	I_{Na}	BrS, ARVC
3q28	*FGF12*	*FHAF1*	I_{Na}	BrS
6q8	*HEY2*	*Transcription factor*	I_{Na}	BrS
7p12.1	*SEMA3A*	*Semaphorin*	I_{to}	BrS
1q42–43	*RyR2*	*Cardiac ryanodine receptor*	*Ca kinetics*	CPVT, LQTS bradycardia, AF, PCCD, DCM, ARVC, LVNC
1p13–21	*CASQ2*	*Cardiac calsequestrin*	*Ca kinetics*	CPVT
6q22.31	*TRDN*	*Triadin*	*Ca kinetics*	CPVT

I_{Ks}, rectifier K current, slow component; I_{Kr}, rectifier K current, rapid component; I_{Na}, inward Na current; I_{Na-K}, Na/-ATPase current (Na/K pump); I_{Na-Ca}, Na-Ca exchanger current; I_{K1}, inward rectifier K channel; I_{Ca}, Ca current; JLN, Jervel and Lange-Nielsen syndrome; SSS, sick sinus syndrome; ERS, early repolarization syndrome; DCM, dilated cardiomyopathy; CPVT, catecholaminergic polymorphic VT; PCCD, progressive conduction system disease; LVNC, left ventricular non-compaction; MEPPC, multifocal ectopic Purkinje-related premature contractions.
Mutations responsible for LQTS and Brugada syndrome are presented by the order these syndromes have been described, i.e. LQTS1, LQTS2, etc.

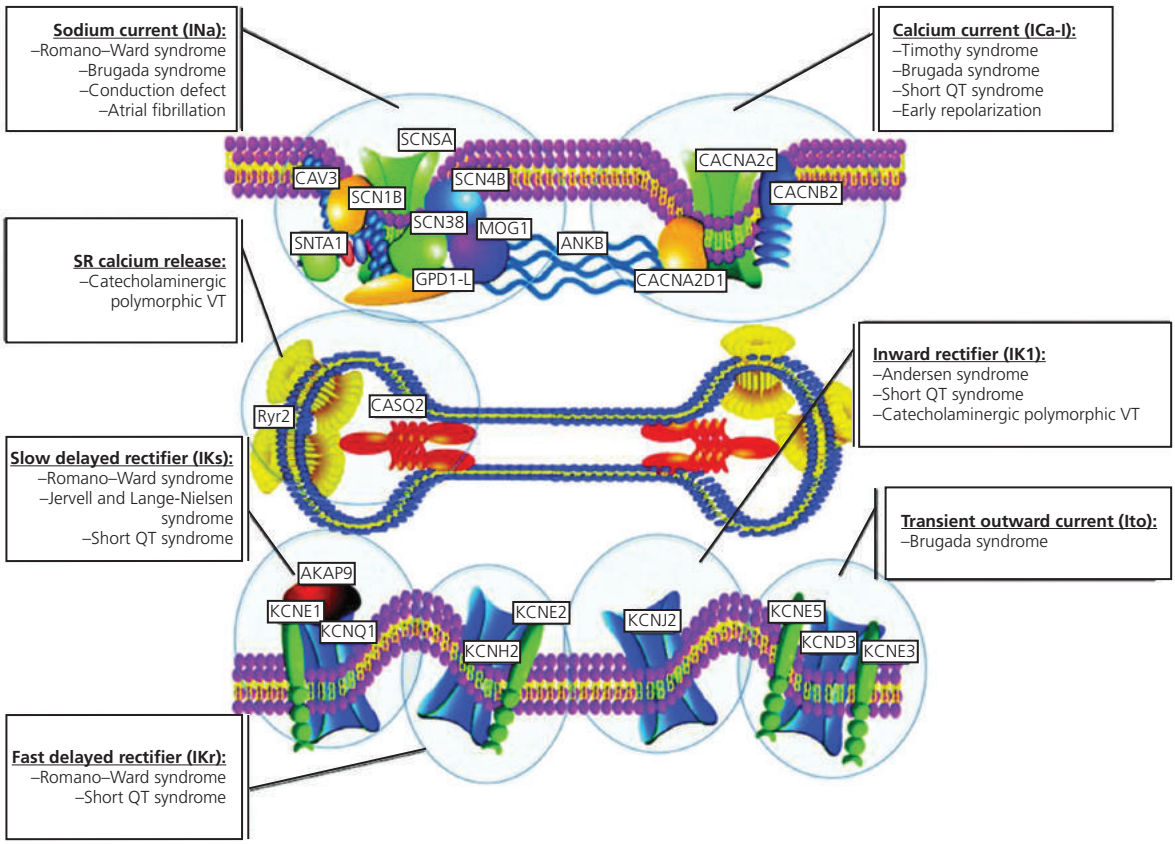

Figure 57.1 Genes associated with inherited arrhythmogenic diseases grouped by ion channel/function.

SR, sarcoplasmic reticulum; VT, ventricular tachycardia.

Napolitano C, *et al*. Sudden cardiac death: Sudden cardiac death and genetic ion channelopathies. Circulation. 2012;125:2027–34 with permission from Wolters Kluwer.

specialty clinics, and other relevant information.[11] In November 2013, the FDA allowed marketing of four diagnostic devices that can be used for high-throughput gene sequencing.

Glossary of terms

Allele: One of several alternative versions of a particular gene. An allele can refer to a segment of DNA or even a single nucleotide. The normal version of genetic information is often considered the 'wildtype' or 'normal' allele. The vast majority of the human genome represents a single version of genetic information. Multiple alleles are when one phenotype is controlled by more than two alleles, but only a combination of two determines the phenotype. For example, blood group has three alleles A, B, and O, but people only have a two-allele phenotype.

Autosomal dominant: The situation in which the disease can be expressed, even when just one chromosome harbours the mutation.

Autosomal recessive: The situation in which the disease is expressed only when both chromosomes of a pair are abnormal.

Cascade testing: Procedure whereby all first-degree relatives of a genotype-positive index (or proband) case are tested in concentric circles of relatedness. If one of the family members is genotype-positive, all his/her first-degree relatives should be tested, continuing this process to follow each genotype-positive family member.

Compound heterozygosity: More than one genetic defect in the same gene.

Digenic heterozygosity: More than one genetic defect in a second complementary gene.

Epigenetics: Mitotically and/or meiotically heritable variations of gene function that cannot be explained by changes of DNA sequence.

Exome: Part of the genome formed by exons, 1–2% of the coding portion of the human genome; it encompasses approximately 19,000 genes.

Exome sequencing: DNA sequencing that targets the exons of all genes in the genome. The exome makes up about 1% of the genome, primarily exons of genes that code for proteins. This type of sequencing is sometimes referred to as 'whole-exome sequencing,' even though coverage of the exons is not 100%.

Exons: Segments of genes that are spliced together after gene transcription to form messenger RNA, which, in turn, is translated into protein.

Expressivity: The level of expression of the phenotype. When the manifestations of the phenotype in individuals who have the same genotype are diverse, the phenotype is said to exhibit variable expressivity.

Filtering analysis: The process of excluding DNA variants from further consideration because of various attributes, with the use of bioinformatics and manual curation. For example, most filtering analyses exclude synonymous variants (DNA variants that are predicted not to change the amino acid sequence of a protein).

Genotype: A person's genetic or DNA sequence composition at a particular location in the genome.

Genotypic heterogeneity: Genetic variability among individuals with similar phenotypes.

Genotype–phenotype plasticity: The concept that the link between genotype and phenotype is subject to broad variability with, as yet, limited predictability.

Genome-wide association studies: Examination of many common genetic variants in individuals, with and without a disease trait, to identify a possible higher frequency (i.e. association) of single-nucleotide polymorphisms in people with the trait.

Genome sequencing: DNA sequencing that targets the entire genome. It is sometimes termed 'genome shotgun sequencing' or 'whole-genome sequencing,' even though coverage is not 100%.

Germline variant: A DNA sequence variant that was transmitted by means of a gamete (sperm or egg) or that was caused by a mutation in the zygote or at a very early stage of fetal development and is presumed to be present in all of a person's nucleated cells.

Haploinsufficiency: The situation in which an individual who is heterozygous for a certain gene mutation or hemizygous at a particular locus, often due to a deletion of the corresponding allele, is clinically affected because a single copy of the normal gene is incapable of providing sufficient protein production to assure normal function. This is an example of incomplete or partial dominance.

Heterozygote: An individual who has different alleles at a particular gene locus on homologous chromosomes (carrier of a single copy of the mutation).

Human genome reference sequence: A reference sequence that provides a haploid mosaic of different DNA sequences from multiple donors, which is revised periodically and is not necessarily normal.

Homozygote: An individual who has the same allele at a particular gene locus on homologous chromosomes (carrier of a double copy of the mutation).

Matrilinear inheritance: Women but not men transmit the disease to offspring (male or female), as happens with disease due to mitochondrial DNA mutations.

Modifier: Gene variants or environmental factors that are insufficient to cause observable disease on their own but which are capable of interacting with the disease gene to alter the phenotype.

Mutation: A change of the DNA sequence within the genome. A mutation considered in the context of a genetic disease usually refers to an alteration that causes a Mendelian disease, whereas a genetic polymorphism refers to a common genetic variation observed in the general population.

Mutation—deletion/insertion: The removal (deletion) or addition (insertion) of nucleotides to the transcript that can be as small as a single nucleotide insertion/deletion or as large as several hundreds to thousands of nucleotides in length.

Mutation—disease-causing: A DNA sequence variation that represents an abnormal allele and is not found in the normal healthy population, but exists only in the disease population and produces a functionally abnormal product.

Mutation—frameshift: Insertions or deletions occurring in the exon that alter the 'reading frame' of translation at the point of the insertion or deletion and produce a new sequence of amino acids in the finished product. Frameshift mutations often result in a different product length from the normal gene product by creating a new stop codon, which produces either a shorter or longer gene product, depending on the location of the new stop codon.

Mutation—germline: Heritable change in the genetic make-up of a germ cell (sperm or ovum) that, when transmitted to an offspring, is incorporated into every cell in the body.

Mutation—in-frame insertion/deletion: In-frame insertions and deletions occur when a multiple of three nucleotides is affected and result in a single or multiple amino acids being removed or added without affecting the remainder of the transcript.

Mutation—missense: A single nucleotide substitution that results in the exchange of a normal amino acid in the protein for a different one.

Mutation—nonsense: A single nucleotide substitution resulting in a substitution of an amino acid for a stop codon. A nonsense mutation results in a truncated (shortened) gene product at the location of the new stop codon.

Mutation—somatic: Variants/mutations are said to be somatic if they occur in cells other than gametes. Somatic mutations cannot be transmitted to offspring.

Penetrance: The likelihood that a gene mutation will have any expression at all. In the situation in which the frequency of phenotypic expression is less than 100%, the genetic defect is said to be associated with reduced or incomplete penetrance, by means of any recognizable symptom, sign, or laboratory feature of the disease associated with that variant.

Phenocopy: An individual who manifests the same phenotype (trait) as other individuals of a particular genotype but does not possess this genotype himself/herself.

Phenotype: A person's observed clinical expression of disease in terms of a morphological, biochemical, or molecular trait.

Phenotypic heterogeneity: Phenotypic variability among individuals with similar genotypes.

Polymorphism: Normal variations at distinct loci in the DNA sequence. The vast majority of the human genome represents a single version of genetic information. The DNA from one person is mostly made up of the same exact nucleotide sequence as another person. However, there are many small sections of sequence, or even single nucleotides, that differ from one individual to another.

Proband or index case or propositus: The first affected family member who seeks medical attention for a genetic disease.

Single-nucleotide polymorphism (SNP): A single nucleotide substitution that occurs with a measurable frequency (i.e. >0.5% allelic frequency) among a particular ethnic population(s).

SNP—non-synonymous: A single nucleotide substitution whereby the altered codon encodes a different amino acid or terminates further protein assembly (i.e. introduces a premature stop codon).

SNP—synonymous: A single nucleotide substitution occurring in the coding region (exon), whereby the new codon still specifies the same amino acid.

X-linked inheritance: A recessive mode of inheritance in which a mutation in a gene on the X chromosome causes the phenotype to be expressed in males (who are necessarily hemizygous for the gene mutation) and in females who are homozygous for the gene mutation.

Variant: A difference in a DNA sequence in comparison with the normal reference sequence. A variant may be benign (sometimes referred to as a polymorphism) or pathogenic (sometimes referred to as a mutation).

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Chapter 58

Long QT syndrome

Definition

Inherited long QT syndrome (LQTS) is characterized by a prolonged QT interval, syncope, and sudden cardiac death due to ventricular tachyarrhythmias, typically torsades de pointes (TdP).[1]

Epidemiology

LQTS has variable penetrance, and the estimated prevalence of clinically overt disease is approximately 1:2000 subjects. Symptomatic patients without therapy have a high mortality rate, 21% within 1 year from the first syncope, but, with proper treatment, mortality is now ≈1% during a 15-year follow-up.[1,2]

Genetics and pathophysiology

The genetic basis of the LQTS is mutations or polymorphisms in genes encoding proteins that form ion channels affecting repolarization (Table 57.1 of Chapter 57). Nearly 1000 mutations have been identified in **16 distinct LQTS susceptibility genes**. Most of LQTS are due to loss-of-function mutations in the genes *KCNQ1* and *KCNH2* encoding for voltage-gated potassium channels that affect the repolarizing currents I_{Ks} (LQT1, 30–35% of all LQTS) and I_{Kr} (LQT2, 25–40% of all LQTS), respectively.[2,3]

LQT1 is the most common type of LQTS, and is due to heterozygous gene mutations of *KCNQ1* (encoding the alpha subunit of the I_{Ks} channel). I_{Ks} reduction increases transmural dispersion of repolarization and sensitivity to catecholamine stimulation. Mutations of *KCNQ1* reduce I_{Ks} but I_{Kr} (i.e. the rapid component of the delayed rectifier K^+ current) could maintain a near-normal duration of action potentials, concealing LQT1. In this case, I_{Kr} blockade (e.g. by drugs) or inactivation (e.g. by hypokalaemia) can induce substantial QT prolongation and trigger torsades de pointes.

LQT2 is the second most common genotype of LQTS, and is associated with reduced I_{Kr} by gene mutations (*KCNH2*) that encode the α-subunit (hERG) of the I_{Kr} channel. Reduced I_{Kr} slows repolarization and increases the transmural dispersion of repolarization. I_{Kr} is unaffected by catecholamine stimulation.[1] Emotional stress and sudden loud noises can cause a rapid increase in heart rate from sympathetic discharge, which acutely prolongs the action potential before subsequent shortening by a slowed enhancement of I_{Ks}. Bradycardia reduces I_{Kr}, delays repolarization, and increases transmural dispersion.

Up to 10% of LQTS (**LQT3**) are due to gain-of-function mutations of the gene *SCN5A* (mostly missense, i.e. single amino acid substitutions) encoding the sodium channel. In patients with such mutations, the channel fails to close properly after initial depolarization, and continued leakage of sodium into the channel results in prolongation of the action potential. LQT3 results in cardiac events leading to sudden death occurring usually at night or rest without arousal and occasionally following sympathetic stimulation. Typical ECG in LQT3 shows a flat, long ST segment with late appearance of a narrow-peaked T wave. LQT3 is caused by *SCN5A* mutations that lead to gain-of-function of Na^+ channels via a late sustained current, that prolongs the plateau phase of the action potential and produces long ST segments and late appearance of T wave in the ECG, which are LQT3 characteristics. Nine minor LQTS-susceptibility genes account for less than 5%, and up to 20% of congenital LQTS cases remain genotype negative.

The classic LQTS is being transmitted as an autosomal dominant trait (initially described by **Romano and by Ward**). A less common but more severe form is transmitted as an autosomal recessive disease (patients carry two abnormal LQT genes), and is associated with neurosensory deafness and higher risk of sudden death (**Jervell and Lange-Nielsen syndrome**).[4] Jervell and Lange-Nielsen syndrome occurs in 1–7% of patients with LQTS. Diagnosis is considered on the basis of the established diagnostic criteria for LQTS and on the presence of congenital neurosensory deafness. An autoimmune-associated form of LQTS has also been recently described. Anti-Ro Abs from patients with autoimmune diseases inhibit I_{Kr} by cross-reacting with the HERG channel.[5]

The QT interval on the ECG represents the longest repolarization in the mid-myocardial M-cell region, i.e. a physiological transmural dispersion of repolarization. Gene mutations or medications that cause selective action potential prolongation in the M-cell region can lead to increased transmural repolarization gradients and thus create the conditions for functional reentry and subsequent torsades. A net decrease in repolarizing currents prolongs action potentials in LQTS, and subsequently promotes the L-type Ca^{2+} current ($I_{Ca,L}$) and phase-2 early after-depolarizations.[1] Prolonged action potentials cause Ca^{2+} overload, leading to the activation of the

inward Na^+-Ca^{2+} exchanger current that causes phase-3 early after-depolarizations. Early after-depolarizations (phase-2 and phase-3) and dispersion of repolarization contribute to torsades de pointes.[5] The trigger for TdP is thought to be a PVC that results from an early after-depolarization generated during the abnormally prolonged repolarization phase of the affected myocardium. A long preceding pause increases the amplitude of early after-depolarizations, which makes them more likely to reach the threshold necessary to produce a PVC or ventricular couplet (short-long-short RR interval sequences mode of TdP onset). Torsades de pointes, therefore, is triggered by early after-depolarizations and can be maintained by repetitive, multifocal early after-depolarizations as well as reentry around shifting pathways.[6] Pause-dependent torsades de pointes is seen in LQT2 and perhaps LQT3, but not in LQT1, in which sympathetic activation is the usual trigger.[7] Sympathetic activity is an important modulator of the disorder and can further delay repolarization, induce early after-depolarizations, and trigger sudden arrhythmic death in patients with LQTS, especially LQT1. Patients with LQTS, despite normal LVEF, have significantly longer contraction duration and greater indices of regional and transmural inhomogeneous contraction times as assessed by strain echocardiography.[8] Thus, LQTS is not considered a pure electrical disease. LQTS is also associated with an increased risk of AF.[9] In the general population, an increased risk of cardiovascular disease has been observed for both very short and long QT interval.[10] In the MESA trial, prolongation of the corrected QT interval was associated with an elevated risk of arrhythmic and sudden death, as well as incident stroke, heart failure, and ischaemic cardiovascular events in patients with and without ischaemic heart disease.[11,12] QTc prolongation is also associated with an increased risk of stroke independent of traditional risk factors and this is also true for drug-induced prolongation.[13]

Presentation

Patients may be entirely asymptomatic. The term 'torsades de pointes' was introduced by Dessertenne in 1866, when he described polymorphic ventricular tachycardia occurring in the setting of bradycardia due to complete heart block. Symptoms caused by this tachyarrhythmia range from dizziness and syncope to cardiac arrest and death in up to 16% of patients. Because torsades de pointes can cause seizures due to cerebral anoxia, LQTS is important to consider in patients with apparent drug-resistant seizure disorders. Both exercise (especially swimming) and emotional stress (sudden loud noise, anger) can trigger syncope in patients with LQTS, possibly via an increase in catecholamine concentrations. Pregnancy reduces the risk of cardiac events, but the risk increases in the 9-month period of post-partum, especially in patients with LQT2. β blockers reduce the occurrence of cardiac events post-partum. Specifically:

LQT1: exercise (especially swimming), emotional stress
LQT2: emotional stress, sudden noise
LQT3: rest, sleep.

Diagnosis

Diagnostic criteria are provided in Table 58.1. Inherited LQTS is considered when electrolyte- or drug-induced QT prolongation has been excluded (see Chapter 56 on ventricular arrhythmias). The most important diagnostic and prognostic characteristic is QT interval prolongation (Figure 58.1), although it might not accurately predict the prognosis in LQT3 (Figure 58.2). The QT interval should be determined as a mean value derived from, at least, 3–5 heart beats and is measured from the beginning of the earliest onset of the QRS complex to the end of the T wave in leads II and V_5 or V_6, with the longest value being used. In situations in which the end of the T wave may be difficult to determine (e.g. biphasic or notched T waves, T waves with superimposed U waves), the end of the T wave can be determined by drawing the tangent from the peak of the T wave following the steepest T wave downslope. The intersection of this line with the isoelectric baseline is considered the end of the T wave (Figure 58.1).[14] In AF, the average of the QTc values of the shortest and longest R-R intervals is used. If the interval from R wave to the peak (or nadir) of the T wave is more than 50% of the R-R interval, there is an indication that it would be longer than the critical threshold of 500 ms if measured. The QT interval is usually corrected for heart rate because the QT interval shortens at fast heart rates and prolongs at slow heart rates. The Bazett formula ($QTc = QT/\sqrt{RR}$, with all intervals in seconds) remains the standard for clinical use, despite some limitations at particularly fast or slow heart rates, in which the formula may overcorrect or undercorrect, respectively. Another method is the Framingham linear regression formula. Diagnostic criteria for LQTS carry a high specificity but low sensitivity.[2,15]

Normal QTc values are <440 for age 1–15 years, <430 for adult males, and <450 ms for adult females.[4]

A **QTc value of ≥430 ms** distinguishes carriers from non-carriers (<430 ms), with a 72% sensitivity and 86% specificity.[16] Increased **QT dispersion** (>100 ms), measured as the difference between the minimum and maximum QT intervals in the 12-lead ECG, indicates ventricular repolarization heterogeneity and is increased in symptomatic patients and reduced by beta blockers.

Prominent **U waves** and T-U complexes are frequently seen.

T-wave alternans, i.e. a beat-to-beat alternation in T-wave morphology, is a marker of high cardiac electrical instability. Notches on the T-wave are rather typical for LQT2 and are associated with a higher proarrhythmia risk.[2]

Sinus bradycardia may be present, and **sinus pauses** are mainly seen in LQT3.

Response to exercise or catecholamine injection In healthy individuals, acute sympathetic stimulation increases inward Ca^{2+} currents, shortens the RR interval, and initially prolongs and then shortens the QT interval by activating the delayed rectifier K^+ current (slow component, I_{Ks}).

LQT1: prolongation of both QT and QTc interval during and after cessation of exercise or catecholamine injection (paradoxical QT response)

LQT2: initial prolongation followed by shortening of the QT and QTc and promotion of the notch on the descending T wave

LQT3: shortening of the QT interval. The QTc is slightly prolonged at the peak effect of exercise and returns to baseline at steady state.

The presence and genotype of LQTS can be established by **exercise testing** that may reveal features, such as inadequate QT shortening, postural T wave change, and exercise-related T wave notching.[17,18] The post-recovery QTc may also be helpful. LQT1 patients begin the recovery period at a very prolonged QTc that decreases during recovery whereas the LQT2 patients begin recovery at a lower QTc that increases during recovery. At the end of recovery, a QTc cut-off value of 445 ms indicates LQTS while a start-of-recovery QTc >460 ms suggests LQT1 and <460 ms LQT2.[19] Symptomatic LQT1 patients have a greater heart rate reduction (≥17%) at the first minute of recovery phase from the peak heart rate during exercise when compared with asymptomatic LQT1 patients, regardless of the use of beta blockers. This does not occur in LQT2 and LQT3 patients. Thus, heart rate reduction immediately after exercise, a marker of vagal reflex response, can be used for risk stratification in LQT1.[20]

Other provocative tests are absence of QT shortening (but prominent QTc increase), with tachycardia induced by standing,[21] and QT prolongation (15%) by **adenosine** boluses of 6–24 mg.[22] Results from the Cardiac Arrest Survivors With Preserved Ejection Fraction Registry (CASPER) have shown that **epinephrine** challenge at doses of 0.05, 0.10, and 0.20 micrograms/kg per minute may also disclose LQTS in unexplained cardiac arrest. A test is considered positive for long QT syndrome if the absolute QT interval is prolonged by ≥30 ms at 0.10 micrograms/kg per minute and borderline if QT prolongation is 1 to 29 ms.[23]

LQTS may be responsible for >10% of unexplained fetal death, and QTc ≥490 ms assessed by fetal magnetocardiography identifies LQTS in utero.[24]

Table 58.1 Diagnosis of LQTS

LQTS risk score	
	Points
ECG findings*	
A. QT_c†	
≥480 $ms^{1/2}$	3
460-470 $ms^{1/2}$	2
450 $m^{1/2}$ (in males)	1
B. Torsade de pointes‡	2
C. T-wave alternans	1
D. Notched T wave in three leads	1
E. Low heart rate for age§	0.5
Clinical history	
A. Syncope‡	
With stress	2
Without stress	1
B. Congenital deafness	0.5

(*Continued*)

Table 58.1 Continued

LQTS risk score	
Family history‖	
A. Family members with definite LQTS#	1
B. Unexplained sudden cardiac death below age 30 among immediate family members	0.5

A. HRAS/EHRA/APHRS 2013 statement on inherited primary arrhythmia syndromes Recommendations on LQTS diagnosis	
1. LQTS is diagnosed:	
a. In the presence of an LQTS risk score >3.5 in the absence of a secondary cause for QT prolongation, *and/or*	
b. In the presence of an unequivocally pathogenic mutation in one of the LQTS genes, *or*	
c. In the presence of a QTc >500 ms in repeated 12-lead ECG and in the absence of a secondary cause for QT prolongation.	
2. LQTS can be diagnosed in the presence of a QTc between 480–499 ms in repeated 12-lead ECGs in a patient with unexplained syncope in the absence of a secondary cause for QT prolongation and in the absence of a pathogenic mutation.	

B. ESC 2015 GL on VA and SCD. Diagnosis of long QTS (in the absence of secondary causes for QT prolongation)	
QTc ≥480 ms in repeated 12-lead ECGs or LQTS risk score >3.	I-C
Confirmed pathogenic LQTS mutation, irrespective of the QT duration.	I-C
QTc ≥460 ms in repeated 12-lead ECGs in patients with an unexplained syncopal episode in the absence of secondary causes for QT prolongation.	IIa-C

Scoring: ≤1 point, low probability of LQTS; 2 to 3 points, intermediate probability of LQTS; ≥4 points, high probability of LQTS.
LQTS, long QT syndrome.
* In the absence of medications or disorders known to affect these electrocardiographic features.
† QT_c calculated by Bazett's formula, where $QT_c = QT / \sqrt{RR}$
‡ Mutually exclusive.
§ Resting heart rate below the second percentile for age.
‖ The same family member cannot be counted in A and B.
Definite LQTS is defined by an LQTS score ≥4.
Schwartz PJ, *et al*. Diagnostic criteria for the long QT syndrome: an update. *Circulation*. 1993;**88**:782–4 with permission from Wolters Kluwer.
HRS/EHRA/APHRS 2013 Expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Heart Rhythm*. 2013;**10**:1932–63 with permission from Elsevier.
ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015;**36**: 2793–2867 with permission from Oxford University Press.

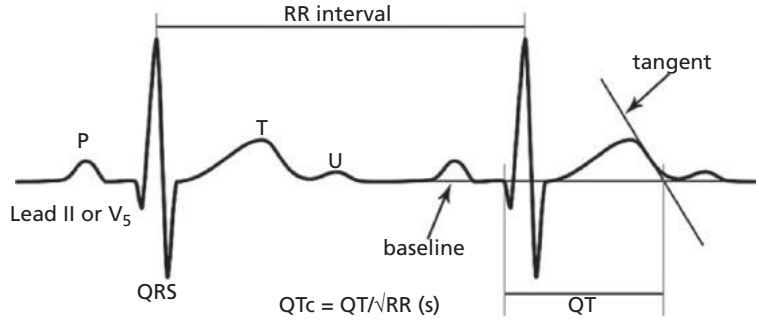

Figure 58.1 Measurement of the QT interval. A tangent is drawn to the steepest slope of the last limb of the T wave in lead II or V_5. The end of the T wave is the intersection of the tangent with the baseline. QT is heart rate corrected with Bazett's formula with use of the preceding RR interval.

Postema PG, *et al*. Accurate electrocardiographic assessment of the QT interval: teach the tangent. *Heart Rhythm*. 2008;**5**:1015–18 with permission from Elsevier.

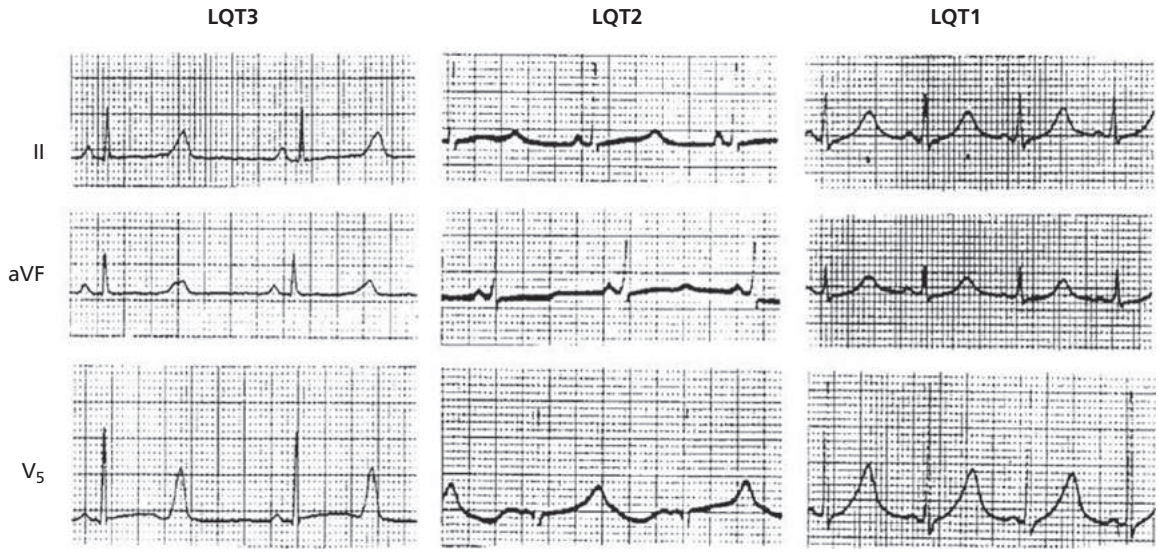

Figure 58.2 QT prolongation in the major three LQT syndromes. T-wave morphology by LQTS genotype: LQT1: typical broad-based T-wave pattern (corrected QT [QTc] 570 ms); LQT2: typical bifid T-wave (QTc 583 ms); and LQT3: typical late-onset peaked/biphasic T-wave (QTc 573 ms).

Goldenberg I and Moss AJ, Long QT syndrome. *J Am Coll Cardiol.* 2008;**52**:2291–300 with permission from Elsevier.

Risk stratification

A history of aborted **cardiac arrest** and/or ECG-documented episodes of **torsades de pointes**, particularly with β blocker treatment, indicates high risk. Children and adolescents who present after an episode of syncope should be considered to be at high risk of development of subsequent syncope episodes and fatal/near-fatal events, regardless of QTc duration.[25] Among symptomatic cases, the untreated 10-year mortality is approximately 50%.[4]

The cumulative probability of aborted cardiac arrest or sudden death at age of 40 years in patients with congenital LQTS is 4% for those with normal QTc intervals and 15% for those with prolonged QTc, as compared to 0.4% for unaffected family members.[26] There is no threshold of QTc prolongation at which TdP is certain to occur. However, there is a gradual increase in risk for TdP as the QTc increases, and a QTc >500 ms is associated with a 2- to 3-fold higher risk for TdP.[27] High-risk patients usually have QTc intervals of, at least, **500 ms** and can also show **T wave alternans** (Table 58.2).

LQT2 females and **LQT3 males with QT >500 ms** are at high-risk, independently of other factors.[28] Patients

Table 58.2 Age-specific risk factors

Childhood (1–12 years) Beta blockers reduce risk by 73%
Prior syncope, especially recent (<2 years)
Male gender
QTc >500 ms
Adolescence (10–20 years) Beta blockers reduce risk by 64%
Prior syncope, especially recent (<2 years) and when ≥2 events
QTc >530 ms
Adulthood (18–40 years) Beta blockers reduce risk by 60%
QTc ≥500 ms
Prior syncope, especially recent (<2 years)
Female gender
Adulthood (41–60 years) Beta blockers may reduce risk
Recent syncope (<2 years)
LQT3 genotype
QTc >530 ms

Goldenberg I and Moss AJ, Long QT syndrome. *J Am Coll Cardiol*. 2008;**52**:2291–300 with permission from Elsevier.

with LQT3 have a lower incidence of cardiac events but higher lethality than those with LQT1 and LQT2, and the risk may not be associated with prolongation of the QTc interval.

Genetic testing is therefore useful in this respect. A risk stratification scheme has also been proposed for LQTS 2: Females >13 years or males with mutations in the pore-loop region of KCNH2 and QTc ≥500 ms indicate intermediate risk while the presence of syncope in this category indicates high risk.[29]

The '**electromechanical window**' (EMW: duration of LV-mechanical systole on echocardiography minus QT interval) is also useful. EMW negativity is most pronounced in patients with documented arrhythmic events.[30]

The presence of missense mutations in distinct functional domains of the **KCNQ1 protein**, the S2-S3 and S4-S5 cytoplasmic loops (C-loops), is associated with a significantly increase d risk for life-threatening cardiac events compared with other mutations, and these patients gain greater benefit when treated with β-blockers compared with patients having other KCNQ1 mutations independently of clinical risk factors.[31] Mutations in these regions are responsible for the condition in 7–15% of patients with LQT1.

A **family history** of premature SCD is not an independent risk factor for subsequent lethal events in an affected individual.

Two well-defined malignant variants are the **Jervell and Lange–Nielsen** syndrome and **LQT8** due to mutations in CACNA1C (Table 57.1). In Jervell and Lange-Nielsen syndrome the first cardiac event often occurs in the first year of life and 90% of patients have syncope during their early lifetime, usually induced by exercise and emotional stress. Subgroups at relatively lower risk for sudden death are females, patients with a QTc <550 ms, those without events in the first year of life, and those with mutations on KCNE1.[4]

Genetic testing

Apart from risk stratification purposes, genetic testing is useful for the identification of concealed LQTS because individuals with genetically proven LQTS may have a non-diagnostic QTc (Table 58.3).[32,33] However, no treatment decision should be influenced solely by either the genotype or the specific LQTS-causative mutation that was identified. In particular, a decision to implant an ICD prophylactically in an asymptomatic LQT3 carrier must include risk factors besides LQT3 genotype status.[2] Genetic testing should be considered for patients with drug-induced torsade, and a 12-lead ECG is recommended for first-degree relatives.

Table 58.3 HRS/EHRS 2011 statement on genetic testing

Comprehensive or LQT1–3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing	
Any patient in whom a cardiologist has established a strong clinical index of suspicion for LQTS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative stress testing with exercise or catecholamine infusion) phenotype.	I
Any asymptomatic patient with QT prolongation in the absence of other clinical conditions that might prolong the QT interval (such as electrolyte abnormalities, hypertrophy, bundle branch block, etc., i.e. otherwise idiopathic) on serial 12-lead ECGs defined as QTc >480 ms (prepuberty) or >500 ms (adults).	I
Mutation-specific genetic testing is recommended for family members and other appropriate relatives, subsequently following the identification of the LQTS-causative mutation in an index case.	I
Any asymptomatic patient with otherwise idiopathic QTc values >460 ms (prepuberty) or >480 ms (adults) on serial 12-lead ECGs.	IIb

HRS/EHRA 2011 Expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Europace*. 2011;**13**:1077– 109 with permission from Oxford University Press.

Therapy

Beta blockers should be administered to all intermediate- or high-risk affected individuals and considered in low-risk patients, unless there is a contraindication. β adrenergic blockade may not shorten QTc at rest but suppresses cardiac events in LQT1 and LQT2, although the efficacy of β blockade is reduced in LQT2 possibly due to the resultant bradycardia. Although no randomized comparative data exist, there has been observational evidence that propranolol and nadolol are preferred over metoprolol.[34] Interestingly, in a recent registry propranolol was found the least effective beta blocker in patients who already had experienced a cardiac event, whereas nadolol was found the only effective beta blocker in LQT2.[35] Targeting of the pathologic, LQT3-associated late sodium current with propranolol (as the preferred beta blocker) and the possible addition of mexiletine, flecainide, or ranolazine represents the preferred pharmacotherapeutic option for LQT3.[4,36] Flecainide may also be useful in the Andersen–Tawil syndrome which is usually due to mutations in KCNJ2 (LQTS7).[37] Potassium supplements shorten QT interval by increasing the I_{Kr} that is inversely regulated by the concentration of extracellular potassium. This approach has been proposed for LQT2, although it has the potential to shorten QT interval in all patients with, at least, one KCNH2 wildtype (functional) allele.[36] The problem is that, in the presence of normal renal function, the additional dietary potassium load typically may be excreted without clinically significant increases in serum potassium levels. In the Jervell and Lange Nielsen

syndrome beta blockers have limited efficacy and early ICD implantation must be considered.

Implantable cardioverter defibrillators are indicated in cardiac arrest survivors and patients with recurrent syncope despite β blocker treatment and for primary prevention in high-risk patients, usually with β blockers (Table 58.4). Recent data suggest that ICDs were implanted in some LQTS patients whose high risk now appears questionable, and the following recommendations have been proposed for ICD implantation:[38,39]

- Patients who have survived a cardiac arrest on therapy
- Many of those who have survived a cardiac arrest off therapy, except those with a reversible/preventable cause, but noting that, for most LQT1 grown-up patients, full-dose beta blockers might be sufficient
- Patients who continue to have syncope, despite full-dose beta blockade, whenever the option of left cardiac sympathetic denervation is either not available or is discarded after discussion with the patients
- Patients with two mutations who continue to have syncope despite beta blockade
- Asymptomatic patients with a QTc >550 ms who also manifest signs of high electric instability (e.g. T wave alternans) or other evidence of being at very high risk (e.g. very long sinus pauses that might favour early after-depolarizations)
- The identification of LQT2 or LQT3 genotypes does not, by itself, constitute an indication of ICD implantation.[38]

Left cardiac sympathetic denervation is considered in patients with recurrent syncope, despite beta-blocker therapy, and in patients who experience arrhythmia storms with an ICD which does not offer full protection.

Permanent pacing may be needed for documented pause-dependent VT (Table 58.5). Although pacemaker implantation may reduce the incidence of symptoms in these patients, the long-term survival benefit is not proven. **RF ablation** of the torsade-triggering PVC has also been reported.[40] **Gene-specific** treatments are investigational.[2]

All LQTS patients should avoid drugs that block the I_{Kr} current (http://www.sts.org) (see also Chapter 56, Drug Induced VT).

Restriction of physical activities depends on the type of LQTS. Asymptomatic patients with short baseline QTc intervals should not be significantly restricted.[4] QTc >470 ms in male subjects or QTc >480 ms in female subjects is an indication for low-intensity only competitive sports (36th Bethesda Conference) while the ESC recommends recreational only sports in QTc >440 ms in male subjects and QTc >460 ms in female subjects.[41]

Recent data suggest that low-risk patients, with genetically confirmed LQTS (especially not LQTS1) but with borderline QTc prolongation, no history of cardiac symptoms, and no family history of multiple sudden cardiac deaths (SCD), may be allowed to participate in competitive sports in special cases after full clinical evaluation, utilization of appropriate LQTS therapy and when competitive activity is performed where automated external defibrillators are available and personnel trained in basic life support.[42] Avoidance of all QT-prolonging medications (see Chapter 56) is advisable to all LQTS patients.

Table 58.4 Therapy of long QT syndrome

ACCF/AHA/HRS 2012 on device therapy. Indications for ICD	
LQTS and syncope and/or sustained VT on beta blockers.	IIa-C
HRAS/EHRA/APHRS 2013 statement on inherited primary arrhythmia syndromes Recommendations on LQTS therapeutic interventions	
The following lifestyle changes are recommended in all patients with a diagnosis of LQTS: a) Avoidance of QT prolonging drugs (www.qtdrugs.org) b) Identification and correction of electrolyte abnormalities that may occur during diarrhoea, vomiting, metabolic conditions or imbalanced diets for weight loss.	I
Beta-blockers for patients with a diagnosis of LQTS who are: a) Asymptomatic with QTc > 470 ms, *and/or* b) Symptomatic for syncope or documented VT/VF.	I
Left cardiac sympathetic denervation (LCSD) for high-risk patients with a diagnosis of LQTS in whom: a) ICD therapy is contraindicated or refused, *and/or* b) Beta-blockers are either not effective in preventing syncope/ arrhythmias, not tolerated, not accepted or contraindicated.	I
ICD for patients with a diagnosis of LQTS who are survivors of a cardiac arrest.	I
All LQTS patients who wish to engage in competitive sports should be referred to a clinical expert for evaluation of risk.	I
Beta-blockers in patients with a diagnosis of LQTS who are asymptomatic with QTc < 470ms.	IIa

(*Continued*)

Table 58.4 Continued

ICD in patients with a diagnosis of LQTS who experience recurrent syncopal events while on beta-blocker therapy.	IIa
LCSD in patients with a diagnosis of LQTS who experience breakthrough events while on therapy with beta-blockers/ICD.	IIa
Sodium channel blockers, as add-on therapy, for LQT3 patients with a QTc 500 ms who shorten their QTc by > 40 ms following an acute oral drug test with one of these compounds.	IIa
Except under special circumstances, ICD implantation is not indicated in asymptomatic LQTS patients who have not been tried on beta-blocker therapy.	III
ESC 2015 GL on VA and SCD. Risk stratification and management in long QT syndrome	
Lifestyle changes: (a) Avoidance of QT-prolonging drugs (http://www.crediblemeds.org). (b) Correction of electrolyte abnormalities (hypokalaemia, hypomagnesaemia, hypocalcaemia) that may occur during diarrhoea, vomiting or metabolic conditions. (c) Avoidance of genotype-specific triggers for arrhythmias (strenuous swimming, especially in LQTS1, and exposure to loud noises in LQTS2 patients).	I-B
Beta-blockers in a clinical diagnosis of LQTS.	I-B
ICD implantation with the use of beta-blockers in LQTS patients with previous cardiac arrest.	IIa-B
Beta-blockers in carriers of a causative LQTS mutation and normal QT interval.	
ICD implantation in addition to beta-blockers in LQTS patients who had syncope and/or VT on an adequate dose of beta-blockers.	IIa-B
Left cardiac sympathetic denervation in patients with symptomatic LQTS when (a) Beta-blockers are either not effective, not tolerated or contraindicated; (b) ICD therapy is contraindicated or refused; (c) Patients on beta-blockers with an ICD experience multiple shocks.	IIa-C
Sodium channel blockers (mexiletine, flecainide or ranolazine) as add-on therapy to shorten the QT interval in LQTS3 patients with a QTc >500 ms.	IIb-C
ICD implantation in addition to beta-blockers in asymptomatic carriers of a pathogenic mutation in KCNH2 or SCN5A when QTc is >500 ms.	IIb-C

ACCF/AHA/HRS 2012 Focused Update Incorporated Into the ACCF/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2013;**61**: e6–e75 with permission for Elsevier.
HRS/EHRA/APHRS 2013 Expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Heart Rhythm*. 2013;**10**:1932–63 with permission from Elsevier.
ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015;**36**: 2793–2867 with permission from Oxford University Press.

Table 58.5 ACCF/AHA/HRS 2012 GL on device therapy

Recommendations for pacing to prevent tachycardia	
Permanent pacing for sustained pause-dependent VT, with or without QT prolongation.	I-C
Permanent pacing for high-risk patients with congenital long QT syndrome.	IIa-C
Permanent pacing for prevention of symptomatic, drug-refractory, recurrent AF in patients with coexisting SND.	IIb-B
Permanent pacing for frequent or complex ventricular ectopic activity without sustained VT in the absence of the long QT syndrome.	III-C
Permanent pacing for torsade de pointes VT due to reversible causes.	III-A

ACCF/AHA/HRS 2012 Focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2013;**61**: e6–e75 with permission for Elsevier.

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Chapter 59

Short QT syndrome

Definition

Short QT syndrome (SQTS) is characterized by abnormally short QT interval (<330 ms), with an increased propensity to atrial and ventricular arrhythmias and a high risk of sudden death (Table 59.1).[1,2]

Genetics and pathophysiology

Gain-of-function mutations affecting the I_{Kr}, I_{Ks}, I_{K1}, and I_{Ca} currents are responsible for heterogenous repolarization and refractoriness that may predispose to arrhythmia (Figure 59.1). However, none of the known disease-

Table 59.1 Diagnosis of SQTS

HRAS/EHRA/APHRS 2013 statement on inherited primary arrhythmia syndromes. Short QT syndrome diagnosis	
SQTS is diagnosed in the presence of a QTc < 330 ms.	
SQTS can be diagnosed in the presence of a QTc < 360 ms and one or more of the following:	
a pathogenic mutation	
family history of SQTS	
family history of sudden death at age <40	
survival of a VT/VF episode in the absence of heart disease.	
ESC 2015 GL on VA and SCD. Diagnosis of short QT syndrome	
QTc ≤340 ms	I-C
SQTS should be considered with a QTc ≤360 ms and one or more of the following: (a) A confirmed pathogenic mutation (b) A family history of SQTS (c) A family history of sudden death at age <40 years (d) Survival from a VT/VF episode in the absence of heart disease.	IIa-C

HRS/EHRA/APHRS 2013 Expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Heart Rhythm*. 2013;**10**:1932–63 with permission from Elsevier.
ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015;**36**: 2793–2867 with permission from Oxford University Press.

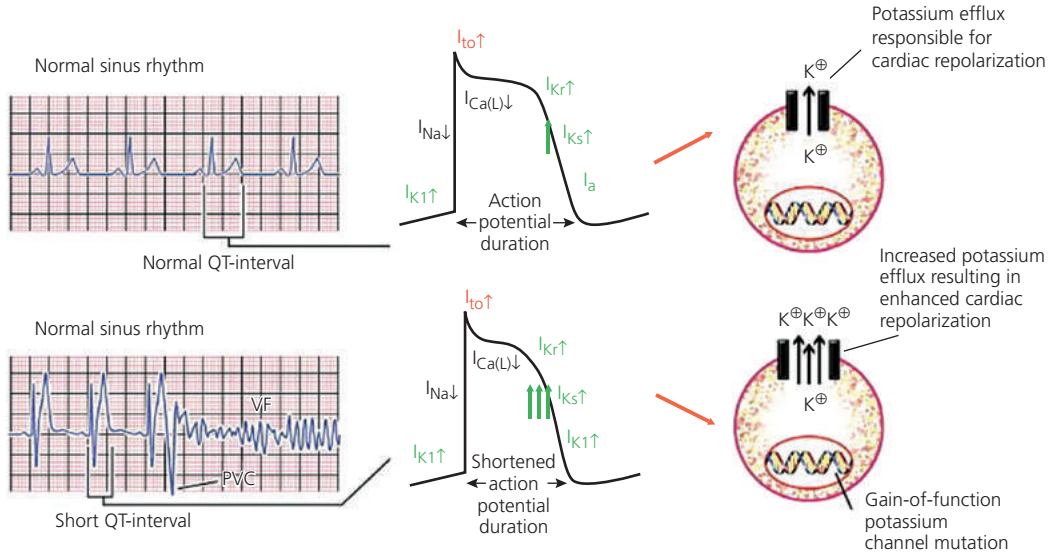

Figure 59.1 Cellular mechanism of short QT interval. A gain-of-function potassium channel mutation results in an increased efflux of potassium current from the cell, resulting in an acceleration of cardiomyocyte repolarization and a shortened action potential duration. Additional cellular mechanisms, possibly due to non-potassium channels, remain to be elucidated.

Gollob MH, *et al*. The short QT syndrome: proposed diagnostic criteria. *J Am Coll Cardiol*. 2011;**57**:802–12 with permission from Elsevier.

associated genes has been shown to account for ≥5% of this disease.[3] Rufinamide, an antiepileptic drug, has been recently shown to significantly shorten the QT interval although not necessarily associated with significant clinical adverse effects.[4] Increasing doses of bupropion have also been found to significantly decrease QTc.[5] In the general population, an increased risk of cardiovascular disease has been observed for both very short and long QT interval.[6]

Presentation

Cardiac arrest is often the first manifestation of the disease, particularly in the first year of life (rate of cardiac arrest 4%), and between 20 and 40 years (rate of cardiac arrest is 1.3% per year).[2,7] Patients often have permanent or paroxysmal **atrial fibrillation** (24%) and occasionally have **depression of the PR** interval. **Tall, peaked T waves** without flat ST segments and impaired rate-dependent QT shortening have been recorded (Figure 59.2). Most events occur during rest, sleep or ordinary activities.[7]

Diagnosis

- Short QTc interval (<330 ms) with J-point to T-wave peak <120 ms.
- Syncope and/or family history of syncope
- Episodes of VF or polymorphic VT and AF (AF and VF can be induced easily by programmed electrical stimulation)
- No obvious heart disease or extracardiac conditions that abbreviate QT interval
- Specific electrocardiographic and clinical diagnostic criteria are presented in Table 59.1.[8] An additional ECG stigma is PQ segment depression ≥0.05 mV (0.5 mm).[9]

Secondary causes of a short QT include hyperkalaemia, hypercalcaemia, acidosis, catecholamines, digitalis, rufinamide (a recently FDA-approved anticonvulsant), and hyperthermia. Ischaemia-induced activation of the K_{ATP} channel and parasympathetic activation of the KA-Ch channel (deceleration-dependent QT shortening) may also cause QT shortening.[10]

Indications for **genetic testing** are presented in Table 59.2.

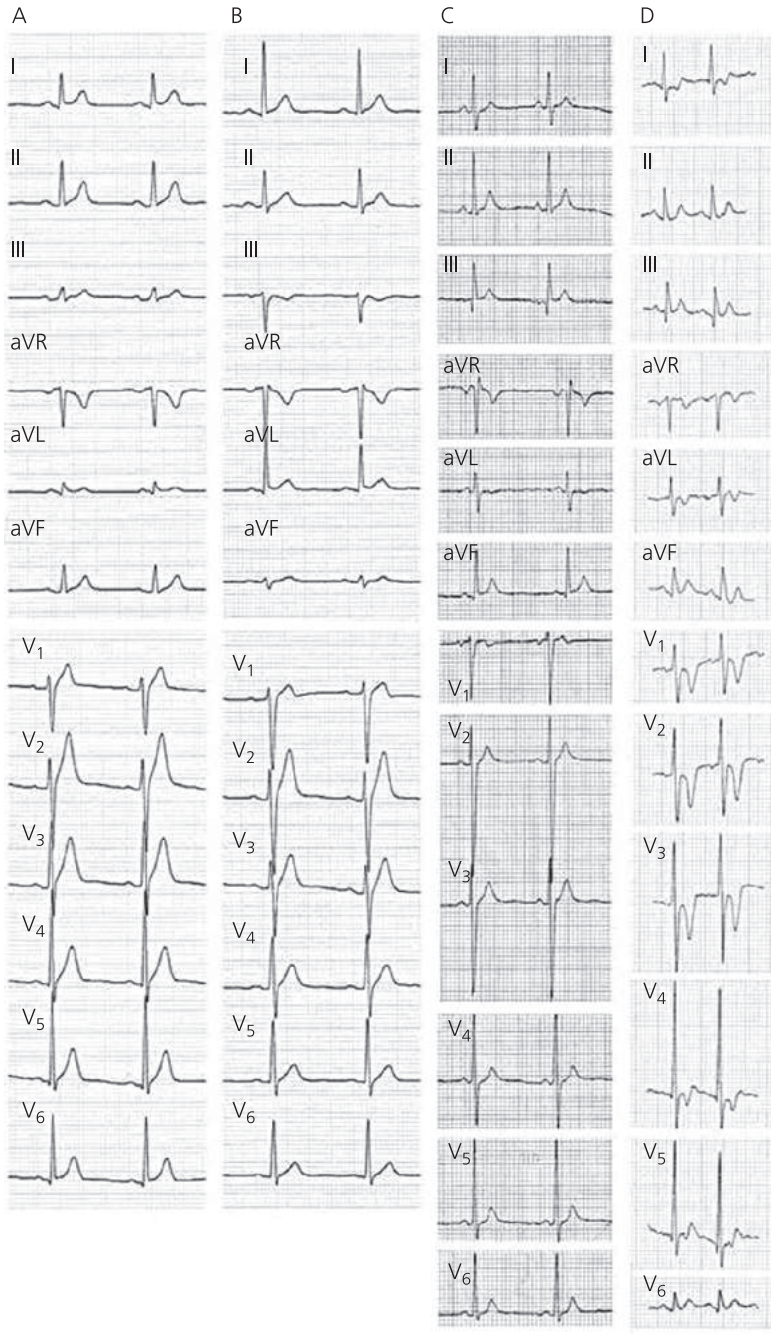

Figure 59.2 ECG of four patients with SQTS. A: 50 years, QTc 313 ms; B: 39 years, QTc 311 ms; C: 6 years, QTc 293 ms; D: 35 months, QTc 324 ms. Heart rate is 143 bpm. The deep negative T waves in leads V_1–V_3 are the equivalent of the high peaked T waves in adult patients.

Giustetto C, *et al*. Short QT syndrome: clinical findings and diagnostic-therapeutic implications. *Eur Heart J*. 2006;**27**: 440–47, with permission from Oxford University Press.

Table 59.2 HRS/EHRA 2011 statement on genetic testing

State of genetic testing for short QT syndrome	
Mutation-specific genetic testing for family members and appropriate relatives following the identification of the SQTS-causative mutation in an index case.	I
Comprehensive or SQT1–3 (KCNH2, KCNQ1, and KCNJ2) targeted SQTS genetic testing may be considered for any patient in whom a cardiologist has established a strong clinical index of suspicion for SQTS based on examination of the patient's clinical history, family history, and electrocardiographic phenotype.	IIb

HRS/EHRA 2011 Expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Heart Rhythm*. 2011;**8**:1308–39 with permission from Elsevier.

Therapy

It is poorly defined (Table 59.3). The sensitivity of electrophysiology study for VF inducibility is about 50%, and non-inducibility does not rule out risk of SCD. Thus, **ICD** may be needed especially in the case of documented previous cardiac arrest.[2,7] T wave oversensing may result in inappropriate shocks and requires careful programming. SCD may occur in young males with a Gollob score >5 (Table 59.1),[11] although the prognostic value of this score has not been verified in other series.[2]

Females are less prone to arrhythmic events, probably due to oestrogen induced QT prolongation, but they can still suffer cardiac arrest.[7] **Quinidine** can be efficacious in SQTS by prolonging the QT interval, normalizing the QT response to RR interval change and preventing cardiac events in some patients.[12] It is proposed for children or patients refusing an ICD.[13] I_{Kr} blockers, such as sotalol, may fail to normalize the QT interval in patients with SQTS. Disopyramide and amiodarone might also be helpful, and propafenone is effective in preventing AF.[10]

Table 59.3 Therapy

HRAS/EHRA/APHRS 2013 statement on inherited primary arrhythmia syndromes. Short QT syndrome therapeutic interventions.	
ICD implantation in symptomatic patients with a diagnosis of SQTS who: a. Are survivors of a cardiac arrest and/or b. Have documented spontaneous sustained VT with or without syncope.	I
ICD in asymptomatic patients with a diagnosis of SQTS and a family history of SCD.	IIb
Quinidine in asymptomatic patients with a diagnosis of SQTS and a family history of SCD.	IIb
Sotalol in asymptomatic patients with a diagnosis of SQTS and a family history of SCD.	IIb
ESC 2015 GL on VA and SCD. Risk stratification and management in short QT syndrome.	
ICD in patients with a diagnosis of SQTS who: (a) Are survivors of an aborted cardiac arrest, and/or (b) Have documented spontaneous sustained VT.	I-C
Quinidine or sotalol in patients with a diagnosis of SQTS who qualify for an ICD but present a contra-indication to the ICD or refuse it.	IIb-C
Quinidine or sotalol in asymptomatic patients with a diagnosis of SQTS and a family history of SCD.	IIb-C
Invasive EPS with PVS is not recommended for SCD risk stratification.	III-C

HRS/EHRA/APHRS 2013 Expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Heart Rhythm*. 2013;**10**:1932–63 with permission from Elsevier.
ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015;**36**: 2793–2867, with permission from Oxford University Press.

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Chapter 60

Brugada syndrome

Definition

The Brugada syndrome is defined as ST segment elevation in the right precordial leads (V_1–V_3) that is unrelated to ischaemia, electrolyte disturbances, or structural heart disease, and is associated with a high incidence of sudden death due to ventricular arrhythmias.[1,2]

Epidemiology

The prevalence of the disease in the general population cannot be accurately assessed due to the dynamic nature of the ECG pattern that can fluctuate over time but is estimated to be 1/5000–10 000 inhabitants in the western world, being 8–10 times more prevalent in males than in females.[1] It is probably more frequent in the Far Eastern countries (initially described as sudden unexplained death syndrome).[3] An increased prevalence of Brugada-type ECG has been observed among patients with schizophrenia.[4] Inheritance in Brugada syndrome occurs as an autosomal dominant trait. In up to 60% of patients, the disease can be sporadic, i.e. absent in parents and other relatives. Patients with Brugada syndrome have an annual incidence of cardiac arrest between 1 and 2%.[5]

Genetics and pathophysiology

The pathophysiological mechanism of the Brugada syndrome is rather elusive, and it has been proposed that the ECG manifestations are the phenotype of a multitude of possible aetiologies.[6] However, it seems that slow discontinuous conduction and steep dispersion of repolarization, that are mainly present in the right ventricular outflow tract and can promote sustained reentry, are the underlying electrophysiologic mechanisms of Brugada syndrome.[7] Genetic mutations in 15 genes that alter ion channel functions have been identified may also affect the QT interval (Table 57.1 of Chapter 57). The first identified mutations were located in *SCN5A*, the gene encoding the α subunit of the cardiac sodium channel ($Na_v1.5$), leading to reduced cardiac sodium current (I_{Na}). Sodium loss-of-function conditions create an imbalance between outward and inward positive currents during phase 1, enhancing repolarization and resulting in the appearance of a particular notch in the action potential mediated by the transient outward potassium current (I_{to}). This gives rise to a transmural voltage gradient between the epicardium and endocardium, resulting in the characteristic ST segment elevation and propensity to ventricular arrhythmias, probably through phase 2 reentry mechanisms. The depolarization hypothesis underlines the role of conduction delay induced by SCN5A mutations, particularly in the RVOT.[1] Mutations in the SCN5A gene account for 11–28% of clinically diagnosed patients,[8] but recently, *SCN10A* was also identified as a major susceptibility gene with a yield up to 17%.[9] Mutations in the plakophilin-2 (*PKP2*) gene that reduce I_{Na} may also yield a Brugada syndrome phenotype.[10]

Other mutations affecting calcium and potassium channels or acting through other mechanisms have also been described but are rare. Overall, more than 300 mutations have been so far identified and can be found in 50% of patients with Brugada syndrome.[9] Delayed onset of right ventricular contraction that can be seen on echocardiography suggest that structural abnormalities are intrinsic to the syndrome and question its characterization as a mere channelopathy.[6] This notion was also supported by the reported efficacy of epicardial RVOT ablation in patients with Brugada syndrome.[11]

Presentation

The syndrome typically manifests during adulthood, with either detection of the typical ECG pattern (type 1) or development of polymorphic VT or VF in 10–25% of patients during their lifetime.[12,13] Sudden cardiac death may occur typically at rest or during sleep and is precipitated by fever or the consumption of large meals, presumably due to glucose-induced insulin secretion, that may enhance ST segment elevation.[14] Syncopal episodes, nocturnal agonal respiration, palpitations and chest discomfort may also occur. Patients may also be entirely asymptomatic, and approximately 20% of them develop supraventricular arrhythmias, such as **AF or atrial flutter, or sick sinus syndrome**. New-onset AF may be the first clinical manifestation of Brugada syndrome.[12]

Diagnosis

Diagnostic criteria are presented in Table 60.1. Placement of the right precordial leads in a superior position can increase the sensitivity of the ECG for detecting the Brugada phenotype, both in the presence or absence of a drug challenge. Conditions that are associated with ST segment elevation (Table 60.2) should be ruled out. A variety of drugs have also been reported to produce a Brugada-like ST segment elevation (Table 60.3), although it is not yet clear whether, or to what extent, a genetic predisposition may be involved.[3] Recent data suggest that lead V_3 does not yield diagnostic information; typical ECG changes in only one of V_1 or V_2 leads should be enough for diagnosis.[15]

Three repolarization patterns are described (Figure 60.1):

- **Type-1 ECG pattern** Coved ST segment elevation ≥2 mm followed by a negative T wave, with little or no isoelectric separation, in >1 right precordial leads (from V_1 to V_3), imitating incomplete right bundle branch block but without the typical widened S wave in the left lateral lead
- **Type-2 ECG pattern** ST segment elevation followed by a positive or biphasic T wave with a saddleback configuration
- **Type-3 ECG pattern** Right precordial ST segment elevation ≤1 mm with either a coved-type or a saddleback morphology.

The ECG typically fluctuates over time in Brugada patients and thus can change from type-1 to type-2 or type-3, or even be transiently normal. Vagal manoeuvres, heavy meals, and beta blockers accentuate the ECG patterns. Only the coved-type ST segment elevation (type-1 ECG pattern) is diagnostic of the syndrome in the presence of clinical criteria described in Table 60.1. Mild prolongation of the PR interval may also be seen.

Patients displaying the characteristic type-2 or -3 ECG without further clinical criteria should be described as having ***Brugada ECG pattern*** and not Brugada syndrome, unless the administration of sodium channel blockers reveals a typical type-1 pattern. Brugada-like ECG can occasionally appear after direct current cardioversion or with the administration of certain drugs that probably should be avoided in diagnosed cases of the syndrome (Table 60.3), but it is not known whether a genetic predisposition is involved. Another confounding factor is the type of ST segment elevation encountered in well-trained athletes (Figures 60.2 and 60.3), which is distinguished by an upslope, rather than a downslope, pattern and by remaining largely unaffected by challenge with a sodium channel blocker (see also Chapter 81 on athlete's heart). Brugada syndrome can be masked by complete RBBB. For diagnosis, relief of RBBB, demonstration of typical ST-segment elevation on repeated ECG recordings, pharmacological tests, or pacing from the right ventricle can be useful (Figure 60.4).[16] Type-2 Brugada pattern presents characteristically an r′-wave in leads V_1–V_2 that may be confused with incomplete RBBB, pectus excavatum, ARVC/D, and athlete's ECG. A duration of the base of the triangle at 0.5 mV from the high take-off ≥160 ms (4 mm) in V_1 and/or V_2 identifies a Brugada pattern (Figure 60.5).[17]

Pharmacological challenge. Drugs used are:

- Ajmaline 1 mg/kg over 5 min IV (probably the best for this purpose)
- Flecainide 2 mg/kg over 10 min IV or 400 mg po
- Procainamide 10 mg/kg over 10 min IV
- Pilsicainide 1 mg/kg over 10 min IV.

In young patients, it can be performed as a bedside test. A pacing electrode may be necessary in patients at high risk for AV block. The pharmacological test should be monitored with a continuous ECG recording and should be terminated when: (1) the diagnostic test is positive; (2) premature ventricular beats or other arrhythmias develop; (3) QRS widens to ≥130% of baseline. Isoproterenol is the antidote when required.

Sodium channel blockade may provoke the Brugada ECG pattern in conditions, such as ARVC/D and Chagas' disease.[5]

Electrophysiology study The value of programmed ventricular stimulation (2–3 extrastimuli from the apex and RVOT) is still controversial (see risk stratification).

Noninvasive mapping with electrocardiographic imaging may also assist differentiation between Brugada syndrome and RBBB.[7]

Echocardiography may reveal the delayed onset of right ventricular contraction that reflects delayed depolarization over the anterior aspect of the RVOT epicardium.

Exercise testing is useful for risk stratification. Augmented ST-segment elevation during recovery from exercise predicts cardiac events.[18]

Genetic testing indications are presented in Table 60.4.[19] The yield of genetic testing approaches 40% for SCN5A-mediated BrS (BrS1) when the PQ interval exceeds 200 ms.[20] The recent identification of SCN10A as a major susceptibility gene raises the possibility of identifying a genotype in more than 50% of Brugada syndrome probands.[9] However, genetic test results should be interpreted in the context of the fact that 2% of healthy Caucasians and 5% of healthy non-white subjects also host rare missense SCN5A variants.[8]

Table 60.1 Diagnosis of Brugada syndrome

HRAS/EHRA/APHRS 2013 statement on inherited primary arrhythmia syndromes	
1. BrS is diagnosed in patients with ST segment elevation with type 1 morphology > 2 mm in > 1 lead among the right precordial leads V1,V2, positioned in the 2nd, 3rd or 4th intercostal space occurring either spontaneously or after provocative drug test with intravenous administration of Class I antiarrhythmic drugs.	
2. BrS is diagnosed in patients with type 2 or type 3 ST segment elevation in > 1 lead among the right precordial leads V1,V2 positioned in the 2nd, 3rd or 4th intercostal space when a provocative drug test with intravenous administration of Class I antiarrhythmic drugs induces a type 1 ECG morphology	
ESC 2015 GL on VA and SCD	
ST-segment elevation with type 1 morphology ≥2 mm in one or more leads among the right precordial leads V1 and/or V2 positioned in the second, third, or fourth intercostal space, occurring either spontaneously or after provocative drug test with IV sodium channel blockers (such as ajmaline, flecainide, procainamide or pilsicainide).	I-C

HRS/EHRA/APHRS 2013 Expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Heart Rhythm*. 2013;**10**:1932–63 with permission from Elsevier.
ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015;**36**:2793–2867.

Table 60.2 Conditions that can lead to ST segment elevation in V_1–V_3

Atypical right bundle branch block
Hyperkalaemia
Hypercalcaemia
Hypothermia
Left ventricular hypertrophy
Early repolarization, especially in athletes
Acute pericarditis
Acute myocardial infarction (especially of RV)
Pulmonary embolism
Dissecting aortic aneurysm
Duchenne muscular dystrophy
Thiamine deficiency
Arrhythmogenic right ventricular cardiomyopathy
Pectus excavatum
Mechanical compression of the right ventricular outflow tract (mediastinal tumour or haemopericardium)

Table 60.3 Drug-induced Brugada-like ECG patterns

1. Antiarrhythmic drugs
Na^+ channel blockers
Class IC drugs (flecainide, pilsicainide, propafenone)
Class IA drugs (ajmaline, procainamide, disopyramide, cibenzoline)
Ca^{2+} channel blockers, beta blockers
2. Nitrates
3. K^+ channel openers (nicorandil)
4. Psychotropic drugs
Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, clomipramine)
Tetracyclic antidepressants (maprotiline)
Phenothiazine (perphenazine, cyamemazine)
Selective serotonin reuptake inhibitors (fluoxetine)
5. Other drugs
Dimenhydrinate
Cocaine
Alcohol intoxication

Antzelevitch C, *et al*. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation*. 2005;**111**:659–70 with permission from Wolters Kluwer.

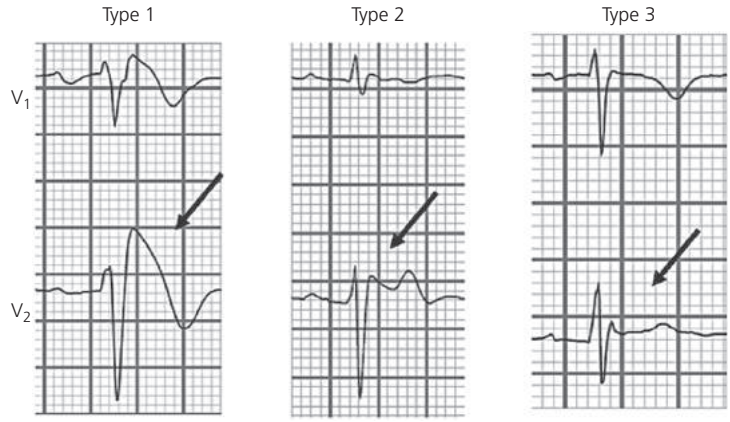

Figure 60.1 ECG abnormality diagnostic or suspected of Brugada syndrome. Type-1 ECG (coved-type ST segment elevation) is the only diagnostic ECG in Brugada syndrome and is defined as a J wave amplitude or an ST segment elevation of ≥2 mm or 0.2 mV at its peak (followed by a negative T wave, with little or no isoelectric separation). Type-2 ECG (saddleback-type ST segment elevation), defined as a J wave amplitude of ≥2 mm, gives rise to a gradually descending ST segment elevation (remaining ≥1 mm above the baseline), followed by a positive or biphasic T wave that results in a saddleback configuration. Type-3 ECG is a right precordial ST segment elevation (saddleback type, coved-type, or both) without meeting the aforementioned criteria.

Mizusawa Y, Wilde AA. Brugada syndrome. Circ Arrhythm *Electrophysiol*. 2012;**5**:606–16 with permission from Wolters Kluwer.

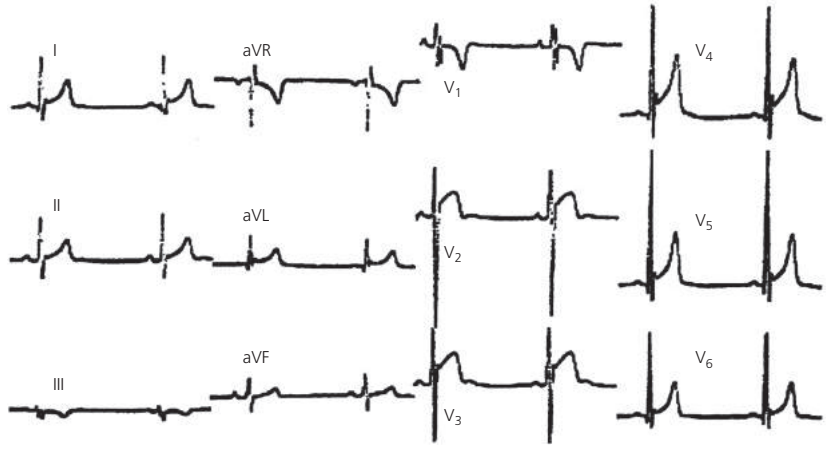

Figure 60.2 ECG of a well-trained, asymptomatic 24-year-old soccer player. ST segment elevation is observed in V_2 to V_6 but with characteristics totally different from those seen in Brugada syndrome. A coved-type ST segment elevation is not observed. A rounded or upsloping ST elevation in seen in V_2 and V_3, whereas V_4 to V_5 show a pattern resembling that commonly encountered in early repolarization syndrome.

Antzelevitch C, *et al*. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation*. 2005;**111**:659–70 with permission from Wolters Kluwer.

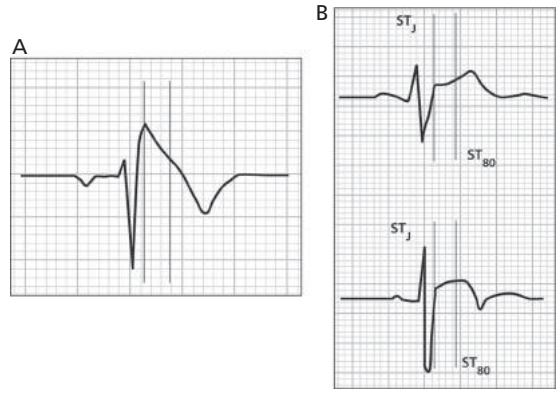

Figure 60.3 Differential diagnosis between representative right precordial ECG patterns from (A) a Brugada patient and (B) two trained athletes. Vertical lines mark the J-point (STJ) and the point 80 ms after the J-point (ST80) where the amplitudes of ST-segment elevation are calculated. 'Coved' type ST-segment elevation in the patient with Brugada syndrome is characterized by a 'downsloping' elevated ST-segment with a STJ/ST_{80} ratio of 1.9. Right precordial early repolarization patterns in both athletes show an 'upsloping' ST-segment elevation with STJ/ST_{80} ratio <1; 0.7 for the 'concave' toward the top (B, top) and 0.68 for the 'convex' toward the top (B, bottom) ST-segment elevation.

European Association of Cardiovascular Prevention and Rehabilitation. Recommendations for interpretation of 12-lead electrocardiogram in the athlete. *Eur Heart J.* 2010;**31**:243–59 with permission from Oxford University Press.

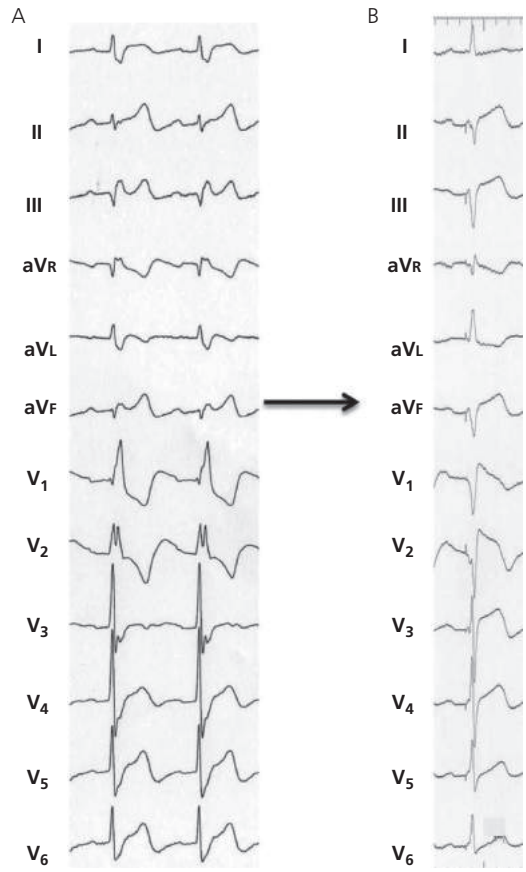

Figure 60.4 The complete RBBB pattern at baseline (A) was normalized by right ventricular pacing (B). The QRS became narrow with left-axis deviation, and leads V_1 and V_2 showed coved-type ST-segment elevation (B).

Aizawa Y, *et al.* Brugada syndrome behind complete right bundle-branch block. *Circulation*. 2013;**128**:1048–54 with permission from Wolters Kluwer.

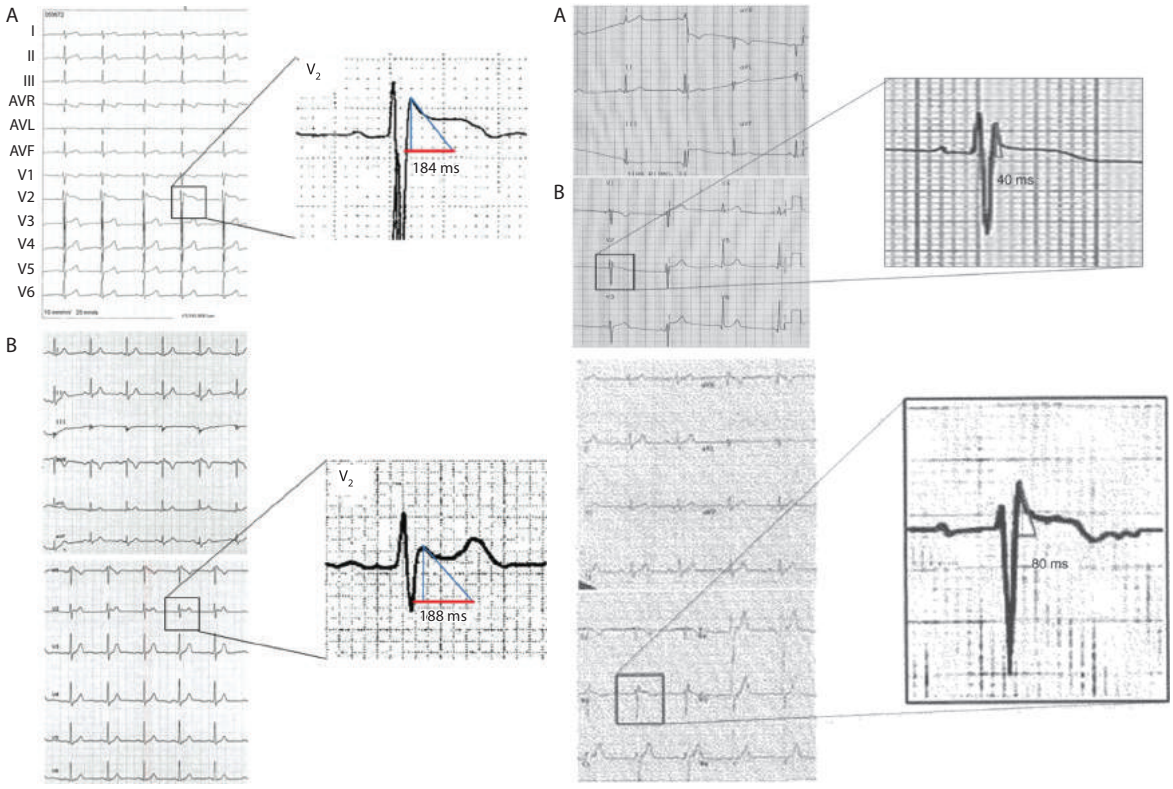

Figure 60.5 Left panel: two examples of healthy athletes' ECG. (A) Healthy athlete with ST–T elevation and r'-wave, but with a base of the triangle at 0.5 mV, measuring 40 ms (1 mm). (B) Electrocardiogram of a healthy athlete with similar ST–T morphology and the base of the triangle measuring 80 ms (2 mm). Right panel: two examples of type-2 Brugada ECG pattern. (A) Type-2 Brugada pattern with the base of the triangle at 0.5 mV, measuring 184 ms (4.6 mm). (B) Type-2 Brugada pattern with the base of the triangle at 0.5 mV, measuring 188 ms (4.7 mm).

Serra G, *et al*. New electrocardiographic criteria to differentiate the Type-2 Brugada pattern from electrocardiogram of healthy athletes with r'-wave in leads V1/V2. *Europace*. 2014;**16**:1639–45 with permission from Oxford University Press.

Table 60.4 HRS/EHRA 2011 statement on genetic testing

Stage of genetic testing for Brugada syndrome (BrS)	
Mutation-specific genetic testing for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case.	I
Comprehensive or BrS1 (SCN5A) targeted BrS genetic testing for any patient in whom a cardiologist has established a clinical index of suspicion for BrS, based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative drug challenge testing) phenotype.	IIa
Genetic testing is not indicated in the setting of an isolated type-2 or type-3 Brugada ECG pattern.	III

HRS/EHRA 2011 Expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Europace*. 2011;**13**:1077–109 with permission from Oxford University Press.

Risk stratification

Previous history of cardiac arrest or syncope, a spontaneous type-1 ECG at baseline, and male gender have been shown to be related to the occurrence of cardiac events during follow-up.[21,22] Patients with aborted sudden death have a cardiac event rate of 7.7%/year, whereas asymptomatic patients with Brugada syndrome have a low although not negligible arrhythmic event rate (0.5–1%/year).[13,22] The presence or absence of a family history of SCD does not carry prognostic ability.[23] The inducibility of ventricular arrhythmias during the EPS (class IIb indication) may also bear ominous prognosis,[21,24,25] but this is disputed.[13,26,27] VF may be induced in up to 9% of apparently healthy individuals when aggressive stimulation protocols are used.[12] In the FINGER registry, inducibility of sustained ventricular arrhythmias was significantly associated with a shorter time to the first arrhythmic event in the univariate analysis,

but in the multivariate analysis, it did not predict arrhythmic events.[13] The PRELUDE registry reported their results on 208 patients followed for approximately 3 years. VT/VF inducibility was unable to identify high-risk patients, whereas the presence of a spontaneous type I ECG, history of syncope, ventricular effective refractory period <200 ms, and QRS fragmentation (Figure 60.6) were indicators of high risk.[26,27] However, in a recent study on a large patient cohort, induced ventricular arrhythmias (stimulation at the apex only) were associated with increased risk of arrhythmic events during long-term follow-up.[25] The combination of a fragmented QRS with an inferolateral early repolarization pattern (Figure 60.7), may also confer an adverse prognostic significance.[28] Type 1 ST elevation in the limb ECG leads can be seen in 10% of the patients with Brugada syndrome and is an independent predictor for a malignant arrhythmic event.[29] Augmentation of ST segment elevation ≥0.05 mV in V_1 to V_3 leads, observed at early recovery (1–4 min) after treadmill exercise, has been reported to predict future arrhythmic events.[18] The prognostic significance of NSVT is not known, but syncope indicates high risk and could be due to sustained or long runs of non-sustained VT. The value of risk stratification in Brugada syndrome, in general, is low.[30]

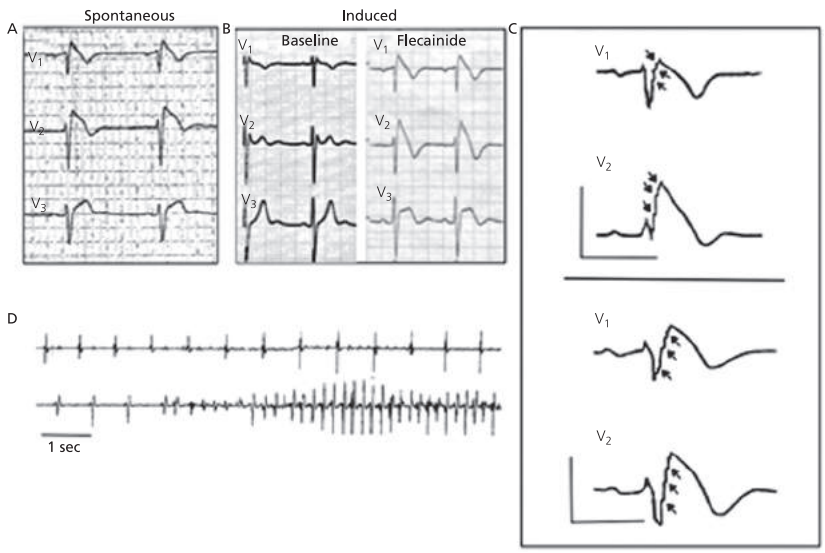

Figure 60.6 Examples of electrocardiographic (ECG) traces (A to C). (A) A 35-year-old male patient presenting with spontaneous type-1 ECG. (B) A 30-year-old male patient presenting with type-3 ECG (left panel), converted to type-1 after 2 mg/L intravenous flecainide (right panel). (C) V_1 and V_2 leads of two patients with spontaneous ST segment elevation presenting with QRS fragmentation at enrolment; arrows indicate the QRS peaks (calibration bars 10 mV/400 ms). (D) Implantable cardioverter-defibrillator-stored ventricular fibrillation in a PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) patient.

Napolitano C, *et al*. Sudden cardiac death: Sudden cardiac death and genetic ion channelopathies. *Circulation*. 2012;**125**:2027–34 with permission from Wolters Kluwer.

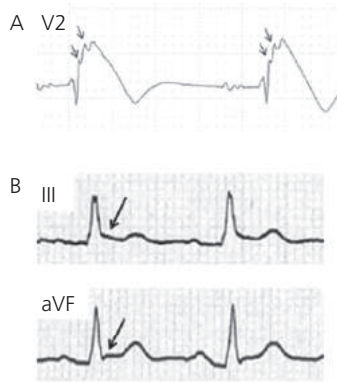

Figure 60.7 Representative ECGs of fragmented QRS (f-QRS) and early repolarization (ER). (A) Fragmented QRS (f-QRS) was observed in lead V_2. Note that there are four spikes (arrows) in this lead. (B) Early repolarization (ER) pattern in the inferior leads. Note that the J-point elevation above the baseline (>1 mm) can be seen in leads III and aVF.

Tokioka K, *et al*. Electrocardiographic parameters and fatal arrhythmic events in patients with Brugada syndrome: combination of depolarization and repolarization abnormalities. *J Am Coll Cardiol*. 2014;**63**:2131–8 with permission from Elsevier.

Therapy

Cardiac arrest or syncope in the presence of a diagnostic ECG are indications for ICD (Table 60.5). These patients have a 48% and 19% chance of appropriate shock within the next 10 years, respectively.[22] The decision to implant an ICD should be weighted against a reported 36% risk of complications such as lead failure and inappropriate shocks.[22] T-wave oversensing is a potential reason of inappropriate shocks, and its incidence is significantly lower using an integrated bipolar lead system when compared with a dedicated bipolar lead system.[31] Avoidance of ICD implantation, or replacement may be considered in elderly BrS patients who remain free from VF until 70 years of age.[32] Quinidine, a drug with I_{to} blocking properties, has been successfully tried, but the evidence for its widespread use is not sufficient.[33] Quinidine-induced diarrhoea is treated with colestyramine.[1] Denopamine, cilostazol, and bepridil have also been proposed for VF suppression.[1] Controversy exists about asymptomatic patients with a spontaneous type-1 ECG at baseline or after pharmacological challenge.[5,21,24]

Catheter ablation over the epicardial RVOT has been recently reported to result in normalization of the Brugada ECG pattern and prevent clinical and inducible VT/VF.[11] Drugs that should be avoided in Brugada syndrome are listed on http://www.brugadadrugs.org.

Although a clear association between exercise and sudden death has not been established in Brugada syndrome, the ESC and the 36th Bethesda Conference recommend abstinence from competitive sports.[34] Recommendations to these patients should be better individualized.[7]

Table 60.5 Therapy of Brugada syndrome

ACCF/AHA 2012 GL on device therapy. Indications for ICD	
Brugada syndrome and syncope or documented VT	IIa-C
HRAS/EHRA/APHRS 2013 statement on inherited primary arrhythmia syndromes Recommendations on Brugada syndrome therapeutic interventions	
The following lifestyle changes are recommended in all patients: avoidance of drugs that may induce or aggravate ST segment elevation in right precordial leads (for example, visit Brugadadrugs.org), avoidance of excessive alcohol intake, immediate treatment of fever with antipyretic drugs.	I
ICD in patients who are survivors of a cardiac arrest, and/or have documented spontaneous sustained VT with or without syncope.	I
ICD implantation in patients with a spontaneous diagnostic Type I ECG and a history of syncope judged to be likely caused by ventricular arrhythmias.	IIa
Quinidine in patients with a history of arrhythmic storms defined as more than two episodes of VT/VF in 24 hours, who qualify for an ICD but present a contraindication to the ICD or refuse it, and/or have a history of documented supraventricular arrhythmias that require treatment.	IIa

(*Continued*)

Table 60.5 Continued

Isoproterenol infusion in suppressing arrhythmic storms	IIa
ICD implantation in patients who develop VF during programmed electrical stimulation (inducible patients).	IIb
Quinidine in asymptomatic patients with a spontaneous type 1 ECG.	IIb
Catheter ablation in patients with a history of arrhythmic storms or repeated appropriate ICD shocks.	IIb
ICD is not indicated in asymptomatic BrS patients with a drug induced type 1 ECG and on the basis of a family history of SCD alone.	III
ESC 2015 GL on VA and SCD. Risk stratification and management in Brugada Syndrome.	
Recommended lifestyle changes: (a) Avoidance of drugs that may induce ST-segment elevation in right precordial leads (http:// www.brugadadrugs.org) (b) Avoidance of excessive alcohol intake and large meals (c) Prompt treatment of any fever with antipyretic drugs.	I-C
ICD in patients with a diagnosis of Brugada syndrome who: (a) Are survivors of an aborted cardiac arrest and/or (b) Have documented spontaneous sustained VT.	I-C
ICD in patients with a spontaneous diagnostic type I ECG pattern and history of syncope.	IIa-C
Quinidine or isoproterenol to treat electrical storms.	IIa-C
Quinidine in patients who qualify for an ICD but present a contraindication or refuse it and in patients who require treatment for supraventricular arrhythmias.	IIa-C
ICD in patients who develop VF during PVS with two or three extrastimuli at two sites.	IIb-C
Catheter ablation in patients with a history of electrical storms or repeated appropriate ICD shocks.	IIb-C

PVS: programmed ventricular stimulation.
ACCF/AHA/HRS 2012 Focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2013;**61**:e6–75 with permission from Elsevier.
ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J.* 2015;**36**:2793–2867 with permission from Oxford University Press.

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Chapter 61

Catecholaminergic polymorphic ventricular tachycardia

Definition

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is VT that typically occurs on exercise, and episodes of provoked tachycardia are sustained or usually non-sustained.[1,2] CPVT is one of the most lethal inherited channelopathies, with sudden death occurring in up to 30% of patients before age 40 in the absence of anti-adrenergic therapy.[1,3] The estimated 4- and 8-year cardiac event rates were 33% and 58%, respectively, in a series of patients without β blockers.[1]

Epidemiology

The prevalence of CPVT is virtually unknown.[4]

Genetics and pathophysiology

CPVT is mainly due to mutations in the genes encoding the **cardiac ryanodine receptor (RyR2)** channel (60% of patients—autosomal dominant inheritance) and **calsequestrin** (CASQ2-autosomal recessive inheritance) that are involved in calcium kinetics. A locus on chromosome 7p14–p22 has also been reported, with an early-onset lethal form of recessive CPVT.[1] Triadin is a new gene involved in an autosomal recessive form of CPVT, and three new mutations in the triadin gene (*TRDN*), a protein that links RyR2 and CASQ2, were recently identified (Table 56.1).[1] Increased leak of Ca^{2+} from the sarcoplasmic reticulum triggers delayed after-depolarization and ultimately leads to CPVT.[5] Adrenergic stimulation increases spontaneous Ca^{2+} release, and this leak is amplified in the presence of CPVT mutations. There has been evidence that delayed after-depolarizations caused by calcium overload are a more common occurrence in Purkinje cells than in ventricular myocytes, and Purkinje cells are probably critical contributors to arrhythmic triggers.[1] Extended clinical phenotypes in patients with RyR2 mutations and CPVT have been described with sinoatrial node and atrioventricular node dysfunction, atrial fibrillation, atrial standstill, and dilated cardiomyopathy.[6]

Presentation

QRS morphology suggests an outflow tract origin of the initiating beat in more than 50% of patients, and subsequent beats portray a polymorphic, or typically bidirectional, VT morphology.[7] They may originate from the LVOT and, less frequently, from the RVOT or the RV apex.[2]

Diagnosis

The resting ECG is normal (Table 61.1). NSVT, induced by treadmill exercise testing aimed at evaluating presumed long QT syndrome, suggests catecholaminergic polymorphic VT rather than long QT syndrome.[8] Provocative testing with epinephrine (infusion of 0.05 microgram/kg/min and increased every 5 min to 0.1 and 0.2 microgram/kg/min for 5 min at each dose) induces VT in 80% of patients, but a negative test does not exclude the diagnosis.[9] Care should be taken since patients diagnosed with CPVT on the basis of the presence of bidirectional ventricular tachycardia on exercise have been identified as possessing KCNJ2 mutations, which are associated with the rarely lethal Andersen–Tawil syndrome (LQTS 7).[10] Polymorphic VT is usually not inducible by programmed ventricular stimulation.[1]

Table 61.1 CPVT diagnosis

HRS/EHRA/APHRS 2013 statement on inherited arrhythmia	
CPVT is diagnosed in the presence of a structurally normal heart, normal ECG, and unexplained exercise or catecholamine induced bidirectional VT or polymorphic ventricular premature beats or VT in an individual <40 years of age.	
CPVT is diagnosed in patients (index case or family member) who have a pathogenic mutation.	
CPVT is diagnosed in family members of a CPVT index case with a normal heart who manifest exercise induced PVCs or bidirectional/polymorphic VT.	
CPVT can be diagnosed in the presence of a structurally normal heart and coronary arteries, normal ECG, and unexplained exercise or catecholamine induced bidirectional VT or polymorphic ventricular premature beats or VT in an individual >40 years of age	
ESC 2015 GL on VA and SCD	
Structurally normal heart, normal ECG and exercise- or emotion-induced bidirectional or polymorphic VT.	I-C
Carriers of a pathogenic mutation(s) in the genes RyR2 or CASQ2.	I-C

HRS/EHRA/APHRS 2013 Expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Heart Rhythm*. 2013;**10**:1932–63 with permission from Elsevier.
ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015;**36**:2793–2867 with permission from Oxford University Press.

Therapy

All phenotypically and/or genotypically diagnosed CPVT patients should receive a **beta blocker without sympathomimetic activity in the highest tolerable dose**, such as nadolol in up to 1.8 mg/kg.[1] A possible exception might be asymptomatic patients >60 years of age who are newly diagnosed by cascade screening. The use of sympathomimetic agents is contraindicated. Complete suppression of asymptomatic VPBs may be mandatory, but the presence of couplets or more successive VPBs during exercise testing is associated with future arrhythmic events, suggesting intensifying the treatment in these cases. A carvedilol analogue, in combination with a non-selective beta blocker, such as metoprolol or bisoprolol, is also under study.[1] **Verapamil** may be added to beta blocker therapy.[11] **Flecainide** directly blocks RyR2 channels, prevents premature Ca^{2+} release, and reduces exercise-induced ventricular arrhythmias in patients with CPVT uncontrolled by conventional drug therapy.[12] Thus, the addition of flecainide (or probably propafenone) to beta blockers may be more effective.[13] ICD (with beta blockers) is recommended in patients with cardiac arrest or documented VT despite beta blocker therapy (Table 61.2). Left cardiac sympathetic denervation may also be helpful.[14,15] Indications for genetic testing are presented in Table 61.3. Catheter ablation of the bidirectional ventricular premature beats that trigger ventricular fibrillation may become an adjunctive therapy in patients with refractory CPVT,[16] but experience is limited. Recently, the possibility of gene therapy by means of viral gene transfer of wild-type CASQ2 into the heart of R33Q mice was also raised.[17] **Competitive exercise** is not allowed. Only recreational, low-intensity sports are permitted (see Chapter 83 on athlete's heart for sports classification).

Table 61.2 Therapy of CPVT

ACCF/AHA 2012 GL on device therapy. Indications for ICD	
CPVT and syncope and/or sustained VT on beta blockers.	IIa-C
HRS/EHRA/APHRS 2013 statement on inherited primary arrhythmia syndromes. Therapeutic interventions in CPVT.	
The following lifestyle changes are recommended in all patients: limit/ avoid competitive sports; limit/avoid strenuous exercise; limit exposure to stressful environments.	I
Beta-blockers in all symptomatic patients.	I
ICD in patients who experience cardiac arrest, recurrent syncope or polymorphic/ bidirectional VT despite optimal medical management, and/or left cardiac sympathetic denervation (LCSD).	I
Flecainide in addition to beta-blockers in patients who experience recurrent syncope or polymorphic/ bidirectional VT while on beta-blockers.	IIa
Beta-blockers in carriers of a pathogenic CPVT mutation without clinical manifestations of CPVT (concealed mutation-positive patients).	IIa
LCSD in patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/bidirectional VT/ several appropriate ICD shocks while on beta-blockers, and in patients who are intolerant of or with contraindication to beta-blockers.	IIb
ICD as a standalone therapy is not indicated in an asymptomatic patient.	III
Electrical stimulation is not indicated in CPVT patients.	III
ESC 2015 GL on VA and SCD	
Recommended lifestyle changes: avoidance of competitive sports, strenuous exercise and stressful environments.	I-C
Beta-blockers with a clinical diagnosis of CPVT, based on the presence of documented spontaneous or stress-induced VAs.	I-C
ICD in addition to beta-blockers with or without flecainide in patients who experience cardiac arrest, recurrent syncope or polymorphic/bidirectional VT despite optimal therapy.	I-C
Beta-blockers for genetically positive family members, even after a negative exercise test.	IIa-C
Flecainide in addition to beta-blockers in patients with recurrent syncope or polymorphic/bidirectional VT while on beta-blockers, when there are risks/contraindications for an ICD or an ICD is not available or rejected by the patient.	IIa-C
Flecainide in addition to beta-blockers in carriers of an ICD to reduce appropriate ICD shocks.	IIa-C
Left cardiac sympathetic denervation in recurrent syncope or polymorphic/ bidirectional VT/several appropriate ICD shocks while on beta-blockers or beta-blockers plus flecainide and in patients who are intolerant or have contraindication to beta-blockers.	IIb-C
Invasive EPS with PVS is not recommended for stratification of SCD risk.	III-C

PVS: programmed ventricular stimulation.
ACCF/AHA/HRS 2012 focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2013;**61**:e6–75 with permission from Elsevier.
HRS/EHRA/APHRS 2013 Expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Heart Rhythm*. 2013;**10**:1932–63 with permission from Elsevier.
ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015;**36**:2793–2867 with permission from Oxford University Press.

Table 61.3 HRS/EHRA 2011 statement on genetic testing

State of genetic testing for catecholaminergic polymorphic ventricular tachycardia	
Comprehensive or CPVT1 and CVPT2 (RYR2 and CASQ2) targeted CPVT genetic testing is recommended for any patient in whom a cardiologist has established a clinical index of suspicion for CPVT, based on examination of the patient's clinical history, family history, and expressed electrocardiographic phenotype during provocative stress testing with cycle, treadmill, or catecholamine infusion.	I
Mutation-specific genetic testing for family members and appropriate relatives following the identification of the CPVT-causative mutation in an index case.	I

HRS/EHRA 2011 Expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Europace*. 2011;**13**:1077–109 with permission from Oxford University Press.

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Chapter 62

Early repolarization syndromes

Definition

Early repolarization pattern is defined electrocardiographically by a distinct J wave or J-point elevation, that is either a notch or a slur of the terminal part of the QRS entirely above the baseline, with or without ST-segment elevation. The peak of the notch or slur (Jp) should be ≥0.1mV in two or more contiguous leads, excluding leads V1 to V2 (Figure 62.1).[1,2] **Early repolarization syndromes** (ERS) refer to sudden cardiac death or documented

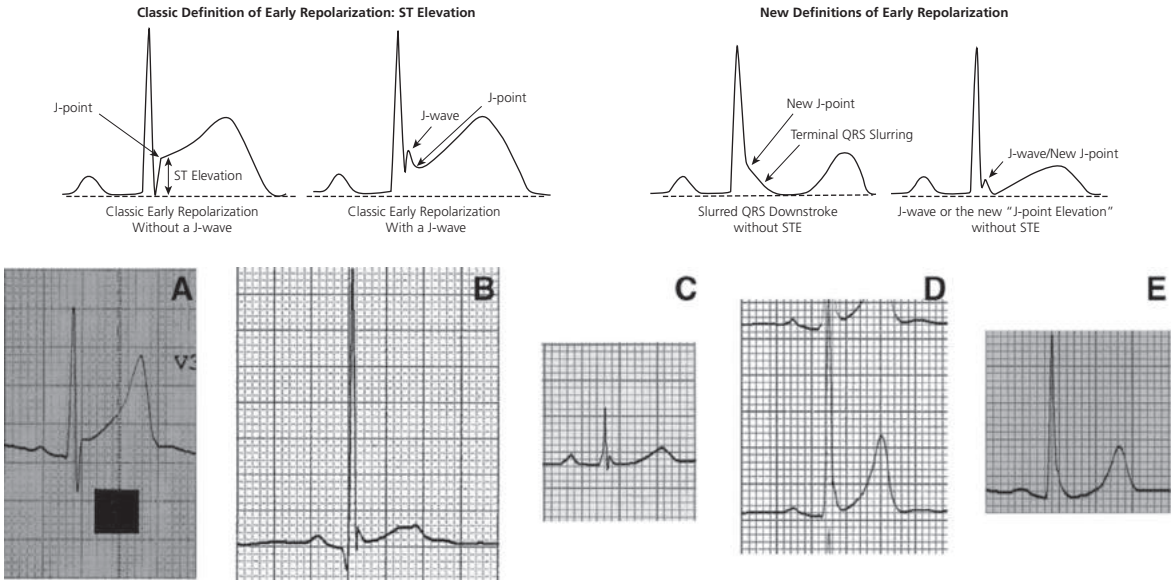

Figure 62.1 **Upper panel**: Patterns of early repolarization. In the upper panel there is 'classic definition' that describes a pattern that is common in the inferior leads of male black athletes. **Lower panel:** Morphologies of the QRS-ST transitions. (A) Early repolarization without J wave; (B) notched J wave with ascending ST segment; (C) notched J wave with horizontal/descending ST segment; (D) slurred J wave with ascending ST segment; (E) slurred J wave with horizontal/descending ST segment.

Perez MV, *et al*. Semantic confusion: the case of early repolarization and the J point. *Am J Med*. 2012;**125**:843–4 with permission from Elsevier.
Biasco L, *et al*. Clinical, electrocardiographic, echocardiographic characteristics and long-term follow-up of elite soccer players with J-point elevation. *Circ* Arrhythm Electrophysiol. 2013;**6**:1178–84 with permission from Wolters Kluwer.

VT/VF in individuals with an early repolarization pattern. A prominent J wave has been long observed in cases of hypothermia, hypercalcaemia, and ischaemia.[3] The term **J-wave syndromes** usually denotes inherited conditions such as ERS and Brugada syndrome,[4] that are due to mutations affecting calcium, potassium, and sodium channels (Table 57.1 of Chapter 57) and may contribute to overlap syndromes.[4,5]

Genetics and pathophysiology

The J wave deflection occurring at the QRS-ST junction (also known as Osborn wave) was first described in 1953 and is seen in many conditions, such as acute ischaemia (especially in true posterior myocardial infarction), hypothermia, hypercalcaemia, brain injury, acidosis, and early repolarization syndromes. An increase in net repolarizing current, due to either a decrease of inward Na^+ or Ca^{2+} currents (I_{Na}, and $I_{Ca,L}$) or augmentation of outward currents, such as I_{to}, $I_{K\text{-}ATP}$, and $I_{K\text{-}ACh}$, lead to augmentation of the J wave or the appearance of ST segment elevation that is more prominent during slow heart rates.[3] Overlap with other syndromes may be seen. Mutations in the *SCN10A* gene may produce patterns of Brugada, early repolarization, and conduction disease,[5] and a high prevalence of early repolarization in short QT syndrome has also been reported.[6] Physiological heterogeneity of electrical properties and transmural gradients in ion channel distribution in the endocardial, mid-myocardial (M-cells), and epicardial layers result in regional differences in electrophysiological properties. Ventricular epicardial (particularly RV) and M-cells, but not endocardial action potentials, display a prominent phase 1 due to a large transient outward potassium current (I_{to}), giving rise to the typical spike-and-dome or notched configuration of the action potential and inscription of the J wave in the ECG. The degree of accentuation of the action potential notch leading to loss of the dome depends on the magnitude of I_{to}. When I_{to} is prominent, as it is in the right ventricular epicardium, an outward shift of current causes phase 1 of the action potential to progress to more negative potentials at which the L-type calcium current ($I_{Ca,L}$) fails to activate, leading to all-or-none repolarization and loss of the dome. Loss of the

action potential dome usually is heterogeneous, resulting in marked abbreviation of the action potential at some sites but not at others. The dome then can propagate from regions where it is maintained to regions where it is lost, giving rise to local transmural reentry and closely coupled extrasystoles (phase 2 reentry). When the extrasystole occurs on the preceding T wave, it results in an R-on-T phenomenon that initiates polymorphic VT or VF.[3]

Clinical significance

The early repolarization pattern has long been considered to be a benign ECG manifestation (6–13% in the general population) that is seen more commonly in young healthy men and athletes (22–44%), and its clinical significance has been questioned.[7] In a recent report on professional athletes, a correlation between J point elevation and interventricular septum thickness was observed, thus suggesting a possible mechanistic role of exercise-induced left ventricular hypertrophy as the basis for J point elevation, and no cardiac death was observed in a median of 13 years' follow-up.[8] Similarly, in the CARDIA study, the presence of early repolarization in young adults was not associated with higher risk of death during long-term follow-up.[9] The possibility that false tendon, i.e. discrete fibromuscular structures that transverse the LV cavity, are related to the genesis of J waves has also been raised.[10]

However, there has been evidence suggesting that the early repolarization pattern may be associated with a risk for VF, depending on the location of early repolarization, magnitude of the J wave, and degree of ST elevation.[2,11,12] In a large study on a community-based general population of 10 864 middle-aged subjects, an early repolarization pattern with J point elevation of at least 0.1 mV in the inferior leads of a resting ECG was associated with an increased risk of death from cardiac causes.[13] In addition, among patients with a history of idiopathic ventricular fibrillation, an increased prevalence of early repolarization (up to 23%), defined as an elevation of the QRS–ST junction of at least 0.1 mV from baseline in the inferior or lateral leads, manifested as QRS slurring or notching, has been detected (Figure 62.2).[11,14] A higher prevalence

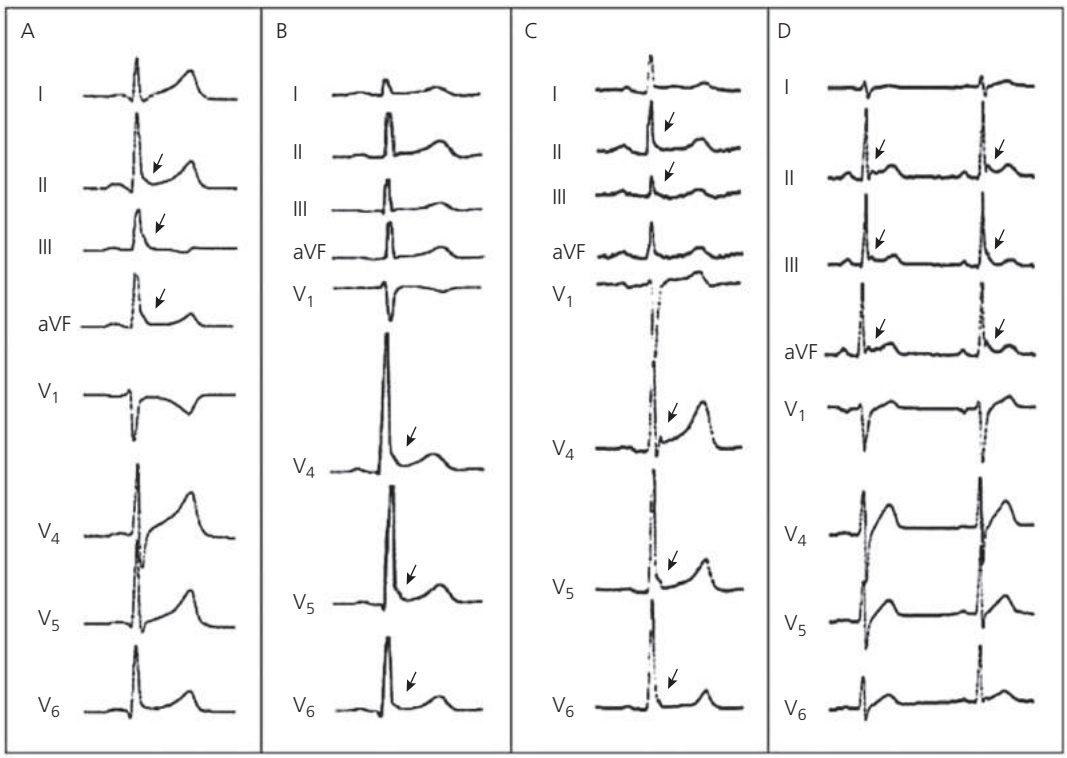

Figure 62.2 J-point elevation patterns. In each panel, early repolarization is evident in the varying patterns of QRS slurring or notching in inferolateral leads (arrows). Panel D shows a beat-to-beat fluctuation in this pattern.

Haissaguerre M, *et al*. Sudden cardiac arrest associated with early repolarization. *N Engl J Med*. 2008;**358**:2016–23 with permission from Massachusetts Medical Society.

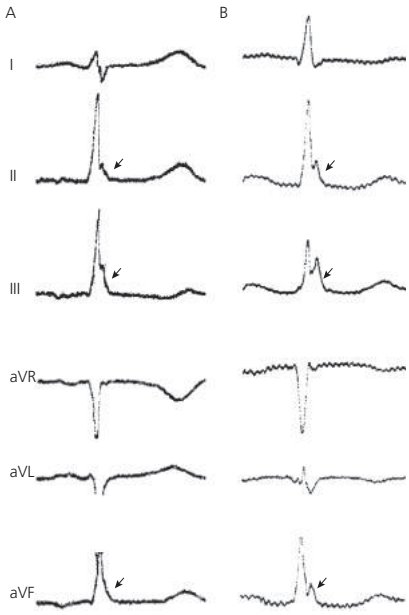

Figure 62.3 Horizontal/descending ST segment patterns from two subjects in the general population.

Tikkanen JT, *et al*. Early repolarization: electrocardiographic phenotypes associated with favorable long-term outcome. *Circulation*. 2011;**123**:2666– 73 with permission from Wolters Kluwer.

of J wave and/or QRS slurring (but not of ST elevation) has been found among athletes with cardiac arrest/sudden death than in controls.[15] A horizontal/descending type (defined as ≤0.1 mV elevation of the ST segment within 100 ms after the J point) in the inferior leads, as opposed to a rapidly ascending ST segment-type, may help to identify those individuals who are clearly at risk (Figures 62.2 to 62.4).[16,17] Coexistence of an anterior early repolarization pattern (i.e. in leads V1–V3)[18] and early repolarization in the inferior leads, especially in cases without other QRS complex abnormalities, predict the occurrence of VT/VF.[19] It has been estimated that the finding of early repolarization pattern in a young adult would increase the probability of idiopathic VF from 3.4 in 100 000 to 11 in 100 000.[2]

Still, several obscure points remain with this syndrome. An early repolarization pattern in the inferolateral leads occurs in 5% of apparently healthy individuals.[13,14] It may not be consistently seen, and even the horizontal/descending ST-type was seen in 3% of controls.[16,17] In the ARIC study, J point elevation was associated with an increased risk of SCD in whites and in females, but not in blacks or males.[20] A pattern of J wave and/or QRS slurring (but not of ST elevation) has been associated with cardiac arrest/sudden death in athletes,[15] but many healthy athletes have early repolarization with a rapidly ascending pattern. Inferolateral ESR pattern is seen in 25–35% of competitive athletes, and inferior only in 4%, and is considered a dynamic phenomenon related to physical activity (see Chapter 83).[8,21,22] Finally, a large genome-wide association study has been unable to identify genetic variants associated with the pattern, possibly reflecting the phenotypic heterogeneity that exists among these individuals.[23] It seems therefore that the majority of individuals with ER and no family history of sudden cardiac death, are at no or minimal risk for arrhythmic events.[2]

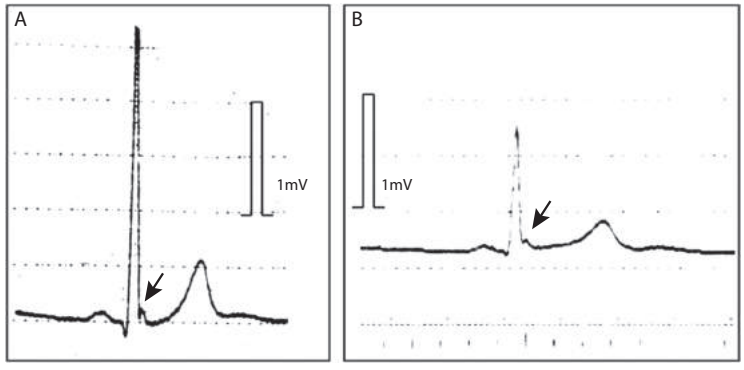

Figure 62.4 Rapidly ascending (A) and horizontal (B) ST segment in the leads deploying J waves (J waves marked with arrowhead). 'Concave/rapidly ascending': when there is 0.1 mV elevation of the ST segment within 100 ms after the J point and the ST segment merged gradually with the T wave. 'Horizontal/descending': when the ST segment elevation is 0.1 mV within 100 ms after the J point and continues as a flat ST segment until the onset of the T wave.

Rosso R, *et al*. Distinguishing 'benign' from 'malignant early repolarization': The value of the ST-segment morphology. *Heart Rhythm*. 2012;**9**:225–9 with permission from Elsevier.

Diagnosis

Specific diagnostic criteria for ER pattern and ER syndrome are presented in Table 62.1. In addition, specific repolarization patterns that have been previously discussed should also be taken into account. The Brugada syndrome is characterized by J point or ST segment elevation in the right precordial leads, and approximately 12% of patients display typical early repolarization abnormalities. However, typically the ST segment elevation is augmented in the right precordial leads by sodium channel blockers, whereas, in ERS, the early repolarization pattern is usually attenuated.[24]

Table 62.1 HRS/EHRA/APHRS 2013 statement on inherited primary arrhythmia syndromes

Diagnosis of ERS
ER syndrome is diagnosed in the presence of J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG in a patient resuscitated from otherwise unexplained VF/ polymorphic VT
ER syndrome can be diagnosed in a SCD victim with a negative autopsy and medical chart review with a previous ECG demonstrating J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG
ER pattern can be diagnosed in the presence of J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG

HRS/EHRA APHRS 2013 Expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Heart Rhythm*. 2013;**10**:1932–63 with permission from Elsevier.

Therapy

The risk stratification and optimum management of these patients are not well defined, and recognition of the truly malignant forms is difficult (Table 62.2). Electrophysiology testing does not appear useful for risk stratification. VF is infrequently induced (22%) and has no predictive value for ICD therapy.[25] Patients with aborted sudden death in the absence of identifiable cause (idiopathic VF) are treated with ICD. Ablation of idiopathic VF, targeted to short coupled VPB that originate predominantly from the Purkinje system and the right ventricular outflow track and trigger VF, has also been reported.[26]

Table 62.2 HRS/EHRA/APHRS 2013 statement on inherited primary arrhythmia syndromes

Therapeutic interventions	
ICD in patients who have survived a cardiac arrest.	I
Isoproterenol infusion for suppressing electrical storms.	IIa
Quinidine in addition to an ICD for secondary prevention of VF.	IIa
ICD in symptomatic family members of ER syndrome patients with a history of syncope in the presence of ST segment elevation >1mm in 2 or more inferior or lateral leads.	IIb
ICD in asymptomatic individuals who demonstrate a high-risk ER ECG pattern (high J-wave amplitude, horizontal/descending ST-segment) in the presence of a strong family history of juvenile unexplained sudden death with or without a pathogenic mutation.	IIb
ICD is not recommended in asymptomatic patients with an isolated ER ECG pattern.	III

HRS/EHRA APHRS 2013 Expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Heart Rhythm*. 2013;**10**:1932–63 with permission from Elsevier.

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Part XI

Bradyarrhythmias

Relevant guidelines

ESC 2013 Guidelines on pacing and cardiac resynchronization

2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Europace*. 2013;**15**:1070–118.

ACCF/AHA/HRS 2012 Guidelines for device-based therapy of cardiac rhythm abnormalities

2012 ACCF/AHA/HRS Focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2013;**61**:e6–75.

PACES/HRS 2014 Consensus statement on arrhythmias in GUCH

PACES/HRS Expert Consensus Statement on the recognition and management of arrhythmias in adult congenital heart disease. *Heart Rhythm*. 2014;**11**:e102–165.

HRS/EHRA 2011 Expert consensus statement on the state of genetic testing

HRS/EHRA Expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Europace*. 2011;**13**:1077–109.

HRS/AACF 2012 Statement on pacemaker device mode selection

HRS/ACCF Expert consensus statement on pacemaker device and mode selection. *Heart Rhythm*. 2012;**9**:1344–65.

HRS/EHRA/APHRS 2013 Expert consensus statement on inherited arrhythmia

HRS/EHRA/APHRS Expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Heart Rhythm*. 2013;**10**:1932–63.

HRS Expert consensus statement on arrhythmias in cardiac sarcoidosis

HRS Expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm*. 2014;**11**:1305–23.

AHA/ACCF/HRS 2009 Recommendations for the standardization and interpretation of the electrocardiogram

AHA/ACCF/HRS Recommendations for the standardization and interpretation of the electrocardiogram. 6 parts have been published in 2009.

2015 ESC 2015 Guidelines on ventricular arrhythmias and prevention of sudden cardiac death

2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015;36:2793–867.

Chapter 63

The cardiac conduction system

Overview

The **sinus node** is a crescent-like, 2.5 mm long subepicardial structure with irregular margins. It is not insulated by a sheath of fibrous tissue, and there are multiple extensions to the atrial myocardium.[1] Pacemaker automaticity is due to spontaneous diastolic repolarization of phase 4 that generates rhythmic action potentials and determines the heart rate through various currents, including the I_f current (see Chapter 50 on mechanisms of arrhythmogenesis).[2] Depolarization spreads within the sinus node and then is transmitted to the atria via several specialized sinoatrial exit pathways.[3] Impulses arrive at the **AV node** that functions as a filter for ventricular protection from fast atrial rates as well as a backup pacemaker in case of sinus node dysfunction.[4] Conduction to the ventricles is then through the **bundle of His** which propagates via the annulus fibrosus and penetrates the membranous intraventricular septum, before separating into the left and right bundle branches at the superior margin of the muscular septum. The **right bundle** crosses the anterior part of the intraventricular septum and reaches the apex of the ventricle and the base of the anterior papillary muscle. The **left bundle** is anatomically less discrete, and subdivides into the **anterior (superior)** and **posterior (inferior) fascicle**. Finally, the bundle branches ramify to produce the endocardial **Purkinje fibres** which activate the ventricles. Dense innervation of the sinus node and the conduction system by post-ganglionic adrenergic and cholinergic nerve terminals determines sinus rate and AV conduction. The sinus nodal branch of the right coronary artery (sinus nodal branch may also originate from the proximal circumflex artery in up to 40% of cases) provides blood supply to the sinus node. In 85–90% of human hearts, the blood supply to the AV node (AV nodal artery) is provided by the distal RCA and by the left circumflex in the remainder. Septal branches of the LAD also provide blood to the upper muscular interventricular septum and the conduction system. The specialized cells of the cardiac conduction system have relatively poor contractility and express specialized ion channels and gap-junction proteins, such as connexins, that mediate electrical coupling with neighbouring cells.

Mutations that affect the cardiac conduction system and are associated with conduction disturbances are presented in Table 63.1.

Table 63.1 Genetic causes of conduction system disease

Gene	Protein	Conduction defect	Associated conditions	Mechanism
	Ion channels			
SCN5A	Nav1.5	AV conduction defect	Brugada syndrome, LQTS 3, sick sinus syndrome, AF, dilated cardiomyopathy	Slowing of conduction velocity and pacemaking rate, AF, dilated cardiomyopathy, tissue degeneration via TGF-beta 1
SCN10A	Nav1.8	Conduction defects, sick sinus syndrome, RBBB	Brugada syndrome, early repolarization syndrome AF, VT/VF	Slowing of conduction velocity and pacemaking rate
TRPM4	TRPM4	AV conduction defect	Possibly elevated density of TRPM4 channels disables action potential propagation on Purkinje fibres	
SCN1B	Scn1b	Bundle branch block	Brugada syndrome, AF	Slowing of conduction velocity mainly in Purkinje fibres
KCNJ2	Kir2.1	AV block, bundle branch block	Andersen–Tawil syndrome (LQTS 7)	Prolongation of action potential and slowing of pacemaking rate
HCN4	HCN4	Sick sinus syndrome	Brugada syndrome, AF, non-compaction cardiomyopathy, mitral valve prolapse	Reduction of pacemaker current I_f
	Structural proteins			
GJA5	Connexin40	AV block, bradycardia	Ventricular arrhythmias	Defective coupling of conducting myocytes
ANK2	Ankyrin-B	Sick sinus syndrome	LQTS 4, AF, CPVT	Abnormal sinoatrial electrical activity due to dysfunction in ankyrin B-based trafficking pathways

(*Continued*)

Table 63.1 Continued

Gene	Protein	Conduction defect	Associated conditions	Mechanism
DES	Desmin	AV block	VT/VF, cardiomyopathy, skeletal myopathy	Desmin-positive aggregates and inability of mutated desmin to interact with cellular structures. Mitochondrial dysfunction
MYH6	Alpha-myosin heavy chain	Sick sinus syndrome	AF, thoracic aortic aneurysm	Unknown. Possibly interference with connexin 40 and microRNA involved in conduction
	Protein kinases			
PRKAG2	γ-2 subunit of AMP-activated protein kinase (AMPK)	Sinus bradycardia, AV block	Wolff–Parkinson–White syndrome, glycogen storage cardiomyopathy	Disruption of annulus fibrosus by glycogen-filled myocytes
DMPK	Myotonic dystrophy protein kinase	AV block, bundle branch block	VT/VF, cardiomyopathy, myotonic dystrophy type I	Toxic mutant RNA impairs conduction with various mechanisms
	TGF-β superfamily			
BMP2	Bone morphogenetic protein 2	AV block	Wolff–Parkinson–White syndrome, cognitive defects, dysmorphic features	Disruption of annulus fibrosus
	Transcription factors			
TBX5	Tbx5	Sinus bradycardia, AV block, bundle branch block	Holt–Oram syndrome	Defective development and coupling of conducting myocytes
NKX2–5	Nkx2–5	AV block, bundle branch block	VSD, Fallot, subvalvar AS, pulmonary atresia	Defective development and coupling of conducting myocytes
	Nuclear membrane proteins			
LMNA	Lamin A/C	AV block	VT/VF, cardiomyopathy Emery–Dreifuss muscular dystrophy, Limb-girdle muscular dystrophy	Possibly hyperactivation of mitogen-activated protein kinase and interference with nucleus integrity and gap junctions
EMD	Emerin	AV block	VT/VF, Emery–Dreifuss muscular dystrophy	Mechanism poorly understood
	Lysosomal enzymes			
GLA	Alpha galactosidase (a-GALA)	AV block	Anderson–Fabry disease	Accumulation of glycosphingolipids
	Ca^{2+} handling proteins			
RYR2	Ryanodine receptor	Sick sinus syndrome, AV block	CPVT, AF, dilated cardiomyopathy	Altered calcium handling. Mechanism of bradycardia and block unknown
CASQ2	Calsequestrin	Sinus bradycardia	CPVT	Altered calcium handling. Mechanism of bradycardia and block unknown

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Chapter 64

Sinus nodal disease

Sinus bradycardia

Definitions

Sinus rates <60 beats/min are defined as bradycardia.[1] It is common in young adults, particularly well-trained athletes. During sleep, the sinus rate may fall to 35 beats/min, with pauses up to 3 s, and is not considered abnormal.

Sinus arrhythmia usually refers to sinus cycle phasic variation that is related to the respiratory cycle and is normal in the youth. Non-respiratory sinus arrhythmia may be seen with digitalis toxicity.

Sinus arrest (sinus pauses) manifests itself as pauses, with the P-P interval containing the pause not being equal or multiple of the basic P-P interval.

In **sinoatrial exit block** (first-, second-, or third-degree), the atrium is not depolarized despite the sinus stimulus, and the duration of the pause is a multiple of the basic P-P interval.

Wandering pacemaker refers to a shift of the dominant pacemaker from the sinus node to an other atrial focus, usually lower at the crista terminalis. It is a normal finding, especially in athletes.

Asymptomatic bradycardia does not require treatment, and no drugs increase the heart rate efficiently and safely. Pacing is considered only in the presence of bradycardia-induced low cardiac output state.

Aetiology

Intracranial and mediastinal tumours, severe hypoxia, hypothermia, myxoedema, Chagas' disease, mental depression, and drugs, such as beta blockers (orally or by conjunctival instillation for glaucoma), verapamil and diltiazem, amiodarone, propafenone, and lithium, may cause sinus bradycardia. Transient sinus bradycardia occurs in 10–25% patients with acute MI (usually inferior) but is an ominous sign if it occurs following resuscitation from cardiac arrest.[1] Intense training has also been associated with bradyarrhythmias, including both sick sinus syndrome and AV block.[2] Genetic causes of sinus bradycardia by means of mutations in ion channel encoding genes are presented in Table 63.1 of Chapter 63.

Sick sinus syndrome

Definition

Sick sinus syndrome (SSS) refers to any of the following conditions that may coexist:

- Persistent spontaneous bradycardia not caused by drugs with or without chronotropic incompetence, i.e. inability to achieve 85% of the age-predicted maximum heart rate on the treadmill[3]
- Sinus pauses either due to sinus arrest or exit block
- Combinations of sinus arrest with AV conduction disturbances
- Alternating episodes of bradycardia, usually following tachycardia (mostly AF).

Sinus nodal disease is the most common cause of bradyarrhythmias requiring pacing in the western world.[4]

Epidemiology

The prevalence of sinus node dysfunction in the USA has been estimated to be approximately 530 per million, with an incidence of 63 per million requiring pacemaker therapy. It accounts for 50% of implantation of permanent pacemakers.[5] SSS is primarily a disease of the elderly, with an average of 68 years of age, equally affecting both sexes but being more prevalent in whites than in blacks.[6]

Pathophysiology

Fibrotic or degenerative destruction of the sinus node, its atrial radiations and the surrounding nerves, and perhaps sinus nodal occlusion comprise the pathological basis of the disease.[7] Genetic causes of SSS are due to mutations in genes that encode ion channels (Table 63.1 of Chapter 63), such as the hyperpolarization-activated cyclic nucleotide channel 4 (HNC4), a major constituent of the pacemaker current (If) in the sinoatrial node. They may result in isolated sick sinus or other syndromes.[8,9]

Diagnosis

SSS is primarily a disease of the elderly. Obesity, diabetes, RBBB, and elevated NT-proBNP are associated comorbidities.[6] SSS is suspected when symptoms, such as light-headedness, fatigue, dizziness, and presyncope or syncope are related to bradycardia. Sinus nodal recovery time (SNRT) is derived from electrophysiology studies by pacing at the right atrium between 600 and 350 ms for 30–60 s. This is corrected for the underlying sinus cycle length (CSNRT = SNRT – SCL). Values >525 ms are considered abnormal and represent a specific, but highly insensitive, test for SSS. Abnormal head-up tilt testing or carotid sinus massage in the presence of normal CSNRT suggest a vasodepressor reflex, rather than SSS (see Chapter 67 on

syncope).[10] Wireless monitoring devices may be useful in the presence of inconsistent symptoms.[11]

Therapy

No drugs can effectively and safely increase the sinus rate. Indications for pacing are presented in Table 64.1.[12,13] Minimally symptomatic patients may be just followed up, unless atrial tachycardias necessitate the use of beta blockers. The natural history of SSS is variable, but the majority of patients who have experienced syncope due to sinus pause or bradycardia will have recurrent syncope. The incidence of sudden death, however, is extremely low, and SSS, treated or untreated, does not affect survival.[12] Supraventricular tachycardia including AF occurs in approximately 30% of patients with sinus node dysfunction.[14,15] Subclinical atrial arrhythmias in patients who had a history of hypertension, but no prior diagnosis of clinical atrial fibrillation, predispose to embolic events and these patients should be considered for anticoagulation (see also Chapter 53).[14] The risk of developing AV block within the next 5 years is 3–35%.[12]

Table 64.1 Pacing in SSS

ACCF/AHA/HRS 2012 GL on device-based therapy	
Recommendations for permanent pacing in sinus node dysfunction (SND)	
SND with documented symptomatic bradycardia, including frequent sinus pauses that produce symptoms.	I-C
Symptomatic chronotropic incompetence.	I-C
Symptomatic sinus bradycardia that results from required drug therapy.	I-C
SND with heart rate <40 bpm when a clear association between significant symptoms consistent with bradycardia and the actual presence of bradycardia has not been documented.	IIa-C
Syncope of unexplained origin when clinically significant abnormalities of sinus node function are discovered or provoked in EP studies.	IIa-C
Minimally symptomatic patients with chronic heart rate <40 bpm while awake.	IIb-C
SND in asymptomatic patients.	III-C
SND in patients for whom the symptoms have been clearly documented to occur in the absence of bradycardia.	III-C
SND with symptomatic bradycardia due to non-essential drug therapy.	III-C
ESC 2013 GL on pacing and CRT	
Indication for pacing in persistent bradycardia (sinus node disease)	
Pacing when symptoms can clearly be attributed to sinus bradycardia.	I-B
Pacing when symptoms are likely to be due to sinus bradycardia, even if the evidence is not conclusive.	IIb-C
Pacing in patients with sinus bradycardia which is asymptomatic or due to reversible causes.	III-C
Indication for pacing in intermittent documented bradycardia	
Pacing in patients affected by sinus node disease (including the tachy-brady form) who have the documentation of symptomatic bradycardia due to sinus arrest or sinus-atrial block.	I-B
Pacing in patients ≥40 years with recurrent, unpredictable reflex syncopes and documented symptomatic pause/s due to sinus arrest or AV block or the combination of the two.	IIa-B
Pacing in patients with history of syncope and documentation of asymptomatic pauses >6 s due to sinus arrest, or sinus-atrial block or AV block.	IIa-C
Pacing in reversible causes of bradycardia.	III-C

ACCF/AHA/HRS 2012 Focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2013;**61**:e6–75 with permission from Elsevier.
ESC 2013 Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J*. 2013;**34**:2281–329, with permission from Oxford University Press.

Choice of the pacemaker mode

Several trials on patients with SSS and/or AV block have compared atrial or dual-chamber with ventricular pacing.[15–20] Although results have not been consistent, atrial-based pacing reduces the incidence of atrial fibrillation and may modestly reduce stroke compared to ventricular pacing, but does not improve survival or reduce heart failure or cardiovascular death.[21] However, ventricular desynchronization imposed by ventricular pacing, even when AV synchrony is preserved, has been shown to increase the risk of heart failure and AF in patients with sinus nodal disease and normal baseline QRS duration.[22] DDDR pacing, with a very short atrioventricular interval and more than 99% ventricular pacing, has been reported to increase the incidence of atrial fibrillation when compared with DDDR pacing with automated features to minimize ventricular pacing by prolonging the atrioventricular interval.[23] AAIR pacing has been associated with a higher incidence of paroxysmal AF and a 2-fold increased risk of pacemaker reoperation compared to DDDR pacing programmed with a moderately prolonged atrioventricular interval,[15] whereas an AAI-DDD changeover mode had no effect on AF when compared with DDD.[24] Atrial antitachycardia pacing and managed ventricular pacing, which minimizes unnecessary right ventricular pacing, have been found superior to conventional DDDR pacing by means of reducing AF in bradycardia patients,[25] but a convincing effect of overdrive atrial pacing or antitachycardia algorithms on reducing AF has not been detected in all trials.[26] Low atrial septal pacing with dual-chamber pacemakers has been reported to reduce AF,[27] but in the recent SAFE trial, pacing at the right atrial septum or continuous atrial overdrive pacing did not prevent the development of persistent AF in patients with paroxysmal AF and SSS.[28] Atrial pacing, in general, appears to be arrhythmogenic.[29] Pacemaker mode selection is presented in Figures 64.1 and 64.2 and Table 64.2.

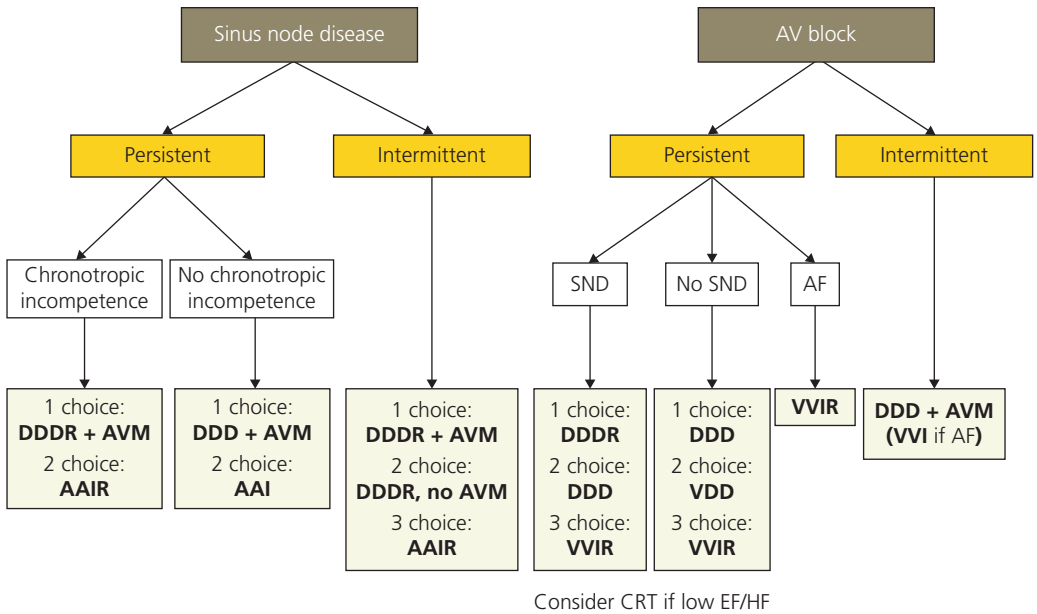

Figure 64.1 ESC 2013 GL on cardiac pacing and CRT. Optimal pacing mode in sinus node disease and AV block.

AF: atrial fibrillation; AV: atrioventricular; AVM: AV delay management, i.e. to prevent unnecessary right ventricular pacing by means of manual optimization of AV interval or programming of AV hysteresis; SND: sinus node disease.

ESC 2013 Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J*. 2013;**34**:2281–329, with permission from Oxford University Press.

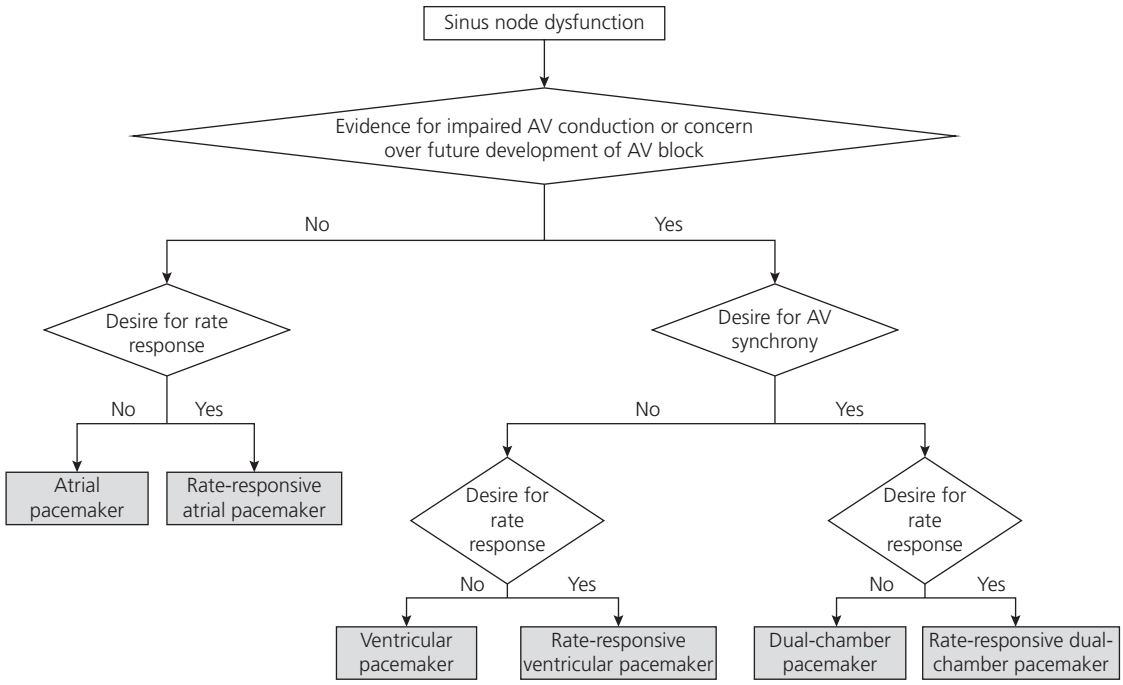

Figure 64.2 ACCF/AHA/HRS 2012 GL on device-based therapy of cardiac rhythm abnormalities. Pacing mode in sick sinus syndrome.

ACCF/AHA/HRS 2012 Focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2013;**61**:e6–75 with permission from Elsevier.

Table 64.2 Selection of pacing mode in SSS

HRS/AACF 2012 statement on pacemaker device mode section	
Pacing mode selection in SSS	
DDD or AAI pacing is recommended over VVI pacing in patients with SND and intact AV conduction.	I-A
DDD or AAI pacing is recommended over AAI pacing in patients with SND.	I-B
Rate adaptive pacing in patients with significant symptomatic chronotropic incompetence, and its need should be re-evaluated during follow-up.	IIa-C
In patients with SND and intact AV conduction, programming DDD pacemakers to minimize ventricular pacing can be useful for prevention of AF.	IIa-B
AAI pacing in selected patients with normal AV and ventricular conduction.	IIb-B
VVI pacing when frequent pacing is not expected or the patient has significant co-morbidities.	IIb-C
DDD or AAI pacing should not be used in patients with permanent or longstanding persistent AF where efforts to restore or maintain SR are not planned.	III-C
ESC 2013 GL on pacing and CRT	
Choice of pacing mode/programming in persistent bradycardia	
Dual-chamber PM with preservation of spontaneous AV conduction for reducing the risk of AF and stroke, avoiding pacemaker syndrome and improving quality of life.	I-A (vs VVI), I-B (vs AAI)
Rate response features should be adopted for patients with chronotropic incompetence, especially if young and physically active.	IIa-C
Choice of pacing mode in intermittent documented bradycardia	
Dual-chamber pacing with rate hysteresis is the preferred mode in reflex asystolic syncope in order to preserve spontaneous sinus rhythm.	I-C

RS/ACCF 2012 Expert consensus statement on pacemaker device and mode selection. *Heart Rhythm*. 2012;**9**:1547–5271 with permission from Elsevier.
ESC 2013 Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J*. 2013;**34**:2281–329, with permission from Oxford University Press.

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Chapter 65

Atrioventricular and intraventricular block

Atrioventricular block

Definitions

First-degree AV block is characterized by a PR interval >200 ms. A narrow QRS complex indicates that the block is most probably at the AV node, whereas a wide QRS can be seen with the block either at the node or His–Purkinje system.

Second degree-AV block is characterized by P waves not conducted to the ventricles.

Type I AV block (Mobitz I or Wenckebach) shows progressively increasing PR intervals until a P wave fails to be conducted to the ventricles. A narrow QRS type I block is almost always AV nodal, whereas a type I block with bundle branch block is infranodal in 60–70% of cases. Type I AV block can be physiological in athletes, resulting from heavy physical training, and occasionally in young people. It may also be normally seen during sleep in patients with high vagal tone.[1]

Type II AV block (Mobitz II) shows consecutive, non-conducted P waves without visible changes in the PR interval (i.e. AV conduction time) before and after the blocked impulse, provided there is normal sinus rhythm. Block is infranodal at the His–Purkinje level.

Third-degree (complete) AV block No P wave is conducted to the ventricles, and ventricular contraction is maintained by an escape nodal or intra- or infra-Hisian rhythm.

Epidemiology

The prevalence of first-degree AV block in healthy, middle-aged subjects ranges from 1 to 7%. Mobitz II block is very rare (0.003%), while the prevalence of third-degree AV block in the general population is approximately 0.03%.[2]

Pathophysiology

Causes of conduction disease are presented in Table 65.1. **Progressive cardiac conduction disease (PCCD)** is diagnosed in the presence of unexplained progressive conduction abnormalities in young (<50 years) individuals with structurally normal hearts and in the absence of skeletal myopathies, especially if there is a family history of PCCD.[3] It was initially described by **Lenegre and Lev** who hypothesized that progressive conduction defects were due to a primary degenerative disease of unknown origin that was exaggerated by ageing. There has been now evidence that progressive conduction system disease has genetic and autoimmune origins.[3,4] *Myocardial ischaemia and infarction, hypertension, inherited degenerative disease affecting the conduction system, sarcoidosis, rheumatic disorders (rheumatoid arthritis, scleroderma), congenital heart deformities, neuromuscular disorders, aortic stenosis, infections, such as Lyme disease and Chagas' disease, electrolyte abnormalities, myocarditis, endocarditis, cardiac surgery, sleep apnoea, and catheter ablation* procedures may affect the conduction system and cause permanent or paroxysmal AV block. *Cardiac sarcoidosis* and a mild form of *giant cell myocarditis* are the causes for more than 25% of initially unexplained AV block in young and middle-aged adults. These patients are at high risk for adverse cardiac events.[5] **Lyme disease** is a common tickborne disease transmitted to humans through the bite of the Ixodes tick.[6,7] The causative bacterium is *Borrelia burgdorferi*, and the disease is characterized by an early localized infection with erythema migrans, fever, fatigue, headache, myalgias, and arthralgias. Erythema migrans usually begins as a small erythematous papule or macule that appears at the site of the tick bite 1–2 weeks later, and subsequently enlarges. It may occur anywhere on the body surface, although common sites are the groin, axilla, waist, back, lower extremities, and, in children, the head and neck.[7] An early disseminated infection may follow days to weeks later, with neurologic (such as facial nerve palsy or aseptic meningitis), musculoskeletal, or cardiovascular symptoms and multiple erythema migrans lesions. Late Lyme disease, with intermittent swelling and pain of one or more joints (especially knees), may also occur.[6] However, although Lyme borreliosis is the most common tickborne infectious disease in North America and in countries with moderate climates in Eurasia, Lyme carditis is rare. AV block may be seen during the acute course of the disease that involves the heart, with a clinical picture similar to acute rheumatic fever, and responds to antibiotics such as doxycycline, amoxicillin, cefuroxime, and macrolides for two weeks. Borrelia antibodies may be sought with ELISA and Western blot in cases of otherwise unexplained acute AV block. Recurrent erythema migrans after antibiotic treatment is caused by reinfection rather than relapse of the original infection,[8] and persistent arthritis is probably due to infection-induced autoimmunity. Thus, prolonged antibiotic therapy for the so-called 'chronic Lyme disease' is not justified. **Mutations** associated with AV conduction disease are presented in Table 63.1 of Chapter 63. Up to 5% of AV conduction disease are due to *SCN5A* mutations.[9]

Table 65.1 Causes of AV conduction disease

Myocardial ischaemia and infarction
Calcified valve disease
Aortic stenosis
Mitral annulus calcification
Electrolyte disturbances
Endocarditis
Myocarditis
Sleep apnoea
Cardiac valve and congenital surgery
Cardiac transplantation
Catheter ablation procedures
Drugs
Digoxin
Beta blockers
Verapamil, diltiazem
Amiodarone
Procainamide
Flecainide, propafenone
Doxorubicin
Methotrexate
Chloroquine
Infective disorders
Lyme borreliosis
Chagas' disease
Autoimmune disorders
Sarcoidosis
Rheumatoid arthritis
Systemic sclerosis
Ankylosing spondylitis (HLA B27)
Systemic lupus erythematosus
Sjögren's syndrome
Wegener's granulomatosis
Behçet's disease
Anti-Ro/SSA, anti-LA/SSA antibodies
Inherited
Isolated (progressive familial heart block type IA and IB)
Genetic arrhythmia syndromes (Brugada syndrome, long QT syndrome 3, arrhythmia-prone cardiomyopathy)
Congenital cardiac defects (Holt–Oram syndrome, non-syndromic cardiac defects)
Wolff–Parkinson–White syndrome and cardiomyopathy
Muscular dystrophies (myotonic dystrophy type 1, Emery–Dreifuss, limb girdle, desmin myopathy)
Anderson-–Fabry disease
Familial amyloidosis
Mucopolysaccharidosis IV
Kearns–Sayre syndrome
Malignancy (lymphomatous or solid tumour)

Vagally induced AV block, i.e. by vomiting, is a benign phenomenon.

Syncope **(Stokes–Adams)** and death may occur due to complete heart block if an escape rhythm at a lower level than the site of block does not intervene.

Torsade de pointes may also occur and probably represents the leading cause of death in unpaced patients. QT and Tpe (peak to T end) intervals as well as the Tpe/QT ratio, T-wave alternans, reversed asymmetry of the T wave, a triphasic T wave, and biphasic T waves where the amplitude of the second peak is greater than the amplitude of the first peak (long QT syndrome type 2–like notched T wave) are predictors of development of torsade.[10]

Congenital AV block is discussed in Chapter 66.

Diagnosis

First-degree AV block

1. Atrial premature beats may produce prolonged PR intervals due to refractory fast pathway of the AV node.
2. Several drugs, such as beta-blockers, non-dihydropyridine calcium channel blockers, flecainide, and amiodarone may prolong the PR interval.
3. In the middle-aged (30–59 years) general population first degree AV block may be a transient phenomenon, and is not associated with increased mortality.

Second-degree AV block

1. Non-conducted atrial premature beats may mimic AV block.
2. An apparent narrow QRS type II block may be a type I block with miniscule increments of the PR interval.
3. Concealed His bundle or ventricular extrasystoles confined to the specialized conduction system without myocardial depolarization can produce electrocardiographic patterns that mimic type I and/or type II block (pseudo-AV block). Occasionally, retrograde P waves may be present.
4. If the PR is >300 ms, the block is in the AV node. If the PR is <160 ms, the block is in the bundle of His or bundle branches.[11]
5. A pattern resembling a narrow QRS type II block, in association with an obvious type I pattern in the same recording, effectively rules out type II block because the coexistence of both types of narrow QRS block is exceedingly rare.[12]
6. If the QRS complex demonstrates bundle branch block, the site of conduction can be anywhere in the AV conduction system. If the QRS complex is normal, the block is in the AV node or bundle of His.
7. If the conduction improves with atropine or exercise or worsens with carotid sinus massage, the block is in the AV node. If the conduction worsens with atropine or exercise or improves with carotid sinus massage, the block is in His or bundle branches.[11]

Table 65.2 Indications for invasive study of second-degree atrioventricular block

Asymptomatic type I second-degree AV block with bundle branch block
Asymptomatic advanced second-degree AV block with bundle branch block
Questionable diagnosis of type II block with a narrow QRS complex
Suspicion of concealed AV junctional or ventricular extrasystoles
Confirmation of bradycardia-dependent (phase 4) infranodal block in selected cases
Transient second-degree AV block with bundle branch block in patients with inferior myocardial infarction where the site of block is suspected to be in the His–Purkinje system rather than the AV node
Third-degree AV block with a fast ventricular rate

Barold SS and Hayes DL. Second-degree atrioventricular block: a reappraisal. *Mayo Clinic Proceedings*. 2001;**76**:44–57 with permission from Elsevier.

Table 65.3 HRS/EHRA 2011 statement on genetic testing

State of genetic testing for progressive cardiac conduction disease (CCD)	
Mutation-specific genetic testing for family members and appropriate relatives following the identification of the CCD-causative mutation in an index case.	I
Genetic testing for patients with either isolated CCD or CCD with concomitant congenital heart disease, especially when there is documentation of a positive family history of CCD.	IIb

HRS/EHRA 2011 Expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Europace*. 2011;**13**:1077–109 with permission from Oxford University Press.

8. Although the diagnosis of type II block is possible with an increasing sinus rate, the absence of sinus slowing is an important criterion of type II block, because a vagal surge can cause simultaneous sinus slowing and AV nodal block, which can superficially resemble type II block. Significant PR prolongation before and after the block and prolonged PP intervals during ventricular asystole are indicative of vagal block that is a benign condition, rather than **paroxysmal AV block**, i.e. pause-dependent phase 4 AV block, that is potentially dangerous for syncope.[13]
9. The diagnosis of type II block cannot be established if the first post-block P wave is followed by a shortened PR interval or is not discernible.
10. A 2:1 AV block is not necessarily a type II block. It can be high-grade if the sinus rate is low or even a normal response of the AV node to an atrial tachycardia or flutter.

Third-degree AV block

1. Unless the escape rhythm is lower than the sinus rate (and usually <45 bpm), complete AV block cannot be differentiated from AV dissociation.
2. In patients younger than 60 years with unexplained second-degree (Mobitz II) or third-degree AV block, sarcoidosis should be considered.[14] In this case, immunosuppression can be useful.

Indications for electrophysiology study in second-degree AV block are presented in Table 65.2 and for genetic testing in progressive conduction disease in Table 65.3.

The value of adenosine or ATP testing for induction of latent AV block is not established.[15] However, there has been evidence that induction of cardiac pauses (due to AV block or sinoatrial block >10 s by an IV bolus of 20 mg ATP) indicates the need for DDD pacing.[16,17] Adenosine may also be used, but its effects are not identical with those of ATP.[17]

Therapy

Marked **first-degree AV block** (PR 0.30 s or greater) can produce a clinical condition similar to that of the pacemaker syndrome. Clinical evaluation often requires a treadmill stress test, because patients are more likely to become symptomatic with mild or moderate exercise when the PR interval cannot adapt appropriately. In patients with marked first-degree AV block and LV systolic dysfunction, it would seem prudent to consider a biventricular DDD device.[1] First-degree AV block during cardiac resynchronization therapy (CRT) predisposes to loss of ventricular resynchronization during biventricular pacing. This is because it favours the initiation of electrical 'desynchronization', especially in association with a relatively fast atrial rate and a relatively slow programmed upper rate. In patients with myotonic dystrophy type I and PR >200 ms, QRS >100 ms, or both, pacing is indicated when HV >70 ms, and improves survival.[18]

In **type I second-degree AV block** the indications for permanent pacing are controversial, unless the conduction delay occurs below the AV node or there are symptoms. However, type I block is not usually benign in patients 45 years of age or older, and pacemaker implantation may be considered, even in the absence of symptomatic bradycardia or organic heart disease.[19]

Type II block progresses to complete heart block, particularly when the QRS is wide, and infranodal blocks require pacing, regardless of form or symptoms.[20,21] In patients with cardiac sarcoidosis a pacemaker (preferably with an ICD) should be implanted, even if the AV block reverses transiently.[14]

In **third-degree block**, pacing improves survival.[20,21]

Indications for permanent pacing and pacemaker mode selection are presented in Table 65.4.

Exercise-provoked distal atrioventricular block, if not due to acute ischaemia, has a poor prognosis and should be paced.[22]

Patients who develop complete atrioventricular block within 24 hours after **valve replacement**, which then persisted for >48 hours, are unlikely to recover.[23] AV block occurs in 1–3% after operations for **congenital heart disease**. Pacemaker implantation is recommended with persistent AV block for 7–10 days post-operatively.

Table 65.4 Indication for pacing in AV block

ACCF/AHA/HRS 2012 GL on device-based therapy	
Recommendations for acquired atrioventricular block in adults	
Third-degree and advanced second-degree AV block at any anatomical level associated with bradycardia with symptoms (including heart failure) or ventricular arrhythmias presumed to be due to AV block.	I-C
Third-degree and advanced second-degree AV block at any anatomical level associated with arrhythmias and other medical conditions that require drug therapy that results in symptomatic bradycardia.	I-C
Third-degree and advanced second-degree AV block at any anatomical level in awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 s or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.	I-C
Third-degree and advanced second-degree AV block at any anatomical level in awake, symptom-free patients with atrial fibrillation and bradycardia with one or more pauses ≥5 s.	I-C
Third-degree and advanced second-degree AV block at any anatomical level after catheter ablation of the AV junction.	I-C
Third-degree and advanced second-degree AV block at any anatomical level associated with post-operative AV block that is not expected to resolve after cardiac surgery.	I-C
Third-degree and advanced second-degree AV block at any anatomical level associated with neuromuscular diseases with AV block, such as myotonic muscular dystrophy, Kearns–Sayre syndrome, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy, with or without symptoms.	I-B
Second degree AV block with associated symptomatic bradycardia, regardless of type or site of block.	I-B
Asymptomatic persistent third-degree AV block at any anatomical site with average awake ventricular rates ≥40 bpm if cardiomegaly or LV dysfunction is present or if the site of block is below the AV node.	I-B
Second- or third-degree AV block during exercise in the absence of myocardial ischaemia.	I-C
Persistent third-degree AV block with an escape rate >40 bpm in asymptomatic adult patients without cardiomegaly.	IIa-C
Asymptomatic second-degree AV block at intra- or infra-His levels found at electrophysiological study.	IIa-B
First- or second-degree AV block with symptoms similar to those of pacemaker syndrome or haemodynamic compromise.	IIa-B
Asymptomatic type II second-degree AV block with a narrow QRS (class I when type II second-degree AV block occurs with a wide QRS, including isolated RBBB).	IIa-B
Neuromuscular diseases, such as myotonic muscular dystrophy, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy with any degree of AV block (including first-degree AV block), with or without symptoms, because there may be unpredictable progression of AV conduction disease.	IIb-B
AV block in the setting of drug use and/or drug toxicity when the block is expected to recur, even after the drug is withdrawn.	IIb-B
Asymptomatic first-degree AV block.	III-B
Asymptomatic type I second-degree AV block at the supra-His (AV node) level or which is not known to be intra- or infra-Hisian.	III-C
AV block that is expected to resolve and is unlikely to recur (e.g. drug toxicity, Lyme disease, or transient increases in vagal tone, or during hypoxia in sleep apnoea syndrome in the absence of symptoms).	III-B
ESC 2013 GL on pacing and CRT	
First-degree AV block	
Permanent pacemaker implantation for patients with persistent symptoms similar to those of pacemaker atrioventricular block (PR >0.3 s).	IIa-C
Indication for pacing in persistent bradycardia	
Pacing with third- or second-degree type 2 acquired AV block irrespective of symptoms.	I-C

(*Continued*)

Table 65.4 Continued

Pacing in second-degree type 1 acquired AV block which causes symptoms or is found to be located at intra- or infra-His levels at EPS.	IIa-C
Pacing in AV block or due to reversible causes.	III-C
Indication for pacing in intermittent documented bradycardia	
Pacing in intermittent/paroxysmal intrinsic third- or second degree AV block (including AF with slow ventricular conduction).	I-C
Pacing in patients ≥ 40 years with recurrent, unpredictable reflex syncopes and documented symptomatic pause/s due to sinus arrest or AV block or the combination of the two.	IIa-B
Pacing in patients with history of syncope and documentation of asymptomatic pauses >6 s due to sinus arrest, or sinus-atrial block or AV block.	IIa-C
Pacing in reversible causes of bradycardia.	III-C
HRS/EHRA/APHRS 2013 expert consensus statement on inherited arrhythmia	
Recommendations on progressive cardiac conduction disease	
Pacemaker implantation is recommended in patients with a diagnosis of PCCD and the presence of: a) Intermittent or permanent third degree or high-grade AV block or b) Symptomatic Mobitz I or II second-degree AV block.	I
Pacemaker implantation can be useful in patients with a diagnosis of PCCD and the presence of bifascicular block with or without first degree AV block.	IIa
ICD implantation can be useful in adult patients diagnosed with PCCD with a mutation in the lamin A/C gene with left ventricular dysfunction and/ or non-sustained VT.	IIa

ACCF/AHA/HRS 2012 focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2013;**61**:e6–75 with permission from Elsevier.
ESC 2013 Guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart *J*. 2013;**34**:2281–329, with permission from Oxford University Press.
HRS/EHRA APHRS 2013 Expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Heart Rhythm*. 2013;**10**:1932–63 with permission from Elsevier.
RS/ACCF 2012 Expert consensus statement on pacemaker device and mode selection. *Heart Rhythm*. 2012;**9**:1547–5271 with permission from Elsevier.

Table 65.5 Mode of pacing in AV block

HRS/ACCF 2012 statement on pacemaker device mode section	
Pacing mode selection in AV block	
DDD pacing is recommended in patients with AV block	I-C
CCI pacing is recommended as an acceptable alternative to DDD pacing in patients with AV block who have specific clinical situations that limit the benefits of DDD pacing (sedentary patients, significant medical co-morbidities, and technical issues, such as vascular access limitations)	I-B
DDD is recommended over VVI pacing in adult patients with AV block who have documented pacemaker syndrome	I-B
VDD pacing can be useful in patients with normal sinus node function and AV block (e.g. the younger patient with congenital AV block)	IIa-C
VVI pacing can be useful in patients with AV junction ablation for rate control of AF due to the high rate of progression to permanent AF	IIa-B
DDD pacing should not be used in patients with AV block in permanent or longstanding persistent AF in whom efforts to restore or maintain SR are not planned	III-C
ESC 2013 GL on Pacing and CRT	
Choice of pacing mode/programming in persistent bradycardia	
In patients with sinus rhythm and acquired AV block, dual-chamber PM should be preferred to single chamber ventricular pacing to avoid pacemaker syndrome and improve quality of life.	IIa-A
Ventricular pacing with rate-response function is recommended in permanent AF and AV block.	I-C
Choice of pacing mode in intermittent documented bradycardia	
Preservation of spontaneous AV conduction is recommended.	I-B

HRS/ACCF 2012 Expert consensus statement on pacemaker device and mode selection. *Heart Rhythm*. 2012;**9**:1547–5271 with permission from Elsevier.
ESC 2013 Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J*. 2013;**34**:2281–329, with permission from Oxford University Press.

Endocardial leads, when feasible, are preferable to epicardial leads.[24]

Genetic therapies and biological pacemakers by means of viral-based or stem cell-based gene delivery systems as well as engineered electrical conduction tracts are under study.[25,26]

Choice of pacing mode

Mode selection for permanent pacing is presented in Table 65.5 and Figure 65.1. DDD pacing has not been shown to offer reduced rates of cardiovascular death or stroke, or even quality of life, compared to VVI pacing.[27–29] However, there may be a significant reduction in the development of atrial fibrillation with physiological pacing,[27] although not in all trials,[29] as well as avoidance of pacemaker syndrome that may be seen in 5–25% of patients with VVI pacing. An AAI-DDD changeover mode (SafeR) reduced ventricular pacing in a general pacemaker population, but had no effect on hospitalization for HF, AF, or cardioversion, when compared with DDD (ANSWER trial).[30] VDD pacing is a viable alternative to DDD pacing in patients with high-degree AV block and normal sinus node function, offering lower cost, high reliability, and abbreviated implantation time.[31] The main problem is the degradation of atrial sensing ability with time. Prolonged ventricular dyssynchrony induced by long-term RV apical pacing is associated with deleterious LV remodelling and deterioration of both LV diastolic and systolic function.[32,33] RV septal pacing sites are probably beneficial by means of intraventricular synchrony and LV function,[34,35] and specific His-bundle pacing is a promising option,[36] with acute results comparable to these of CRT.[37] Theoretically, a mid-septal position should be the optimum site, at least in patients without a previous anteroseptal myocardial infarction, but no benefit over apical pacing has been shown in randomized but not very long-term studies.[38,39] Biventricular pacing may be preferable,[40] especially in patients with reduced LVEF. In the BLOCK-HF trial, biventricular pacing was preferable to RV pacing in the presence of LVEF <50% and AV block,

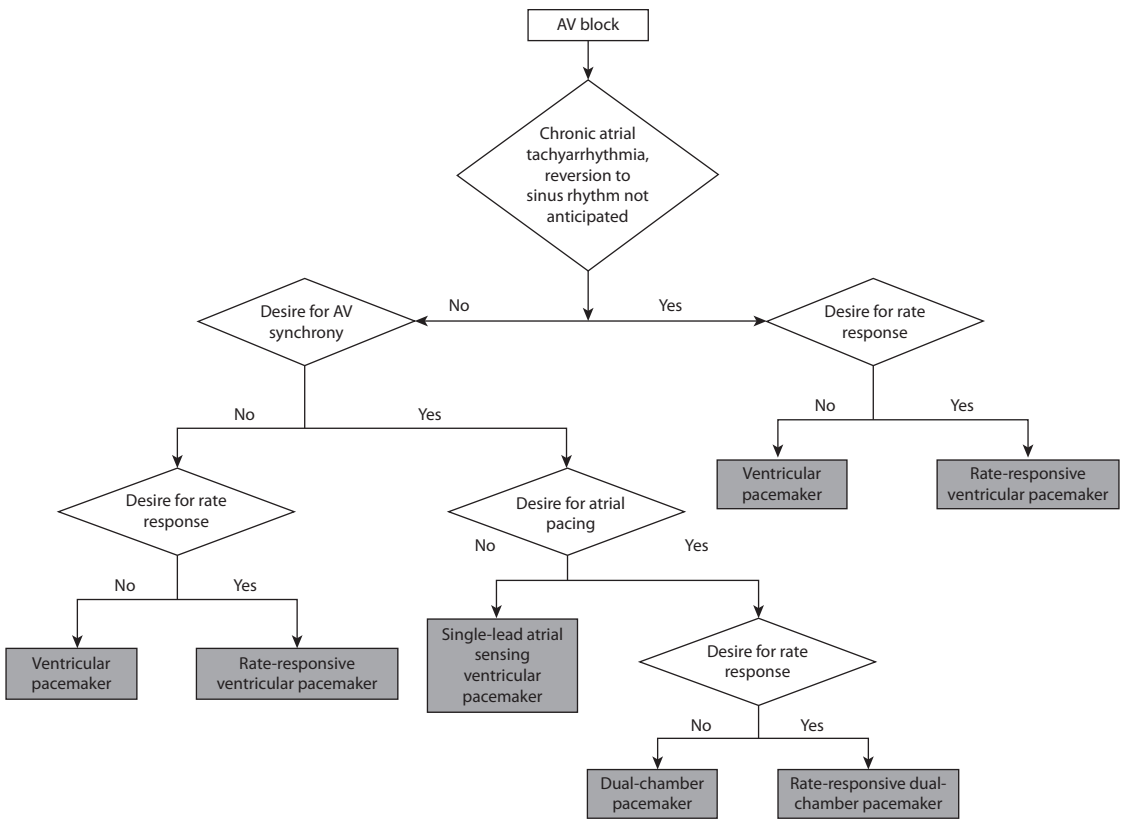

Figure 65.1 ACCF/AHA/HRS 2012 on Device-based therapy of cardiac rhythm abnormalities. Pacing mode in sick sinus syndrome. Selection of pacemaker systems for patients with atrioventricular block.

ACCF/AHA/HRS 2012 Focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2013;**61**:e6–75 with permission from Elsevier.

but the potential of increased LV lead-related complications should be considered (BLOCK-HF trial).[41]

Atrioventricular dissociation

AV dissociation is independent beating of the atria and ventricles due to:

1. Slowing of the sinus rate which allows escape of a subsidiary or latent pacemaker
2. Acceleration of a latent pacemaker, as happens in non-paroxysmal AV junctional tachycardia or VT
3. Complete heart block with junctional or ventricular escape rhythm.

Intraventricular block

Definition

This is a block at any level of the His–Purkinje system and is usually due to ischaemic heart disease and hypertension as well as the causes described in AV block. It may also be seen in apparently healthy persons. Definitions have been provided by the AHA/ACCF/HRS[42] (Table 65.6). Current criteria for LBBB include a QRS duration ≥120 ms, and this threshold is also used for CRT recommendations. However, certain patients may not have true complete LBBB but likely have a combination of left ventricular hypertrophy and left anterior fascicular block, and stricter criteria, such as a QRS duration ≥140 ms for men and ≥130 ms for women, along with mid-QRS notching or slurring in ≥2 contiguous leads, have been recently proposed.[43]

Left bundle branch block (LBBB) or **right bundle branch block (RBBB)** leads to interventricular dyssynchrony. The prevalence of bundle branch block increases from 1% at age 50 years to 17% at age 80 years, resulting in a cumulative incidence of 18%.[44]

RBBB may display normal axis or 180° (common type or Wilson block). Left or extreme right axis deviation suggest coexistent hemiblock. Pure RBBB and bifascicular blocks are associated with S waves in leads I and aVL. An ECG pattern of RBBB in lead V_1 with absent S wave in leads I and aVL indicates concomitant LBB delay and bilateral block.[44] Both RBBB and incomplete RBBB are two to three times more common among men than women.[46] RBBB can be seen in hypertensives, and as opposed to LBBB, was considered not to be associated with increased mortality. There has been recent evidence, however, that complete RBBB (but not incomplete) is associated with increased cardiovascular risk and all-cause mortality.[20]

LBBB may display normal or, more often, left axis deviation that implies worse prognosis. Right axis deviation may be seen in dilated cardiomyopathy. Preexisting left bundle branch block in the absence of clinical evidence of heart disease is rare but carries a slightly increased mortality. The presence of an initial r wave of ≥1 mm in lead V_1 usually indicates intact left to right ventricular septal activation,[47] unless the r wave is due to a large septal scar.[48] Newly acquired LBBB is most often a hallmark of advanced hypertensive and/or ischaemic heart disease, and carries a 10-fold increase in mortality.[49] Patients with bifascicular or trifascicular conduction defects have a 4.9% cumulative incidence of high-degree AV block at 5 years (17% if they present with syncope).[50] A prolonged HV interval (>70 ms) may,[51,52] or may not,[50] indicate increased risk for development of advanced block. In patients with LVEF <35%, RBBB is associated with a significantly greater scar size than LBBB and occlusion of a proximal LAD septal perforator causes RBBB.[53]

Fascicular block (left anterior, LAH; or left posterior hemiblock, LPH) leads to intraventricular dyssynchrony. LAH (left axis deviation with Q in I and aVL) and LPH (right axis deviation with Q in inferior leads) may mimic or mask anterior or inferior myocardial infarction.

Left anterior hemiblock is more common in men and increases in frequency with advancing age (Figure 65.2). Evidence is presented regarding the relationship of spontaneous closure of ventricular septal defects, which may explain the finding of this and other conduction defects in young populations. Isolated left anterior hemiblock is a relatively frequent finding in subjects devoid of evidence of structural heart disease. Conversely, isolated **left posterior hemiblock** is a very rare finding; its prognostic significance is unknown and is commonly associated with right bundle branch block, and there is great propensity to develop complete atrioventricular block and Stoke–Adams seizures (Figure 65.3).[54]

Bifascicular block refers to LBBB or RBBB plus a hemiblock.

Trifascicular block refers to block of both the left and right bundles or to first-degree AV block with additional bifascicular block.

Atypical intraventricular conduction defects refer to wide QRS without any typical ECG pattern and usually occur in patients with ischaemic or non-ischaemic heart failure. Prolonged QRS duration in a standard 12-lead ECG is associated with increased mortality in a general population, with intraventricular conduction delay being most strongly associated with an increased risk of arrhythmic death.[55] Subjects with prolonged QRS durations, even without bundle branch block, are at increased risk for future pacemaker implantation. Such individuals may warrant monitoring for progressive conduction disease.[56]

Indications for permanent pacing are presented in Table 65.7.

Table 65.6 AHA/ACC/HRS 2009 recommendations for standardization and interpretation of ECG

Criteria for intraventricular block

Complete RBBB

1. QRS duration ≥120 ms in adults, >100 ms in children aged 4 to 16 years, and <90 ms in children <4 years of age.
2. rsr′, rsR′, or rSR′ in leads V_1 or V_2. The R′ or r′ deflection is usually wider than the initial R wave. In a minority of patients, a wide, and often notched, R wave pattern may be seen in leads V_1 and/or V_2.
3. S wave of greater duration than R wave or >40 ms in leads I and V_6 in adults.
4. Normal R peak time in leads V_5 and V_6 but >50 ms in lead V_1.

Of the above criteria, the first three should be present to make the diagnosis. When a pure dominant R wave, with or without a notch, is present in V_1, criterion 4 should be satisfied.

Incomplete RBBB

Incomplete RBBB is defined by QRS duration 110–120 ms in adults, 90–100 ms in children 4 to 16 years of age, and 86–90 ms in children <8 years of age.

Other criteria are the same as for complete RBBB.

Complete LBBB

1. QRS duration ≥120 ms in adults, >100 ms in children 4 to 16 years of age, and >90 ms in children <4 years of age.
2. Broad notched or slurred R wave in leads I, aVL, V_5, and V_6 and an occasional RS pattern in V_5 and V_6 attributed to displaced transition of QRS complex.
3. Absent q waves in leads I, V_5, and V_6, but, in the lead aVL, a narrow q wave may be present in the absence of myocardial pathology.
4. R peak time >60 ms in leads V_5 and V_6 but normal in leads V_1, V_2, and V_3, when small initial r waves can be discerned in the above leads.
5. ST and T waves usually opposite in direction to QRS.
6. Positive T wave in leads with upright QRS may be normal (positive concordance).
7. Depressed ST segment and/or negative T wave in leads with negative QRS (negative concordance) are abnormal.
8. The appearance of LBBB may change the mean QRS axis in the frontal plane to the right, to the left, or to a superior, in some cases in a rate-dependent manner.

Incomplete LBBB

1. QRS duration 110–119 ms in adults, 90–100 ms in children 8 to 16 years of age, and 80–90 ms in children <8 years of age.
2. Presence of left ventricular hypertrophy pattern.
3. R peak time greater than 60 ms in leads V_4, V_5, and V_6.
4. Absence of q wave in leads I, V_5, and V_6.

Left anterior fascicular block

1. Frontal plane axis between –45° and –90°.
2. qR pattern in lead aVL.

Left anterior fascicular block

3. R peak time in lead aVL of 45 ms or more.
4. QRS duration less than 120 ms.

These criteria do not apply to patients with congenital heart disease in whom left axis deviation is present in infancy.

Left posterior fascicular block

1. Frontal plane axis 90°–180° in adults. Owing to the more rightward axis in children up to 16 years of age, this criterion should only be applied to them when a distinct rightward change in axis is documented.
2. rS pattern in leads I and aVL.
3. qR pattern in leads III and aVF.
4. QRS duration <120 ms.

AHA/ACCF/HRS Recommendations for the standardization and interpretation of the electrocardiogram: Part III: Intraventricular conduction disturbances. *Circulation*. 2009;**119**:e235–40 with permission from Wolters Kluwer.

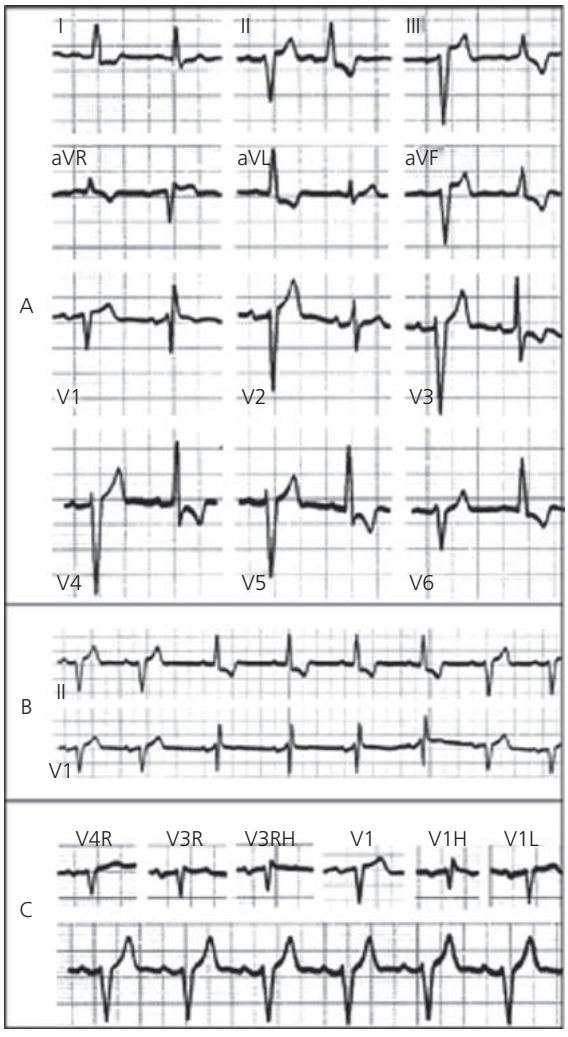

Figure 65.2 Permanent RBBB with intermittent left anterior hemiblock (LAH). The LAH conceals the signs of RBBB. (A) In every lead, the first beat shows LAH (plus RBBB), and the second beat shows RBBB alone. (B) Simultaneous recording of leads II and V_1. LAH is seen only in the first two beats and the last two beats. When LAH is absent, a typical RBBB pattern is uncovered. (C) The precordial chest leads recorded at the time when LAH was present (as seen in lead II) show the pattern of RBBB when V_3R and V_1 were recorded one intercostal space above the normal level (V_3RH and V_1H).

Elizari MV, *et al*. Hemiblocks revisited. *Circulation*. 2007;**115**:1154–63 with permission from Wolters Kluwer.

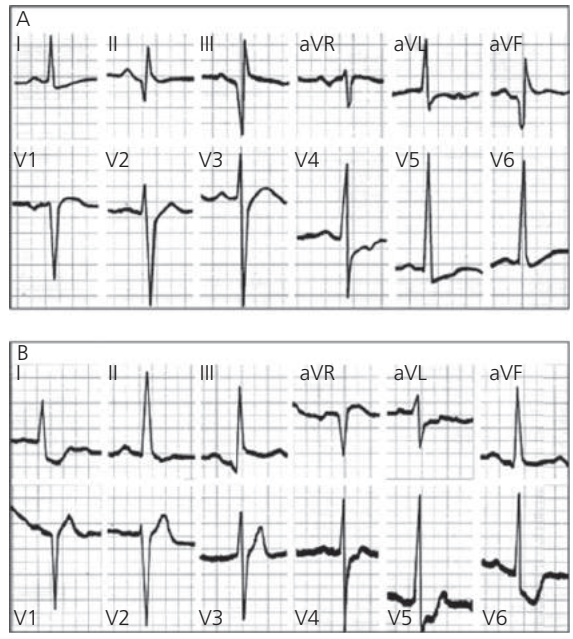

Figure 65.3 Transient left posterior hemiblock (LPH) caused by subepicardial inferior wall injury greatly conceals the pattern of inferior wall myocardial infarction in a 62-year old patient with unstable angina. (A) Clear-cut signs of inferior infarction. (B) During an episode of angina, the ECG shows a transient LPH, which almost completely conceals the signs of the inferior wall myocardial infarction.

Elizari MV, et al. Hemiblocks revisited. *Circulation*. 2007;**115**:1154–63 with permission from Wolters Kluwer.

Therapy

Pacing is indicated in the presence of syncope (Figure 65.4), particularly in the presence of a prolonged HV interval. However, up to 14% of patients with BBB and preserved LV function may have induced SVT or VT at electrophysiology study.[57] In patients without syncope, the rate of progression to high-degree AV block is low, and there is no non-invasive technique with a high predictive value. An HV interval >100 ms or the demonstration of intra- or infra-Hisian block during incremental atrial pacing at a pacing rate >150 bpm is predictive for the development of high-grade AV block, but the sensitivity of these findings is low. Wireless monitoring devices may be useful in the presence of inconsistent symptoms.[58] Permanent pacing, apart from preventing future symptoms, has been found to have no beneficial effect on survival.

Table 65.7 Pacing in chronic bifascicular block

ACCF/AHA/HRS 2012 GL on device-based therapy	
Recommendations for permanent pacing in chronic bifascicular block	
Advanced second-degree AV block or intermittent third-degree AV block.	I-B
Type II second-degree AV block.	I-B
Alternating bundle branch block.	I-C
Syncope not demonstrated to be due to AV block when other likely causes have been excluded, specifically VT.	IIa-B
Incidental finding at electrophysiological study of a markedly prolonged HV interval (≥100 ms) in asymptomatic patients.	IIa-B
Incidental finding at electrophysiological study of pacing-induced infra-His block that is not physiological.	IIa-B
Neuromuscular diseases, such as myotonic muscular dystrophy, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy with bifascicular block or any fascicular block, with or without symptoms.	IIb-C
Fascicular block without AV block or symptoms.	III-B
Fascicular block with first-degree AV block without symptoms.	III-B
ESC 2013 on pacing and CRT	
Indication for cardiac pacing in patients with BBB	
BBB, unexplained syncope and abnormal EPS	
Pacing in syncope, BBB and HV ≥70 ms, or second- or third-degree His–Purkinje block during incremental atrial pacing or with pharmacological challenge.	I-B
Alternating BBB	
Pacing is indicated in alternating BBB with or without symptoms.	I-C
BBB, unexplained syncope non diagnostic investigations	
Pacing in selected patients with unexplained syncope and BBB.	II-B
Asymptomatic BBB	
Pacing for BBB in asymptomatic patients.	III-B

ACCF/AHA/HRS 2012 Focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2013;**61**:e6–75 with permission from Elsevier.
ESC 2013 Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J*. 2013;**34**:2281–329, with permission from Oxford University Press.

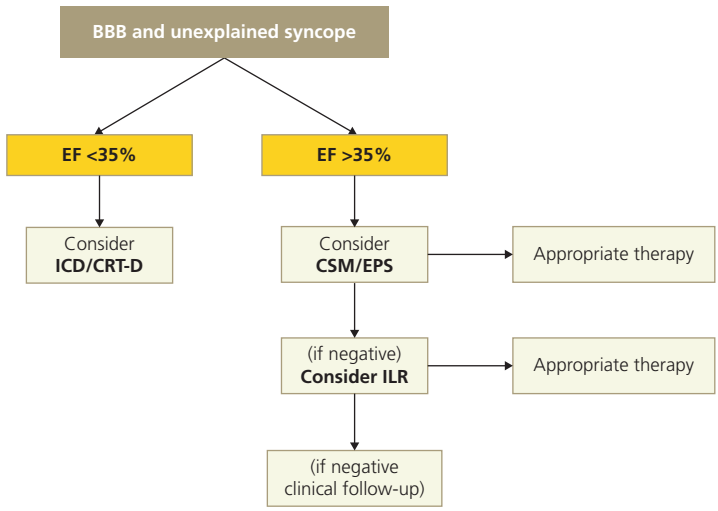

Figure 65.4 ESC 2013 GL on pacing and CRT.

ESC 2013 Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J*. 2013;**34**:2281–329, with permission from Oxford University Press.

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Chapter 66

Conduction disease in specific conditions

Recent myocardial infarction

In the reperfusion era, the incidence of AV block has decreased to 7%,[1] whereas the incidence of bundle branch block remains at 5% (and an additional 18% as transient).[2] They both predict higher mortality. Indications for permanent pacing (>14 days after MI) are presented in Chapter 29.

Congenital AV block

Congenital AV block may be immune (usually) or non-immune. Transplacental penetration of anti-Ro/SSA and anti-La/SSB ribonucleoprotein antibodies from the mother, who may have systemic lupus erythematosus, systemic sclerosis, or Sjögren's syndrome, or may even be entirely asymptomatic, into the fetal circulation is associated with congenital conduction disturbances. Half of these asymptomatic women develop symptoms of a rheumatic disease, most commonly arthralgias and xerophthalmia, but few develop lupus nephritis.[3] Anti-Ro/SSA antibodies may cross-react with T- and L-type calcium channels and the potassium channel hERG, and induce AV block.[4] Congenital complete heart block is the more severe manifestation of so-called 'neonatal lupus'. It occurs in approximately 2% of neonates whose mothers are positive for anti-Ro/SSA and anti-La/SSB, suggesting that additional

genetic and environmental as well as other factors, such as, possibly, vitamin D deficiency, may also play a role in the development of block.[4–6] It is typically detected *in utero* or within the neonatal period (0–27 days after birth).[7] Of affected fetuses, 17.5% die, 30% *in utero*, and the cumulative probability of survival at 10 years for a child born alive is 86%, with a higher case fatality rate in non-white patients.[8] The risk of recurrence of complete heart block in a subsequent child is 10–18%.[9] A pacemaker is required in about 66% of cases in childhood, and eventually almost 100% of children will require one by adulthood.[10] Complete AV block is irreversible while incomplete AV block may be potentially reversible after fluorinated steroid therapy.[7] Maternal use of hydroxychloroquine is also associated with a reduced risk of recurrent cardiac manifestations.[11] Anti-Ro/SSA antibodies might also be pathogenic for the adult heart with second-degree AV block, sinus bradycardia, QT prolongation, and ventricular arrhythmias seen in adults.[7] Anti-Ro Abs from patients with autoimmune diseases inhibit I_{Kr} by cross-reacting with the HERG channel l.[12] The adult AV node is generally thought to be resistant to the damaging effect of anti-Ro (SSA) and anti-La (SSB) autoantibodies. However, anecdotal case reports suggest that heart block developing in adult SS-positive patients may be associated with such concurrent autoantibodies. Congenital or childhood non-immune AV block may also occur. Recently, ECG screening in parents of children affected by idiopathic AV block revealed a high prevalence of conduction abnormalities, thus suggesting an inheritable trait.[13] Theoretically, permanent pacing should avoid the right ventricular apex, and prefer a septal position,[14] but the issue is rather controversial since no long-term studies exist (see Chapter 65 for discussion).[13] Indications for permanent pacing in congenital heart block are presented in Table 66.1.

Pacing in adult congenital heart disease

Indications for permanent pacing in adults with congenital conditions are presented in Table 66.1. Endocardial leads are generally avoided in adults with congenital heart disease and intracardiac shunts. Risk assessment regarding haemodynamic circumstances, concomitant anticoagulation, shunt closure prior to endocardial lead placement, or alternative approaches for lead access should be individualized.[15] Devices that minimize ventricular pacing are preferred in SSS, and device with antitachycardia-pacing properties should be considered if the underlying anatomic substrate carries a high likelihood of developing atrial reentrant tachycardia.[16]

Sleep apnoea

Sleep apnoea syndrome should be considered in the differential diagnosis of bradyarrhythmias (ESC 2015 GL on VA and SCD, IIa-B), and the presence of sleep apnoea and reduced oxygen saturation may be considered as a risk factor for SCD in subjects with sleep disordered breathing (ESC 2015 GL on VA and SCD, IIb-C).[17] Nasal continuous positive airway pressure (CPAP) therapy is effective in reducing sleep apnoea episodes, whereas atrial overdrive pacing may not be.[18] Pacing may be needed in patients with symptomatic bradycardia despite CPAP, but its value is not established.

Neuromuscular disorders

Several different types of muscular dystrophies, such as Emery-Dreifuss muscular dystrophy, limb girdle

Table 66.1 Pacing in congenital heart disease

ESC 2013 GL on cardiac pacing and CRT	
Indications for pacing therapy in congenital heart disease	
Congenital AV block	
Pacing in high degree and complete AV block in symptomatic patients and in asymptomatic patients with any of the following risk conditions: ventricular dysfunction, prolonged QTc interval, complex ventricular ectopy, wide QRS escape rhythm, ventricular rate <50 bpm ventricular pauses >three-fold the cycle length of the underlying rhythm.	I-C
Pacing in asymptomatic patients with high degree and complete AV block in absence of the above risk conditions.	IIb-C
Post-operative AV block in congenital heart disease.	
Permanent pacing for advanced second degree or complete AV block persisting >10 days postoperatively.	I-B
Permanent pacing for persistent, asymptomatic bifascicular block (with or without PR prolongation) associated with transient, complete AV block.	IIa-C
Sinus node disease.	
Permanent pacing for symptomatic sinus node disease, including brady-tachy syndrome, when a correlation between symptoms and bradycardia is judged to be established.	I-C
Permanent pacing for asymptomatic resting heart rate <40 bpm or ventricular pauses lasting >3 s.	IIb-C

(*Continued*)

Table 66.1 Continued

AHA 2015 statement on congenital heart disease in the older adult	
AAIR or DDDR pacemaker implantation in symptomatic patients with sinus node dysfunction, including tachy-brady syndrome, and those with pause-dependent VT	I-C
Pacemaker implantation for any patient with postoperative Möbitz II second- or third-degree AV block that is not expected to resolve	I-C
Pacemaker implantation for asymptomatic ACHD patients with resting heart rates <40 bpm or sinus pauses >3 seconds	IIb-C
Because of the risk of pacing-induced ventricular dysfunction, programming in dual-chamber pacemakers should aim to maintain native AV conduction	I-C
ACCF/AHA/HRS 2012 GL on device-based therapy*	
Recommendations for permanent pacing in children, adolescents, and patients with congenital heart disease	
Advanced second- or third-degree AV block associated with symptomatic bradycardia, ventricular dysfunction, or low cardiac output.	I-C
Sinus nodal disease with correlation of symptoms during age-inappropriate bradycardia. The definition of bradycardia varies with the patient's age and expected heart rate.	I-B
Post-operative advanced second- or third-degree AV block that is not expected to resolve or that persists at least 7 days after cardiac surgery.	I-B
Permanent pacemaker implantation is indicated for congenital third-degree AV block with a wide QRS escape rhythm, complex ventricular ectopy, or ventricular dysfunction.	I-B
Permanent pacemaker implantation is indicated for congenital third-degree AV block in the infant with a ventricular rate <55 bpm or with congenital heart disease and a ventricular rate <70 bpm.	I-C
Patients with congenital heart disease and sinus bradycardia for the prevention of recurrent episodes of intra-atrial reentrant tachycardia; SND may be intrinsic or secondary to antiarrhythmic treatment.	IIa-C
Congenital third-degree AV block beyond the first year of life with an average heart rate <50 bpm, abrupt pauses in ventricular rate that are 2 or 3 times the basic cycle length, or associated with symptoms due to chronotropic incompetence.	IIa-B
Sinus bradycardia with complex congenital heart disease with a resting heart rate <40 bpm or pauses in ventricular rate >3 s.	IIa-C
Patients with congenital heart disease and impaired haemodynamics due to sinus bradycardia or loss of AV synchrony.	IIa-C
Unexplained syncope in the patient with prior congenital heart surgery complicated by transient complete heart block with residual fascicular block after a careful evaluation to exclude other causes of syncope.	IIa-B
Transient post-operative third-degree AV block that reverts to sinus rhythm with residual bifascicular block.	IIb-C
Congenital third-degree AV block in asymptomatic children or adolescents with an acceptable rate, a narrow QRS complex, and normal ventricular function.	IIb-C
Asymptomatic sinus bradycardia after biventricular repair of congenital heart disease with a resting heart rate <40 bpm or pauses in ventricular rate >3 s.	IIb-C
Transient post-operative AV block with return of normal AV conduction in the otherwise asymptomatic patient.	III-B
Asymptomatic bifascicular block with or without first-degree AV block after surgery for congenital heart disease in the absence of prior transient complete AV block.	III-C
Asymptomatic type I second-degree AV block.	III-C
Asymptomatic sinus bradycardia with the longest relative risk interval <3 s and a minimum heart rate >40 bpm.	III-C

* Similar recommendations have been provided by the PACES/HRS 2014 Consensus Statement on Arrhythmias in ACHD.
ESC 2013 Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J*. 2013;**34**:2281–329, with permission from Oxford University Press.
American Heart Association Council on Clinical Cardiology. Congenital heart disease in the older adult: a scientific statement from the American Heart Association. *Circulation*. 2015;**131**:1884–931 with permission from Wolters Kluwer.
ACCF/AHA/HRS 2012 Focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2013;**61**:e6–75 with permission from Elsevier.

muscular dystrophy (Erb's muscular dystrophy), myotonic dystrophy type 1 (Steinert's disease), and desmin-related myopathy, are associated with cardiac conduction defects.[19] Patients typically present with sinus bradycardia, first or higher degree AV block or bundle branch block, and vulnerability for sudden cardiac death. Prophylactic permanent pacing or ICD may be indicated (Table 66.2).

Pacing after cardiac surgery, TAVI, and cardiac transplantation

Pacemaker requiring bradyarrhythmias occur in 10% of patients after cardiac transplantation.[18] The bicaval surgical technique and young donor/recipient age are protective against a post-operative pacemaker requirement.[20] Following orthotopic heart transplantation, a degree of

Table 66.2 2015 ESC 2015 GL on VA and SCD. Arrhythmic risk in patients with neuromuscular disorders

Annual follow-up in patients with muscular dystrophies, even in the concealed phase of the disease when patients are asymptomatic and the ECG is normal.	I-B
Patients with ventricular arrhythmias are treated in the same way as patients without neuromuscular disorders.	I-C
Permanent pacemaker in third-degree or advanced second-degree AV block at any anatomical level.	I-B
Permanent pacemaker in myotonic dystrophy type 1 (Steinert disease), Kearns–Sayre syndrome or limb-girdle muscular dystrophy with any degree of AV block (including first-degree)	IIb-B
ICD in myotonic dystrophy type 1 (Steinert disease), Emery–Dreifuss and limb-girdle type 1B muscular dystrophies when there is an indication for pacing and evidence of ventricular arrhythmias.	IIIb-B

ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015; 2015;**36**:2793–867 with permission from Oxford University Press.

chronotropic incompetence is inevitable, but both sinus node and AV node functions improve during the first weeks after the operation. The optimal timing for permanent pacing should be individualized (Table 66.3).[21] Late-onset AV block occurs in 2.4% of patients with orthotopic heart transplant or heart-lung transplant. AV block is predominantly intermittent and often does not progress to permanent AV block. There are no predictable factors for its onset.[2]

Pacing in pregnancy

For women who have a stable, narrow, complex junctional escape rhythm, pacemaker implantation can be deferred until after delivery.[21] Complete heart block with a slow, wide QRS complex escape rhythm needs permanent pacing. This can be performed safely, especially if the fetus is beyond 8 weeks' gestation using echo guidance (ESC 2013 GL on pacing, IIa-C) or, ideally, electro-anatomic navigation.

Other pacing indications

Pacing for **hypertrophic cardiomyopathy** is discussed in Chapter 37, and pacing for **tachyarrhythmias** is presented in Table 66.4.

Table 66.3 Pacing after cardiac surgery and cardiac transplantation

ESC 2013 GL on cardiac pacing and CRT	
Pacing after cardiac surgery, transcatheter aortic valve implantation and heart transplantation	
High degree or complete AV block after cardiac surgery and TAVI	
A period of clinical observation up to 7 days is indicated in order to assess whether the rhythm disturbance is transient and resolves. In case of complete AV block with low rate of escape rhythm this observation period can be shortened since resolution is unlikely.	I-C
Sinus node dysfunction after cardiac surgery and heart transplantation	
A period of clinical observation from 5 days up to some weeks is indicated in order to assess if the rhythm disturbance resolves.	I-C
Chronotropic incompetence after heart transplantation	
Cardiac pacing for chronotropic incompetence impairing the quality of life late in the post-transplant period.	IIa-C
ACCF/AHA/HRS 2012 for device-based therapy of cardiac rhythm abnormalities	
Recommendations for pacing after cardiac transplantation	
Persistent inappropriate or symptomatic bradycardia not expected to resolve and for other class I indications for permanent pacing.	I-C
Relative bradycardia is prolonged or recurrent, which limits rehabilitation or discharge after post-operative recovery from cardiac transplantation.	IIb-C
Syncope after cardiac transplantation, even when bradyarrhythmia has not been documented.	IIb-C

ESC 2013 Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J*. 2013;**34**:2281–329, with permission from Oxford University Press. ACCF/AHA/HRS 2012 Focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2013;**61**:e6–75 with permission from Elsevier.

Table 66.4 Antitachycardia pacing

ACCF/AHA/HRS 2012 GL on device-based therapy	
Recommendations for permanent pacemakers that automatically detect and pace to terminate tachycardias	
Symptomatic recurrent supraventricular tachycardia that is reproducibly terminated by pacing when catheter ablation and/or drugs fail to control the arrhythmia or produce intolerable side effects.	IIa-C
Presence of an accessory pathway that has the capacity for rapid anterograde conduction.	III-C
Recommendations for pacing to prevent tachycardia	
Sustained pause-dependent VT, with or without QT prolongation.	I-C
High-risk patients with congenital long QT syndrome.	IIa-C
Prevention of symptomatic, drug-refractory, recurrent atrial fibrillation in patients.	IIb-B
Frequent or complex ventricular ectopic activity without sustained VT in the absence of the long QT syndrome.	III-C
Torsade de pointes VT due to reversible causes.	III-A
Prevention of atrial fibrillation in patients without any other indication for pacemaker implantation.	III-B
ESC 2013 GL on cardiac pacing and CRT	
Prevention and termination of atrial tachyarrhymias is not a stand-alone indication for pacing.	III-A

ACCF/AHA/HRS 2012 Focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2013;**61**:e6–75 with permission from Elsevier.
ESC 2013 Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J*. 2013;**34**:2281–329, with permission from Oxford University Press.

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Part XII

Syncope and sudden cardiac death

Relevant guidelines

Syncope

ESC/EHRA/HFA/HRS 2009 Guidelines on syncope

ESC/EHRA/HFA/HRS Guidelines for the diagnosis and management of syncope. *Eur Heart J*. 2009;**30**:2631–71.

AHA/ACCF 2006 Statement on syncope

AHA/ACCF Scientific statement on the evaluation of syncope. *Circulation*. 2006;**113**:316–27.

ACCF/AHA/HRS 2012 Guidelines for device-based therapy of cardiac rhythm abnormalities

2012 ACCF/AHA/HRS Focused update incorporated into the ACCF/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2013;**61**: e6–75.

ESC 2013 Guidelines on pacing and cardiac resynchronization

2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J*. 2013;**34**:2281–329

HRS/AACF Statement on pacemaker device mode selection 2012

HRS/ACCF Expert consensus statement on pacemaker device and mode selection: *Heart Rhythm*. 2012;**9**:1344–65.

2015 Heart Rhythm Society statement on postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope

2015 Heart Rhythm Society Expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *HeartRhythm* 2015;**12**:e41–63.

Sudden cardiac death

ESC 2015 GL on VA and SCD

2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Eur Heart J. 2015;**36**:2793–867.

HRS/EHRA 2011 Statement on genetic testing

HRS/EHRA Expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Europace*. 2011;**13**:1077–109.

AHA 2010 Guidelines for cardiopulmonary resuscitation

2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2010;**122**(18 Suppl 3): Parts 1–16.

HRS/EHRA/APHRS 2013 Expert consensus statement on inherited arrhythmia

HRS/EHRA/APHRS Expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Heart Rhythm*. 2013;**10**:1932–63

Chapter 67

Syncope

Definition

Syncope is a transient loss of consciousness due to transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery.[1] Syncope is also defined as a transient loss of consciousness associated with an inability to maintain postural tone, rapid and spontaneous recovery, and the absence of clinical features specific for another form of transient loss of consciousness, such as epileptic seizure.[2]

Epidemiology

The estimated incidence of self-reported syncope was 6.2 per 1000 person-years in the Framingham study. The age-adjusted incidence was 7.2 per 1000 person-years among both men and women.[3] In the United States, 1 to 2 million patients are evaluated for syncope annually; 3% to 5% of emergency department visits are for syncope evaluation, and 1% to 6% of urgent hospital admissions are for syncope.[3,4] There is a higher prevalence of first faints in patients between 10 and 30 years and after the age of 70.[1,3]

Classification

Neurally mediated, or reflex, syncope is the commonest form of syncope and can be divided to vasodepressor, mixed, or cardioinhibitory types (Table 67.1). Vasovagal syncope refers to 'common faint' that is mediated by emotion or orthostatic stress, is seen in young adults (about 1% of toddlers may have a form of vasovagal syncope), and may be preceded by prodromal symptoms of autonomic activation.[1] Vasovagal syncope is also defined as a syncope syndrome that usually: (1) occurs with upright posture held for more than 30 seconds or with exposure to emotional stress, pain, or medical settings; (2) features diaphoresis, warmth, nausea, and pallor; (3) is associated with hypotension and relative bradycardia, when known; and (4) is followed by fatigue.[2] There is absence of heart disease, and syncope occurs after prolonged standing in crowded, hot places, during a meal or postprandial, with head rotation, pressure on carotid sinus, or after exertion. Vasovagal syncope seldom occurs when a person is seated or reclining or, especially, during exercise.

Table 67.1 Classification of syncope (modified from ESC/EHRA/HFA/HRS 2009 GL on syncope)

Reflex (neurally mediated syncope)
Vasovagal
Emotional distress (fear, pain, instrumentation, blood phobia)
Orthostatic stress
Situational
Cough, sneeze
GI stimulation (swallow, defecation, visceral pain)
Post-micturition
Post-exercise
Postprandial
Others (laughter, brass instrument playing, weightlifting)
Carotid sinus syncope
Atypical forms (no apparent trigger)
Orthostatic hypotension
Primary autonomic failure
Diabetes, amyloidosis, uraemia, spinal cord injuries
Secondary autonomic failure
Pure autonomic failure (Bradbury–Eggleston syndrome), multiple system atrophy (Shy–Drager syndrome)
Drug-induced orthostatic hypotension
Alcohol, vasodilators, diuretics, phenothiazines, antidepressants
Volume depletion
Haemorrhage, diarrhoea, vomiting
Cardiovascular syncope
Arrhythmia
Bradycardia (SSS, AV disease, PPM malfunction)
Tachycardia (SVT, VT, VF due to channelopathies)
Drug-induced arrhythmia
Structural disease
Cardiac (CAD, valve disease, HCM, cardiac tumours, tamponade, congenital coronary anomalies, prosthetic valve malfunction)
Others (PE, aortic dissection, pulmonary hypertension)

EHRA/HFA 2009 Guidelines for the diagnosis and management of syncope. *Eur Heart J.* 2009;**30**:2631–71 with permission from Oxford University Press.

Orthostatic hypotension is defined by a fall >20 mmHg systolic and/or >10 mmHg diastolic in response to standing from the supine position within 3 minutes or during head-up tilt at 60–70 degrees and is seen in ages over 40 years and typically in the elderly. Abnormal BP responses taking longer than 30 s to stabilize during standing increase significantly with age, affecting 40% of those ≥80 years of age.[5] In the general population the prevalence of orthostatic hypotension is 6%.[6] 'Initial' (i.e. immediate decrease >40 mmHg) and restoration of blood pressure) and 'delayed' (progressive decrease without bradycardic reflex) orthostatic hypotension seen in the elderly are atypical forms.[7] **Postural orthostatic tachycardia syndrome (POTS)** is characterized by orthostatic intolerance associated with marked heart rate increases (>30 bpm or to >120 bpm). Dependent acrocyanosis of the legs that occurs with standing may be present and is characteristic of POTS.[8] The aetiology of this condition is still elusive and has been attributed to various forms of autonomic dysfunction, although in young ages a small-sized heart in the context of reduced blood volume may also be responsible.[9]

Cardiac syncope is the second most common cause and is mostly due to arrhythmias, and less due to sick sinus or AV nodal disease (Stokes–Adams syndrome). Structural heart disease may cause syncope due to restricted cardiac output and inappropriate reflex vasodilation and arrhythmia.

Pathophysiology

Syncope is due to a fall in systemic blood pressure (systolic BP to 60 mmHg or lower), with resultant decrease in global cerebral blood flow that can be as short as 6–8 s.[1] Systemic BP is determined by cardiac output and total peripheral vascular resistance. A low peripheral resistance can be due to inappropriate reflex activity, causing vasodilatation and bradycardia, or to drug-induced, primary, and secondary autonomic nervous system failure. Low cardiac output can be due to reflex bradycardia, arrhythmia, structural heart disease (i.e. aortic stenosis or pulmonary embolus), and inadequate venous return due to volume depletion or venous pooling.

Presentation

Typically, syncope is brief and occurs without warning. Recovery is characterized by immediate restoration of appropriate behaviour and orientation. In some forms, however, prodromal symptoms (light-headedness, nausea, visual disturbances) may be present, and the episode may last longer, rarely even minutes. Minor injury, such as laceration and bruises, are reported in 29% of patients with syncope whereas fractures and motor vehicle accidents in 6% of patients. In older patients with syncope complicated by a severe trauma, carotid sinus syndrome is the most common cause.[10] Recurrent syncope has serious effects on quality of life, with psychological impairment occurring in up to 33% of patients. Indications of admission are shown in Figure 67.1.

Aetiologic diagnosis

The causes of syncope are highly age-dependent. Paediatric and young patients are most likely to have

Admit if <u>any</u> of the following are present:

B	**B** NP level ≥ 300pg/ml **B** radycardia ≤ 50 in Emergency Department or pre-hospital
R	**R** ectal examination showing faecal occult blood (if suspicion of gastrointestinal bleed)
A	**A** naemia-Haemoglobin ≤ 9 g/l
C	**C** hest pain associated with syncope
E	**E** CG showing Q wave (not in lead III)
S	**S** aturation ≤94% on room air

Figure 67.1 The ROSE rule.

Reed MJ, *et al*. The ROSE (risk stratification of syncope in the emergency department) study. *J Am Coll Cardiol*. 2010;**55**:713–21 with permission from Elsevier.

neurocardiogenic syncope, conversion reactions (psychiatric causes), and primary arrhythmic causes, such as genetic channelopathies and Wolff–Parkinson–White syndrome. In middle age, neurocardiogenic syncope remains the most frequent cause of syncope. Elderly patients have a higher frequency of syncope caused by obstructions to cardiac output, e.g. aortic stenosis and pulmonary embolus, arrhythmias resulting from underlying heart disease, orthostatic hypotension, and carotid sinus syndrome.[10–12] In patients with LVEF <35% and an ICD, syncope is caused by arrhythmias in 40% of cases, whereas 60% of all syncopal events are caused by non-arrhythmic events, such as orthostatic hypotension syncope or vasodepressor reflex syncope (MADIT-RIT study).[13] Initial evaluation, especially in multidisciplinary syncope units,[1] defines the cause of syncope in 23–50% of patient whereas diagnosis is not established in up to 40% of cases. Conditions incorrectly diagnosed as syncope are presented in Table 67.2, and diagnostic criteria are presented in Table 67.3. A careful history about the onset and end of the attack, the circumstances under which syncope occurred, and the medical background of the patient are crucial for diagnosis.[14] Pseudosyncope usually occurs without a recognizable trigger many times in a day and lasts longer than syncope (up to 15 minutes). Trauma is more common in pseudoseizures. The eyes are usually open in epileptic seizures and syncope, but are usually closed in functional transient loss of consciousness. During tilt testing, the combination of apparent unconsciousness with loss of motor control, normal BP, HR, and EEG rules out syncope and most forms of epilepsy. Differentiation from epilepsy is presented in Table 67.4. Early impotence, disturbed micturition, and later parkinsonism and ataxia suggest autonomic failure.

Table 67.2 ESC/EHRA/HFA/HRS 2009 GL on syncope. Conditions incorrectly diagnosed as syncope

Disorders with partial or complete loss of consciousness but without global cerebral hypoperfusion
Epilepsy
Metabolic disorders (hypoglycaemia, hypoxia, hyperventilation with hypocapnia)
Intoxication
Vertebrobasilar TIA
Disorders without impairment of consciousness
Cataplexy
Drop attacks
Falls
Functional (psychogenic pseudosyncope)
TIA of carotid origin

EHRA/HFA 2009 Guidelines for the diagnosis and management of syncope. *Eur Heart J.* 2009;**30**:2631–71 with permission from Oxford University Press.

Table 67.3 ESC/EHRA/HFA/HRS 2009 GL on syncope. Diagnostic criteria for syncope

Vasovagal if precipitated by emotional or orthostatic distress with typical prodrome	I-C
Situational if during or immediately after specific triggers (Table 67.1)	I-C
Orthostatic when it occurs after standing up and there is hypotension	I-C
Arrhythmia-related when: Sinus bradycardia (<40 bpm) if awake or sinus pauses ≥3 s Mobitz II second- or third-degree AV block Alternating LBBB and RBBB VT or rapid SVT Polymorphic NSVT and long or short QT PPM or ICD malfunction with pauses	I-C
Cardiac, ischaemia-related when syncope presents with ECG evidence of acute ischaemia with or without MI	I-C
Cardiovascular when syncope presents in patients with prolapsing atrial myxoma, severe AS, pulmonary hypertension, PE, or acute aortic dissection	I-C

EHRA/HFA 2009 Guidelines for the diagnosis and management of syncope. Eur *Heart J.* 2009;**30**:2631–71 with permission from Oxford University Press.

Table 67.4 ESC/EHRA/HFA/HRS 2009 GL on syncope. Epilepsy vs syncope

Clinical findings that suggest the diagnosis	Seizure likely	Syncope likely
Symptoms before the event	Aura (such as funny smell)	Nausea, vomiting, abdominal discomfort, feeling of cold sweating (neurally mediated) Light-headedness, blurring of vision
Findings during loss of consciousness (as observed by an eyewitness)	Tonic-clonic movements are usually prolonged, and their onset coincides with loss of consciousness Hemilateral clonic movement Clear automatisms, such as chewing or lip smacking or frothing at the mouth (partial seizure) Tongue biting Blue face	Tonic-clonic movements are always of short duration (<15 s), and they start after the loss of consciousness
Symptoms after the event	Prolonged confusion Aching muscles	Usually of short duration Nausea, vomiting, pallor (neurally mediated)
Other clinical findings of less value for suspecting seizure (low specificity)		
Family history		
Timing of the event (night)		
'Pins and needles' before the event		
Incontinence after the event		
Injury after the event		
Headache after the event		
Sleepy after the event		
Nausea and abdominal discomfort		

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Investigations

ECG It is necessary to exclude conditions of cardiovascular syncope as shown in Table 67.5. The ECG may display conduction disturbances (atrioventricular or intraventricular block), pre-excited complexes, or signs of cardiomyopathy or genetic channelopathies.

Electrocardiographic monitoring Indications are presented in Table 67.5. Implantable loop recorders (ILR) may be necessary in patients with unexplained falls, suspected AV block or VT, or unsuccessful treatment for suspected epilepsy.[15,16] A high incidence of bradyarrhythmias and asystole, i.e. convulsive cardioinhibitory reflex syncope, has been found with the use of ILR in patients previously diagnosed with epilepsy.[17] Wireless monitoring devices may also be useful in this respect.[18] A classification of ECG recordings has been proposed (Table 67.6).

Echocardiography is necessary to diagnose structural disease and evaluate the LVEF.

TOE, **computed tomography**, or **magnetic resonance** may be needed in selected cases (suspicion of aortic dissection, pulmonary embolus, etc.).

Exercise testing is indicated in syncope during or after exertion (Table 67.7).

Tests for ischaemia are indicated in clinical suspicion of IHD.

Orthostatic challenge produces a displacement of blood from the thorax to the lower limbs, with resultant decrease in venous return and cardiac output. **Active standing** (Table 67.8) should be evaluated with sphygmomanometers. If more than four measurements per minute are necessary, continuous beat-to-beat non-invasive BP measurement can be used. **Tilt testing** reproduces a neurally mediated reflex and can also be positive in sick sinus syndrome (Table 67.9). It may be accelerated by provocative agents such as isoproterenol.

Carotid sinus massage Diagnosis of carotid sinus syndrome (CSS) requires the reproduction of spontaneous symptoms during 10 s of sequential right and left CSM, performed supine and erect, under continuous monitoring of HR and periodic measurement of BP, permitting better evaluation of the vasodepressor component (Table 67.10). In up to 30% of patients, an abnormal reflex is present only in the upright position.

Electrophysiology study Sensitivity and specificity of EPS is not good,[1] and positive results occur predominantly in patients with structural heart disease.[19] Indications are presented in Table 67.11. Values of sinus node recovery time (SNRT) ≥1.6 s or of corrected SNRT ≥525 ms are defined as abnormal responses, but the prognostic value of SNRT is not well defined.[1] Although a history of syncope and prolonged HV interval increase the risk of subsequent AV block in patients with BBB, neither of these factors are associated with a higher risk of death as opposed to increasing age, congestive heart failure, and coronary artery disease.[20] Furthermore, the absence of these findings does not exclude the development of AV block, and the prognostic value of a pharmacologically prolonged HV interval to a value ≥120 ms without induction of AV block is uncertain. In patients with previous myocardial infarction and preserved LVEF (>40%), induction of sustained monomorphic VT is strongly predictive of the cause of syncope,[21] whereas the induction of ventricular fibrillation may be a non-specific finding, particularly when three extrastimuli are used.[22] However, the absence of induction of ventricular arrhythmias identifies a group of patients at lower risk of arrhythmic syncope.[23] The adenosine triphosphate test is no longer recommended for the selection of patients for cardiac pacing.[1] However, there has been recent evidence that elderly patients with syncope of unknown origin and a positive ATP test (20 mg IV bolus causing pause due to sinoatrial or atrioventricular block >10 s) may benefit from DDD pacing.[24]

Electroencephalography is indicated only when epilepsy is suspected (Table 67.12).

Brain imaging (CT or MRI) are not indicated unless based on a neurological evaluation.[1]

Carotid Doppler ultrasonography is rarely indicated since TIA related to carotid artery disease do not cause loss of consciousness.

Subclavian ultrasonography may detect 'steal' due to subclavian artery stenosis (usually left), but most cases are asymptomatic.

Table 67.5 ESC/EHRA/HFA/HRS 2009 GL on syncope. Recommendations for electrocardiographic monitoring

Indications	
ECG features suggesting arrhythmic syncope	
Duration of monitoring according to risk and predicted recurrence rate:	I-B
Immediate in-hospital (in bed or telemetric) in high risk (see below)	I-C
Holter in very frequent syncope or pre-syncope (≥1 per week)	I-B
Implantable loop recorder (ILR) in:	
Recurrent syncope of uncertain origin, absence of high risk, and high likelihood of recurrence within battery life	I-B
High-risk patients with comprehensive evaluation unable to indicate diagnosis or specific treatment	I-B
ILR should be considered before implantation of cardiac pacemaker in suspected reflex syncope presenting with frequent or traumatic syncopal episodes	IIa-B
External loop recorders in patients with intersymptom interval ≤4 weeks	IIa-B
Diagnostic criteria	
ECG monitoring is diagnostic when a correlation between syncope and arrhythmia is detected.	I-B
If no such correlation, ECG monitoring is diagnostic when periods of Mobitz 2nd or 3rd degree AV block or a ventricular pause >3s (with the possible exception of young trained persons, during sleep, medicated pts, or rate-controlled AF), or rapid, prolonged SVT/VT are detected.	I-C
ECG documentation of pre-syncope without relevant arrhythmia is not an accurate surrogate for syncope.	III-C
Asymptomatic arrhythmias (other than listed above) are not an accurate surrogate for syncope.	III-C
Sinus bradycardia (in the absence of syncope) is not an accurate surrogate for syncope.	III-C

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Table 67.6 ESC/EHRA/HFA/HRS 2009 GL on syncope. Classification of ECG recordings obtained with ILR, with their probable-related mechanism (adapted from ISSUE classification)

	Classification	Suggested mechanism
Type 1, asystole: R-R pause ≥3 s	Type 1A, sinus arrest: progressive sinus bradycardia or initial sinus tachycardia, followed by progressive sinus bradycardia until sinus arrest	Probably reflex
	Type 1B, sinus bradycardia plus AV block: progressive sinus bradycardia followed by AV block (and ventricular pause/s), with concomitant decrease in sinus rate, or sudden-onset AV block (and ventricular pause/s), with concomitant decrease in sinus rate	Probably reflex
	Type 1C, AV block: sudden-onset AV block (and ventricular pause/s), with concomitant increase in sinus rate	Probably intrinsic
Type 2, bradycardia: decrease in HR >30% or <40 bpm for >10 s		Probably reflex
Type 3, no or slight rhythm variations: variations in HR <30% and heart rate >40 bpm		Uncertain
Type 4, tachycardia: increase in heart rate >30% of >120 bpm	Type 4A, progressive sinus tachycardia	Uncertain
	Type 4B, atrial fibrillation	Cardiac arrhythmia
	Type 4C, SVT (except sinus)	Cardiac arrhythmia
	Type 4D, VT	Cardiac arrhythmia

AV, atrioventricular; bpm, beats per minute; ECG, electrocardiographic; HR, heart rate; ILR, implantable loop recorder; ISSUE, International Study on Syncope of Unknown Etiology; SVT, supraventricular tachycardia; VT, ventricular tachycardia.
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Table 67.7 ESC/EHRA/HFA/HRS 2009 GL on syncope. Exercise testing

Indications	
Syncope during or shortly after exertion	I-C
Diagnostic criteria	
Exercise testing is diagnostic when syncope is reproduced during or immediately after exercise in the presence of ECG abnormalities or severe hypotension	I-C
Exercise testing is diagnostic if Mobitz second- or third-degree AV block develops during exercise, even without syncope	I-C

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Table 67.8 ESC/EHRA/HFA/HRS 2009 GL on syncope. Active standing

Indications	
Manual intermittent determination with sphygmomanometer of BP supine and during active standing for 3 min when orthostatic hypotension is suspected	I-B
Continuous beat-to-beat non-invasive pressure measurement in cases of doubt	IIb-C
Diagnostic criteria	
Symptomatic fall in systolic BP ≥20 mm Hg or diastolic BP ≥10 mm Hg, or a decrease in systolic BP to <90 mm Hg	I-C
Asymptomatic fall in systolic BP ≥20 mm Hg or diastolic BP ≥10 mm Hg, or a decrease in systolic BP to <90 mm Hg	IIa-C

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Table 67.9 ESC/EHRA/HFA/HRS 2009 GL on syncope. Tilt testing

Methodology	
Supine pre-tilt phase of at least 5 min when no venous cannulation is undertaken, and of at least 20 min when cannulation is undertaken	I-C
Tilt angle between 60 and 70°	I-B
Passive phase of a minimum of 20 min and a maximum of 45 min	I-B
For nitroglycerin, a fixed dose of 300–400mg sublingually is administered in the upright position	I-B
For isoproterenol, an incremental infusion rate from 1 up to 3 microgram/min in order to increase average heart rate by ~20–25% over baseline is recommended	I-B
Indications	
Unexplained single syncopal episode in high-risk settings (e.g. occurrence, or potential risk, of physical injury or with occupational implications), or recurrent episodes in the absence of organic heart disease, or in the presence of organic heart disease after cardiac causes of syncope have been excluded	I-B
To demonstrate susceptibility to reflex syncope to the patient	I-C
To discriminate between reflex and orthostatic hypotension syncope	IIa-C
For differentiating syncope with jerking movements from epilepsy	IIb-C
For evaluating patients with recurrent unexplained falls	IIb-C
For evaluating patients with frequent syncope and psychiatric disease	IIb-C
Not recommended for assessment of treatment	III-B
Isoproterenol tilt testing is contraindicated in patients with ischaemic heart disease	III-C
Diagnostic criteria	
In patients without structural heart disease, the induction of reflex hypotension/bradycardia with reproduction of syncope or progressive orthostatic hypotension (with or without symptoms) are diagnostic of reflex syncope and orthostatic hypotension, respectively	I-B
In patients without structural heart disease, the induction of reflex hypotension/bradycardia without reproduction of syncope may be diagnostic of reflex syncope	IIa-B
In patients with structural heart disease, arrhythmia or other cardiovascular cause of syncope should be excluded prior to considering positive tilt results as diagnostic	IIa-C
Induction of loss of consciousness in absence of hypotension and/or bradycardia should be considered diagnostic of psychogenic pseudosyncope	IIa-C

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Table 67.10 ESC/EHRA/HFA/HRS 2009 GL on syncope. Carotid sinus massage

Indications	
Patients >40 years with syncope of unknown aetiology after initial evaluation	I-B
Avoided in pts with previous TIA or stroke within the past 3 months and in pts with carotid bruits (unless Doppler excluded significant stenosis)	III-C
Diagnostic criteria	
Syncope is reproduced in the presence of asystole >3 s and/or fall in systolic BP<90 mm Hg	I-B

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Table 67.11 ESC/EHRA/HFA/HRS 2009 GL on syncope. Electrophysiology study

Indications	
In ischaemic heart disease when initial evaluation suggests an arrhythmic cause of syncope, unless there is already an established indication for ICD	I-B
In BBB when non-invasive tests have failed to make the diagnosis	IIa-B
In syncope preceded by sudden and brief palpitations when other non-invasive tests have failed to make the diagnosis	IIb-B
In Brugada syndrome, ARVC, and hypertrophic cardiomyopathy in selected cases	IIb-C
In selected cases of patients with high-risk occupations, in whom every effort to exclude a cardiovascular cause of syncope is warranted	IIb-C
Patients with normal ECG, no heart disease, and no palpitations	III-B

(*continued*)

Table 67.11 Continued

Diagnostic criteria	
EPS is diagnostic, and no additional tests are required in:	
Sinus bradycardia and prolonged CSNRT (>525 ms)	I-B
BBB and either a baseline HV interval ≥100ms, or second- or third-degree His-Purkinje block is demonstrated during incremental atrial pacing, or with pharmacological challenge	I-B
Induction of sustained monomorphic VT in patients with previous MI	I-B
Induction of rapid SVT which reproduces hypotensive or spontaneous symptoms	I-B
HV interval between 70 and 100 ms	IIa-B
Induction of polymorphic VT or VF in Brugada syndrome, ARVC, and patients resuscitated from cardiac arrest	IIb-B
Induction of polymorphic VT or VF in ischaemic cardiomyopathy or DCM cannot be considered a diagnostic finding	III-B

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Table 67.12 ESC/EHRA/HFA/HRS 2009 GL on syncope

Indications for neurological evaluation	
Patients in whom transient loss of consciousness is suspected to be epilepsy	I-C
When syncope is due to autonomic failure in order to evaluate the underlying disease	I-C
EEG, ultrasound of neck arteries, and brain CT or MRI are not indicated, unless a non-syncopal cause of transient loss of consciousness is suspected	III-B

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Table 67.13 ESC/EHRA/HFA/HRS 2009 GL on syncope

Indications for psychiatric evaluation	
Patients in whom transient loss of consciousness is suspected to be psychogenic pseudosyncope	I-C
Tilt testing, preferably with concurrent EEG recording and video monitoring, for diagnosis of transient loss of consciousness mimicking syncope ('pseudosyncope') or epilepsy	IIb-C

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Table 67.14 HRS 2015 statement on syncope

Investigation of patients assessed for POTS	
A complete history and physical examination with orthostatic vital signs and 12-lead ECG	I-E
Complete blood count and thyroid function studies for selected patients	IIa-E
24-h Holter monitor	IIb-E
Detailed autonomic testing, transthoracic echocardiogram, tilt-table testing, and exercise stress testing for selected patients	IIb-E
Investigation of Vasovagal Syncope	
Tilt-table testing for suspected vasovagal syncope and without a confident diagnosis after the initial assessment	IIa-BNR
Tilt-table testing for differentiating between convulsive syncope and epilepsy, for establishing a diagnosis of pseudosyncope, and for testing patients with suspected vasovagal syncope but without clear diagnostic features	IIa-BNR
Implantable loop recorders (ILRs) for assessing older patients with recurrent and troublesome syncope who lack a clear diagnosis and are at low risk of a fatal outcome	IIa-BR
Tilt testing is not recommended for predicting the response to specific medical treatments for vasovagal syncope	III-BR

Level B evidence is of a moderate level, either from randomized trials (B-R) or well-executed nonrandomized trials (B-NR).
Level of evidence E indicates simply consensus opinion.
HRS 2015 Expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Heart Rhythm*. 2015;**12**:e41–63 with permission from Elsevier.

Table 67.15 ESC/EHRA/HFA/HRS 2009 GL on syncope. Risk stratification

Short-term high risk criteria which require prompt hospitalization or intensive evaluation
Severe structural or coronary artery disease (heart failure, low LVEF, or previous myocardial infarction)
Clinical or ECG features suggesting arrhythmic syncope
• Syncope during exertion or supine
• Palpitations at the time of syncope
• Family history of SCD
• Non-sustained VT
• Bifascicular block (LBBB or RBBB combined with left anterior or left posterior fascicular block) or other intraventricular conduction abnormalities with QRS duration ≥120 ms
• Inadequate sinus bradycardia (<50 bpm) or sinoatrial block in absence of negative chronotropic medications or physical training
• Pre-excited QRS complex
• Prolonged or short QT interval
• RBBB pattern with ST elevation in leads V_1–V_3 (Brugada pattern)
• Negative T waves in right precordial leads, epsilon waves, and ventricular late potentials suggestive of ARVC
Important co-morbidities
• Severe anaemia • Electrolyte disturbance

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Vertebral artery ultrasonography may reveal stenosis that usually causes focal signs and oculomotor palsies and, possibly, also loss of consciousness.

Psychiatric consultation may be needed (Table 67.13). Table 67.14 presents investigations for patients with suspected POTS or vasovagal syncope.

Risk stratification

The prognosis is good, provided that structural heart disease and genetic channelopathies are excluded (Table 67.15). In patients with heart failure and ICD, syncope is associated with increased mortality irrespective of the cause.[13] The San Francisco Syncope Rule (history of congestive heart failure, haematocrit <30%, abnormal ECG result [new changes or non-sinus rhythm], complaint of shortness of breath, and systolic blood pressure (<90 mm Hg during triage) has a sensitivity of 96% and specificity 62% for predicting adverse outcomes.[25]

The ROSE rule has also shown high sensitivity and negative predictive value in the identification of high-risk patients with syncope.[26] In the EGSYS 2 trial, death of any cause occurred in 9.2% of patients with syncope during a mean follow-up of 614 days; 82% had an abnormal ECG and/or heart disease, and only six deaths (3%) occurred in patients without any apparent cardiac abnormality.[27] Orthostatic hypotension is associated with increased total and cardiac mortality.[28]

Therapy

Reflex syncope

Avoiding precipitating factors, maintaining hydration, and non-pharmacological physical isometric counterpressure manoeuvres are the treatment of choice (Table 67.16).[29]

Beta blockers are not generally effective.[30,31] The value of **midodrine** is questionable.[1] Selective serotonin reuptake inhibitors such as **paroxetine** may also be of value in refractory vasovagal syncope.[31] **Pacing** is not indicated in general.[32,33] It is effective in reducing recurrence of syncope in patients ≥40 years with severe asystolic neurally mediated syncope (syncope with ≥3 s asystole or ≥ 6 s asystole without syncope—ISSUE-3 trial).[34] It might be also considered in unresponsive patients over 40 years, with tilt-induced pure cardioinhibitory response, but its value is not established.[31,35,36] If pacing is deemed necessary, a dual-chamber unit is implanted.[36] Carotid sinus massage causing a pause >3 s is also an indication for pacing (DDD or VVI)[36] in symptomatic patients (Table 67.16). In patients >40 years old with recurrent attacks without a prodrome, a policy of carotid sinus massage, followed by tilt testing, followed by an implantable loop recorder, may identify those patients (up to 47%) who may benefit from cardiac pacing.[37]

Table 67.16 Therapy of reflex syncope

ESC/EHRA/HFA/HRS 2009 GL on syncope	
Treatment of reflex syncope	
Explanation of the diagnosis, provision of reassurance, and explanation of risk of recurrence in all patients	I-C
Isometric physical counterpressure manoeuvres in patients with prodromal symptoms	I-B
Cardiac pacing in patients with dominant cardioinhibitory CSS	IIa-B
Cardiac pacing in patients with frequent recurrent reflex syncope, age >40 years, and documended spontaneous cardioinhibitory response during monitoring	IIa-B
Midodrine in patients with vasovagal syncope refractory to lifestyle measures	IIb-B
Tilt training for education of patients, but long-term benefit depends on compliance	IIb-B
Cardiac pacing in patients with tilt-induced cardioinhibitory response with recurrent, frequent unpredictable syncope and age >40 after alternative therapy has failed	IIb-C
Cardiac pacing is not indicated in the absence of a documended cardioinhibitory reflex	III-C
Beta adrenergic blocking drugs are not indicated	III-A
HRS 2015 Statement on syncope	
Lifestyle and medical treatment for vasovagal syncope	
Education, reassurance, and promoting salt and fluid intake unless contraindicated	I-E
Reducing or withdrawing medications that can cause hypotension	IIa-E
Physical counterpressure manoeuvres for vasovagal syncope with a sufficiently long prodromal period	IIa-BR
Fludrocortisone for frequent vasovagal syncope and no contraindications	IIb-E
Beta blockers for patient >40 years and frequent vasovagal syncope	IIb-BR
Midodrine for frequent vasovagal syncope and no hypertension or urinary retention	IIb-E
ESC 2013 GL on Pacing and CRT	
Indication for pacing in intermittent documented bradycardia	
Pacing in patients ≥40 years with recurrent, unpredictable reflex syncopes and documented symptomatic pause/s due to sinus arrest or AV block or a combination of the two.	IIa-B
Dual-chamber pacing with rate hysteresis is the preferred mode in reflex asystolic syncope in order to preserve spontaneous sinus rhythm.	I-C
Indication for pacing in undocumented reflex syncope	
Carotid sinus syncope	
Pacing in patients with dominant cardioinhibitory carotid sinus syndrome and recurrent unpredictable syncope.	I-B
Tilt-induced cardioinhibitory syncope	
Pacing in patients with tilt-induced cardioinhibitory response with recurrent frequent unpredictable syncope and age >40 years after alternative therapy has failed.	IIb-B
Tilt-induced non-cardioinhibitory syncope	
Cardiac pacing in the absence of a documented cardioinhibitory reflex	III-B
Choice of pacing mode in undocumented reflex syncope	
Carotid sinus syncope	
Dual-chamber pacing is the preferred mode of pacing.	I-B
Tilt-induced cardioinhibitory syncope	
In cardioinhibitory vasovagal syncope, dual-chamber pacing is the preferred mode of pacing.	I-C
Lower rate and rate hysteresis should be programmed in order to achieve back-up pacing function which preserves native heart rhythm and AV conduction.	IIa-C
ACCF/AHA/HRS 2012 GL for device-based therapy	
Recommendations for permanent pacing in hypersensitive carotid sinus syndrome and neurocardiogenic syncope	
Permanent pacing for recurrent syncope caused by spontaneously occurring carotid sinus stimulation and carotid sinus pressure that induces ventricular asystole >3 s	I-C
Permanent pacing for syncope without clear, provocative events and with a hypersensitive cardioinhibitory response of 3 s or longer	IIa-C

(*continued*)

Table 67.16 Continued

Permanent pacing for significantly symptomatic neurocardiogenic syncope associated with bradycardia documented spontaneously or at the time of tilt table testing	IIb-B
Permanent pacing for a hypersensitive cardioinhibitory response to carotid sinus stimulation without symptoms or with vague symptoms	III-C
Permanent pacing for situational vasovagal syncope in which avoidance behaviour is effective and preferred	III-C

Level B evidence is of a moderate level, either from randomized trials (B-R) or well-executed nonrandomized trials (B-NR). Level of evidence E indicates simply consensus opinion.
EHRA/HFA 2009 Guidelines for the diagnosis and management of syncope. *Eur Heart J*. 2009;**30**:2631–71 with permission from Oxford University Press.
ESC 2013 Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J*. 2013;**34**:2281–329, with permission from Oxford University Press.
HRS 2015 Expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Heart Rhythm*. 2015;**12**:e41–63 with permission from Elsevier.
ACCF/AHA/HRS 2012 Focused Update Incorporated Into the ACCF/AHA/HRS2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities. *J Am Coll Cardiol*. 2013;**61**: e6–e75 with permission for Elsevier.

Orthostatic intolerance syndromes

The principal treatment strategy in drug-induced autonomic dysfunction is elimination of the offending agent. Expansion of extracellular volume is important (Table 67.17). In the absence of hypertension, patients should be instructed to take sufficient **salt and water** intake, targeting 2–3 L of fluids per day and 10 g of NaCl. Rapid cool water ingestion is reported to be effective in orthostatic intolerance and postprandial hypotension.[38] The norepinephrine precursor **droxidopa** (100-600 mg tds) has been recently approved by the FDA for the therapy of orthostatic hypotension.[6] **Midodrine** (5–20 mg tds)[39] and **fludrocortisone** (0.1–0.3 mg od) may also be effective. The norepinephrine transporter blockade **atomoxetine** has been found superior to midodrine for the treatment of orthostatic hypotension in autonomic failure.[40]

Postural orthostatic tachycardia syndrome (POTS)

Short-term exercise training and low-dose propranolol (20 mg) may be useful in POTS (Table 67.18).[2,41] Increased negative intrathoracic pressure with the use of an impedance

Table 67.17 ESC/EHRA/HFA/HRS 2009 GL on syncope. Treatment of orthostatic hypotension

Adequate hydration and salt intake	I-C
Midodrine as adjunctive therapy if needed	IIa-B
Fludrocortisone as adjunctive therapy if needed	IIa-C
Physical counterpressure manoeuvres	IIb-C
Abdominal binders and/or support stockings to reduce venous pooling	IIb-C
Head-up tilt sleeping (>10°) to increase fluid volume	IIb-C

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Table 67.18 HRS 2015 statement on syncope. Treatment of POTS

A regular, structured, and progressive exercise program	IIa-BR
Acute intravenous infusion of up to 2 L of saline for patients with short-term clinical decompensations	IIa-C
Patients might be best managed with a multidisciplinary approach	IIb-E
Consumption of up to 2–3 L of water and 10–12 g of NaCl daily	IIb-E
Fludrocortisone or pyridostigmine	IIb-C
Midodrine or low-dose propranolol	IIb-BR
Clonidine or alpha-methyldopa for patients with prominent hyperadrenergic features	IIb-E
Drugs that block the norepinephrine reuptake transporter can worsen symptoms	III-BR
Regular intravenous infusions of saline are not recommended, and chronic or repeated intravenous cannulation is potentially harmful	III-E
Radiofrequency sinus node modification, surgical correction of a Chiari malformation type I, and balloon dilation or stenting of the jugular vein are potentially harmful.	III-BNR

Level B evidence is of a moderate level, either from randomized trials (B-R) or well-executed nonrandomized trials (B-NR).
Level of evidence E indicates simply consensus opinion.
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threshold device that increases inspiratory resistance has also been shown to reduce upright heart rate and increases stroke volume while maintaining cardiac output and blood pressure.[42]

Cardiac arrhythmias

Recommendations for treatment are provided in Table 67.19. Cardiac pacing in sick sinus syndrome relieves symptoms but may not affect survival, and syncope recurs in 20% of patients.[1] Device malfunction and pacemaker syndrome should also be considered. ICD is indicated in patients with syncope of undetermined origin with clinically relevant, haemodynamically significant sustained VT or VF induced at EPS, or in patients with syncope and advanced structural heart disease in whom thorough invasive and non-invasive investigations have failed to define a cause.

Table 67.19 Treatment of syncope due to cardiac arrhythmias

ESC/EHRA/HFA /HRS 2009 GL on syncope	I-B
Cardiac pacing	
Sinus node disease with syncope demonstrated to be due to sinus arrest (symptom-ECG correlation) without a correctable cause	I-C
Sinus node disease with syncope and abnormal CSNRT	I-C
Sinus node disease with syncope and asymptomatic pauses ≥3 s (with the possible exceptions of young trained persons, during sleep, and in medicated patients)	I-C
Syncope and second-degree Mobitz II, advanced or complete AV block	I-B
Syncope, BBB, and positive EPS	I-B
Unexplained syncope and BBB	IIa-C
Unexplained syncope and sinus node disease with persistent sinus bradycardia, itself asymptomatic	IIb-C
Unexplained syncope without evidence of any conduction disturbance	III-C
Catheter ablation	
Symptom-arrhythmia ECG correlation in both SVT and VT in the absence of structural heart disease (with the exception of atrial fibrillation)	I-C
Syncope due to onset of rapid atrial fibrillation	IIb-C
Antiarrhythmic drug therapy	
Syncope due to onset of rapid AF	I-C
Symptom-arrhythmia ECG correlation in both SVT and VT when catheter ablation cannot be undertaken or has failed	IIa-C
Implantable cardioverter defibrillator	
Documented VT and structural heart disease	I-B
Sustained monomorphic VT is induced at EPS in patients with previous MI	I-B
Documended VT and inherited cardiomyopathies or channelopathies	IIa-B
HRS 2015 Statement on Syncope	
Pacemakers for Syncope	
Dual-chamber pacing for patients ≥40 years with recurrent and unpredictable syncope and a documented pause ≥3 during clinical syncope or an asymptomatic pause ≥6	IIa-BR
Tilt-table testing to identify patients with a hypotensive response who would be less likely to respond to permanent cardiac pacing	IIb-BNR
Pacing for paediatric patients with recurrent syncope with documented symptomatic asystole who are refractory to medical therapy	IIb-BR
Dual-chamber pacing in adenosine-susceptible older patients with unexplained syncope without a prodrome, a normal ECG, and no structural heart disease	IIb-C

Level B evidence is of a moderate level, either from randomized trials (B-R) or well-executed non-randomized trials (B-NR).
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Structural heart disease

Treatment is discussed in relevant chapters. ICD may be indicated (Table 67.20), and appropriate shocks in patients with heart failure are more likely in patients with syncope.[43] Of course, ICD reduces arrhythmic death but may not prevent syncope. Syncope is an ominous sign in hypertrophic cardiomyopathy, ARVC, and, most probably, genetic channelopathies, although not as much as documented cardiac arrest.

Table 67.20 Indications for ICD

ESC/EHRA/HFA/HRS 2009 GL on syncope. Indications for implantable cardioverter defibrillator (ICD) in patients with unexplained syncope and at high risk of sudden cardiac death	
In patients with ischaemic or non-ischaemic cardiomyopathy with severely depressed LVEF or HF, according to current guidelines for ICD-CRT.	I-A
In patients with non-ischaemic cardiomyopathy with several depressed LVEF or HF, according to current guidelines for ICD-cardiac resynchronization therapy implantation.	I-A
In hypertrophic cardiomyopathy, ICD therapy should be considered in patients at high risk. In non-high risk, consider ILR.	IIa-C
In right ventricular cardiomyopathy, ICD therapy should be considered in patients at high risk. In non-high risk, consider ILR.	IIa-C
In Brugada syndrome, ICD therapy should be considered in patients with spontaneous type I ECG. In the absence of spontaneous type I ECG, consider ILR.	IIa-B
In long QT syndrome, ICD therapy, in conjunction with beta blockers, should be considered in patients at risk. In non-high risk, consider ILR.	IIa-B
In patients with ischaemic or non-ischaemic cardiomyopathy without severely depressed LVEF or HF and negative programmed electrical stimulation. Consider ILR to help define the nature of unexplained syncope.	IIb-C
ACCF/AHA 2012 GL on device therapy. Indications for ICD*	
Patients with syncope of undetermined origin with clinically relevant, haemodynamically significant sustained VT or VF induced at electrophysiological study	I-B
Unexplained syncope, significant LV dysfunction, and non-ischaemic cardiomyopathy	IIa-C
Syncope and advanced structural heart disease	IIb-C
ICD is not indicated for syncope of undetermined cause without inducible ventricular tachyarrhythmias and without structural heart disease.	III-C

* For patients who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status >1 year.
CRT, cardiac resynchronization therapy; ILR; implantable loop recorder.
EHRA/HFA 2009 Guidelines for the diagnosis and management of syncope. *Eur Heart J*. 2009;**30**:2631–71 with permission from Oxford University Press.
ACCF/AHA/HRS 2012 Focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm Abnormalities. *J Am Coll Cardiol*. 2013;**61**: e6–e75 with permission for Elsevier.

Syncope in the elderly

The most common causes of syncope in the elderly are orthostatic hypotension, reflex syncope, especially CSS, and cardiac arrhythmias.[1] Syncope occurring in the morning favours orthostatic hypotension. Symptoms, such as nausea, blurred vision, and sweating, are predictive of non-cardiac syncope, whereas only dyspnoea is predictive of cardiac syncope in elderly people.[44] One-third of individuals over 65 years are taking three, or more, prescribed medications, which may cause, or contribute, to syncope. Their withdrawal reduces recurrences of syncope and falls.[45] Medication history should include the time relationship with the onset of syncope. History should include co-morbidity, association with physical frailty, and locomotor disability. Gait, balance instability, and slow protective reflexes are present in 20–50% of community-dwelling elderly. In these circumstances, moderate haemodynamic changes, insufficient to cause syncope, may result in falls.[44] Cognitive impairment is present in 5% of 65-year olds and 20% of 80-year olds. This may attenuate the patient's memory of syncope and falls.[1] Cardioinhibitory CSS is the recognized cause of symptoms in up to 20% of elderly patients with syncope. The elderly should be managed according to the identified cause.

Unexplained syncope

Pacing has not been shown to prevent recurrences in patients with unexplained falls, and ILR monitoring is probably the optimal diagnostic strategy. Recommendations are presented in Table 67.21.

Driving

Recommendations are provided in Table 67.22.

Table 67.21 ESC 2013 on pacing and CRT. Indication for cardiac pacing in patients with unexplained syncope

Unexplained syncope and positive adenosine triphosphate test	
Pacing may be useful to reduce syncopal recurrences.	IIb-B
Unexplained syncope	
Pacing is not indicated in patients with unexplained syncope without evidence of bradycardia or conduction disturbance.	III-C
Unexplained falls	
Pacing is not indicated in patients with unexplained falls	III-B

ESC 2013 Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J*. 2013;**34**:2281–329, with permission from Oxford University.

Table 67.22 ESC/EHRA/HFA/HRS 2009 GL on syncope. Recommendations for driving

Diagnosis	Group 1 (private drivers)	Group 2 (professional drivers)
Cardiac arrhythmias		
Cardiac arrhythmia, medical treatment	After successful treatment is established	After successful treatment is established
Pacemaker implant	After 1 week	After appropriate function is established
Successful catheter ablation	After successful treatment is established	After long-term success is confirmed
ICD implant	In general, low risk, restriction according to current recommendations	Permanent restriction
Reflex syncope		
Single/mild	No restrictions	No restriction, unless it occurred during high-risk activity*
Recurrent and severe*	After symptoms are controlled	Permanent restriction, unless effective treatment has been established
Unexplained syncope		
	No restrictions, unless absence of prodrome, occurrence during driving, or presence of severe structural heart disease	After diagnosis and appropriate therapy is established

Group 1: private drivers of motorcycles, cars, and other small vehicles with and without a trailer; group 2: professional drivers of vehicles over 3.5 tons or passenger-carrying vehicles exceeding eight seats, excluding the driver. Drivers of taxicabs, small ambulances, and other vehicles form an intermediate category between the ordinary private driver and the vocational driver and should follow local legislation.

* Neurally mediated syncope is defined as severe if it is very frequent or occurring during the prosecution of a 'high-risk' activity or recurrent or unpredictable in 'high-risk' patients.

EHRA/HFA 2009 Guidelines for the diagnosis and management of syncope. *Eur Heart J.* 2009;**30**:2631–71 with permission from Oxford University Press.

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Chapter 68

Sudden cardiac death

Definition

Sudden cardiac death (SCD) is usually defined as death of cardiac origin, occurring within 1 h from onset of symptoms.

Unexplained sudden death occurring in an individual older than 1 year of age is known as **'sudden unexplained death syndrome' (SUDS)**.

SUDS death with negative pathological and toxicological assessment is termed **'sudden arrhythmic death syndrome' (SADS)**.[1]

Unexplained sudden death occurring in an individual younger than one year of age is known as **'sudden unexplained death in infancy' (SUDI)**.

Epidemiology

In 2011, approximately 326 200 people (approximately 0.1% of the population) experienced emergency medical services-assessed out-of-hospital cardiac arrests in the USA.[1,2] Of the 19 300 bystander-witnessed out-of-hospital cardiac arrests in 2011, 31.4% of victims survived. The annual incidence of SCD increases as a function of advancing age, being 100-fold lower in adolescents and adults younger than 30 years (0.001%) than it is in adults older than 35 years.[4,5] A similar incidence occurs probably in Europe, with reports of out of hospital cardiac arrest ranging from 0.04–0.1%.[6–8] When the aetiologic definition is limited to coronary artery disease and its tachyarrhythmic burden, the estimate is <200 000 events per year.[9] Approximately 50% of all cardiac deaths are sudden, and this proportion remains the same despite the overall decrease in cardiovascular mortality over the last decades. The proportion of all natural deaths due to SCD is 13% whereas, if a '24 h from onset of symptoms' definition is used, it becomes 18.5%.[9] Analysis of data from the Department of Defense Cardiovascular Death Registry in the USA reveals that the incidence of sudden unexplained death is 1.2 per 100 000 person-years for persons 18–35 years of age, and 2.0 per 100 000 person-years for those <35 years of age.[10] Higher numbers were provided by the King County (Washington) Cardiac Arrest Database: 2.1 (0–2 years of age), 0.61 (3–13 years of age), 1.44 (14–24 years of age), and 4.4 (25–35 years of age) per 100 000 person-years, respectively.[11] The annual incidence of sudden cardiac arrest among blacks was >2-fold higher than in whites in both men and women, in the Oregon Sudden Unexpected Death Study.[12] In Denmark, the annual incidence of SCD is 2.3 (1–35 years of age), and 21.7 (36–49 years of age) per 100 000 persons.[6] Population movement and especially major train stations are associated with a higher risk of SCD.[13]

The main problem with SCD is that the majority of out-of-hospital sudden cardiac arrests occur among either those patients in whom cardiac arrest is the first clinical expression of the underlying disease or those in whom disease was previously identified but classified as low-risk (Figure 68.1).[9] There is an inverse relationship between incidence and absolute numbers of events, indicating that a large portion of the total population burden emerges from subgroups with lower risk indexes (Figure 68.2),[9] thus making identification and prevention of future events particularly difficult.

The incidence of **sports-related sudden death of any cause** in the general population is 0.5 to 2.1/100 000 persons per year.[8,14–16] Although the vast majority of sports-associated sudden cardiac arrest cases occur during middle

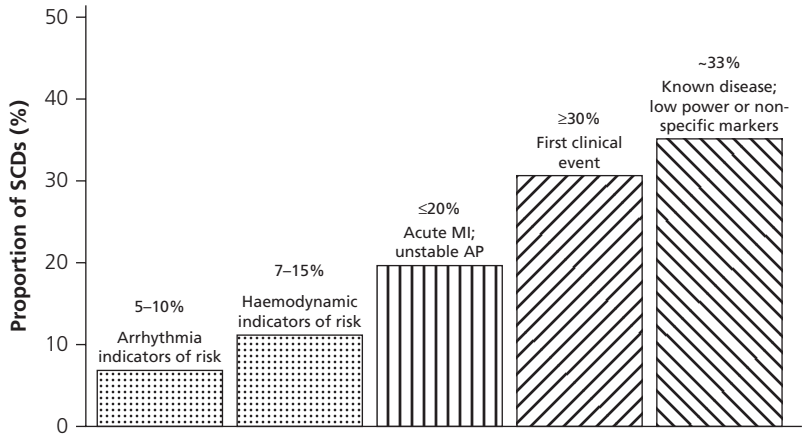

Figure 68.1 Clinical circumstance at the time of sudden cardiac arrest. The majority of out-of-hospital sudden cardiac arrests occur among either those patients in whom cardiac arrest is the first clinical expression of the underlying disease or those in whom disease was previously identified but classified as low risk. The high-risk subgroups that have achieved clinical attention, such as post-myocardial infarction (MI) patients at high risk for or who manifest life-threatening arrhythmias and those with haemodynamic abnormalities, including heart failure, constitute a smaller proportion of the total sudden cardiac death (SCD) burden (<25%). The remainder occurs during the evolution of acute coronary syndromes.

AP indicates angina pectoris.

Myerburg RI, *et al*. Sudden cardiac death caused by coronary heart disease. *Circulation*. 2012;**125**:1043–52 with permission from Wolters Kluwer.

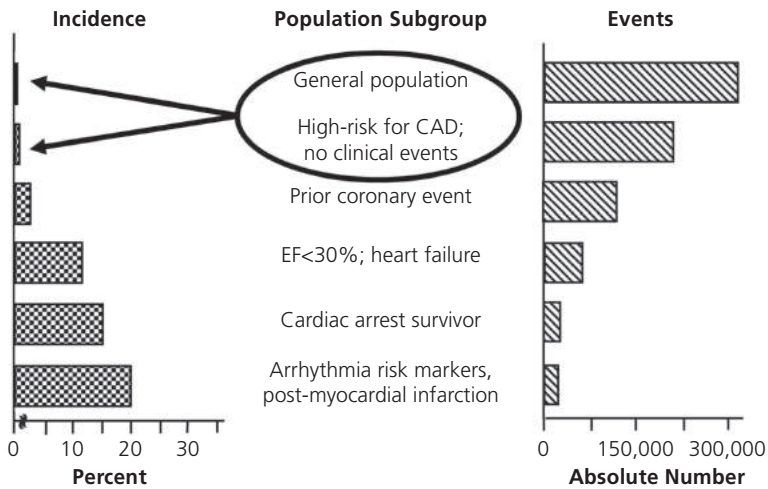

Figure 68.2 Incidence and total population burden of sudden cardiac death. Event rates are compared with total numbers of events for the general population and for specific subgroups with coronary artery disease (CAD). There is an inverse relationship between incidence and absolute numbers of events, indicating that a large portion of the total population burden emerges from subgroups with lower risk indexes, namely the general population and those with risk profiles for atherogenesis but free of events (circled).

EF indicates ejection fraction.

Myerburg RI, *et al*. Sudden cardiac death caused by coronary heart disease. *Circulation*. 2012;**125**:1043–52 with permission from Wolters Kluwer.

age, they represent a relatively small proportion (5%) of overall sudden cardiac arrest cases.[17] It is higher in ***professional athletes***, with a reported incidence of SCD as 1:43 770 participants per year in the National Collegiate Athletic Association (NCAA). Among NCAA Division I male basketball players, the incidence was 1:3100 per year.[16] In other studies, the reported incidence of SCD ranges from 0.24 to 3.8:100 000 per year with higher rates seen in African/Afro-Caribbean (black) athletes (see also Chapter 83).[18–21]

Aetiology

Coronary artery disease is the most common substrate underlying SCD in the western world (75–80%), and cardiomyopathies and genetic channelopathies account for most of the remainder (Table 68.1).[6,22] SCD accounts for 50% of all coronary artery disease-related deaths.[9] The incidence of SCD-related atherosclerotic coronary artery disease is 0.7 per 100 000 person-years in persons 18–35 year-old, whereas it becomes 13.7 per 100 000 person-years for those >35 years of age.[10] Female survivors of cardiac arrest are less likely to have underlying coronary artery disease (45%), whereas valve disease and dilated or arrhythmogenic cardiomyopathy are more common compared to men.[23] Following **acute MI** there is increased risk during the first months either due to tachyarrhythmias or other complications such as re-infarction or myocardial rupture,[24] and myocardial scar predisposes to monomorphic VT. Apart from patients with ST-segment elevation, certain resuscitated comatose patients without ST-segment elevation may also be suitable for coronary angiography.[25] However, although most patients with a cardiac arrest have demonstrable coronary artery disease, less than half seem to have suffered an acute myocardial infarction.[26,27] Only 38% of cardiac arrest survivors will develop evidence of myocardial infarction,[2] and the use of tenecteplase during advanced life support for out-of-hospital cardiac arrest did not improve outcome.[28] In the current era, **cardiomyopathy related to obesity or alcoholism** and **fibrotic cardiomyopathy** are the most common causes of non-ischaemic sudden cardiac death.[29] In patients with preserved ejection fraction (CASPER Registry), an aetiologic diagnosis was possible in approximately half of cardiac arrest survivors, the rest being considered cases of idiopathic VF presumambly due to intrinsic electric abnormalities, such as early repolarization.[30] **Idiopathic VF** is defined as a resuscitated cardiac arrest victim, preferably with documentation of VF, in whom known cardiac, respiratory, metabolic and toxicological aetiologies have been excluded through clinical evaluation.[1] Several mutations of ion channels coding and other genes have been associated with idiopathic ventricular fibrillation (see also Chapters 56 and 57).[31] In families whose members have had SCD, genetic testing may diagnose an inherited arrhythmia (genetic channelopathy) in up to 29%.[32] Several studies have also demonstrated a familial predisposition to SCD that may or may not be related to genetic channelopathies.[33–35] **Coronary spasm** is also a cause of cardiac arrest, particularly in male smokers with minimal or no pre-existing coronary artery disease.[36] **Mitral valve prolapse** in female patients with ECG repolarization abnormalities, and frequent complex ventricular ectopy, has also been associated with out of hospital cardiac arrest.[37,38] Recently, an association of **air pollution** (fine particulate matter with an aerodynamic diameter <2.5 microns and ozone) with out of hospital cardiac arrest was demonstrated.[39] SCD accounts for most cardiac and many non-AIDS natural deaths in HIV-infected patients.[40] **Lower socioeconomic status**, **depression, anxiety, social isolation, and acute emotional stress** have all been linked to an increase risk of SCD.[41,42] A **circadian variation** is documented with the peak incidence of SCD occurring in

Table 68.1 Common causes of sudden cardiac arrest

Ischaemic heart disease
Myocardial infarction (including NSTEMI)
Anomalous coronary origin
Coronary spasm
Inherited channelopathies
Long QT syndrome
Short QT syndrome
Brugada syndrome
Early repolarization syndrome
Catecholaminergic polymorphic ventricular tachycardia
Cardiomyopathies
Alcoholic
Obesity-related
Fibrotic
Hypertrophic
ARVC
Myocarditis
Heart failure
LVEF <35%
Valve disease
Aortic stenosis
Congenital diseases
Tetralogy of Fallot
Other causes
Severe electrolyte disturbances
Massive pulmonary embolus
Vigorous activity in sedentary individuals
Acute psychosocial and economic stress

the morning hours from 6 a.m. to noon (and is blunted by beta blockers) with a smaller peak in the late afternoon for out-of-hospital VF arrests, and is highest on Monday.[43]

In the **young** (<35 years), the most common cause of SCD is arrhythmias, mostly in the context of an apparently normal heart.[1,44] In particular, causes of SCD are congenital abnormalities (0–13 years of age), primary arrhythmia (14–24 years), and coronary artery disease (>25 years).[11] In 5–20% of cases a significant cardiac abnormality is not found at autopsy,[10,44] and in a recent Danish registry report on individuals aged <50 years, sudden death was caused by noncardiac diseases, such as pulmonary embolism, meningitis and cerebrovascular bleeding, in 28% of cases.[45]

In **sports-related sudden death**, in the general population, a clear diagnosis is made in less than 25% of the cases, and is usually an acute coronary syndrome (75%).[14] In professional athletes, a diagnosis is usually made in up to 65% of the cases and HCM was considered the main cause, at least in the US, followed by ARVC (especially in the Veneto region of Italy), congenital coronary anomalies, and genetic channelopathies, myocarditis, WPW syndrome, and Marfan syndrome, with blunt trauma, commotio cordis, and heat stroke being less frequent causes.[19,46,47] There has been evidence, however, that HCM may not be the major cause of SCD in athletes.[16,20] In a recent report, autopsies in deceased NCAA athletes most often revealed a structurally normal heart (25%), followed by coronary artery anomalies (11%), myocarditis (9%), ARVC (5%), and aortic dissection (5%), with HCM demonstrated in 8%.[16] Findings from the RACER initiative indicate that marathons and half-marathons are associated with a low overall risk of cardiac arrest or sudden death (1/100 000), most commonly attributable to hypertrophic cardiomyopathy (26%) or atherosclerotic coronary disease (16%).[48] However, some of these cardiac arrests might have been provoked by heat stroke.[49] CAD is the predominant cause of SCD in older athletes.[50] **Vigorous exertion** can trigger cardiac arrest or SCD, especially in untrained persons, but habitual vigorous exercise diminishes the risk of sudden death during vigorous exertion.[51] Most studies have found inverse associations between regular physical activity and SCD.[52]

Pathophysiology

Mechanisms

Ventricular tachycardia or fibrillation was thought to be the most common cause of out-of-hospital cardiac arrest, accounting for approximately three-quarters of cases, the remaining 25% were caused by bradyarrhythmias or asystole.[52,53] More recent studies suggest that the incidence of ventricular fibrillation or pulseless ventricular tachycardia as the first recorded rhythm in out-of-hospital cardiac arrest has declined to less than 30% in the past several decades.[54–56] Pulseless electrical activity (electromechanical dissociation) and asystole are proportionally more frequent mechanisms than VT/VF, with recent data demonstrating an incidence of 19–23%, with the remaining patients (approximately 50%) having asystole.[57] However, the majority of survivors are in the subgroup of persons whose initial rhythm is ventricular fibrillation or pulseless ventricular tachycardia.[55] Ventricular fibrillation is a cause of cardiac arrest and, if untreated, the arrhythmia is usually fatal, but spontaneous reversions to sinus rhythm have been recorded. Non-arrhythmic mechanisms such as myocardial rupture or aortic aneurysm rupture may also result in SCD.

Investigations in survivors

Overall survival after out of hospital cardiac arrest remains low approximately 7.6%,[58] but quality of life is good at least for the next 12 months.[59] A full cardiac assessment is needed in cardiac arrest survivors.[36] Patients presenting with ventricular fibrillation or sustained monomorphic ventricular tachycardia are at a considerable risk of recurrence, particularly in the presence of reduced left ventricular function. Studies of out-of-hospital cardiac arrest survivors, as well as of patients with sustained ventricular tachycardia, have shown that the actual incidence of sudden death at two years following the presenting arrhythmia varies from 15 to 30%. Up to 74% of patients with out-of-hospital cardiac arrest have VF recurrence during pre-hospital care, and the time in VF is associated with worse outcome.[60] However, long-term survival among patients who have undergone rapid defibrillation after out-of-hospital cardiac arrest is similar to that among age-, sex-, and disease-matched patients who did not have out-of-hospital cardiac arrest, although only 40% of survivors had an ICD implanted.[61] Family members of young SCD victims are at increased risk for ventricular arrhythmias and ischaemic heart disease. Screening of first-degree relatives, especially those <35-year-old, is important.[62] When findings suggest cardiomyopathy or genetic channelopathy evaluation of family members is also necessary. Examination of relatives (cascade family screening) may have a significant diagnostic yield (Figure 68.3).[63] It should be noted, however, that no reported history of sudden death among the relatives of most young (aged<35 years) decedents may be identified.[44] Investigations of a genetic basis of SCD such as the candidate gene approach, have explored the potential association between SCD in CAD and genes associated with genetic channelopathies, and genome-wide association studies are promising but of limited clinical value.[9]

The following tests are useful for establishing a diagnosis in SCD survivors:[36]

- ECG (ischaemia, MI, inherited channelopathies).
- Echocardiography (heart failure, cardiomyopathies, valve disease, congenital heart disease).
- Coronary angiography (coronary artery disease, congenital coronary anomalies, coronary spasm).
- Exercise test (ischaemia, LQTS, CPVT).
- Electrophysiology testing (induction of arrhythmia, pharmacological provocation for Brugada, LQTS, CPVT). Procainamide testing may provoke a Brugada pattern irrespective of baseline ECG and should be considered in the workup of SCD.[64]
- Cardiac MRI (ARVC, sarcoidosis, myocarditis, myocardial injury from coronary spasm).
- Genetic testing is indicated when an inherited phenotype is detected (ARVC, Brugada, CPVT, LQTS). Its role in phenotypically ambiguous or negative patients is not established since the differentiation between disease-causing mutations and irrelevant genetic variants is not always possible. Recommendations for genetic testing are presented in Table 68.2.
- Cardiac biopsy may also be needed in elusive cases.

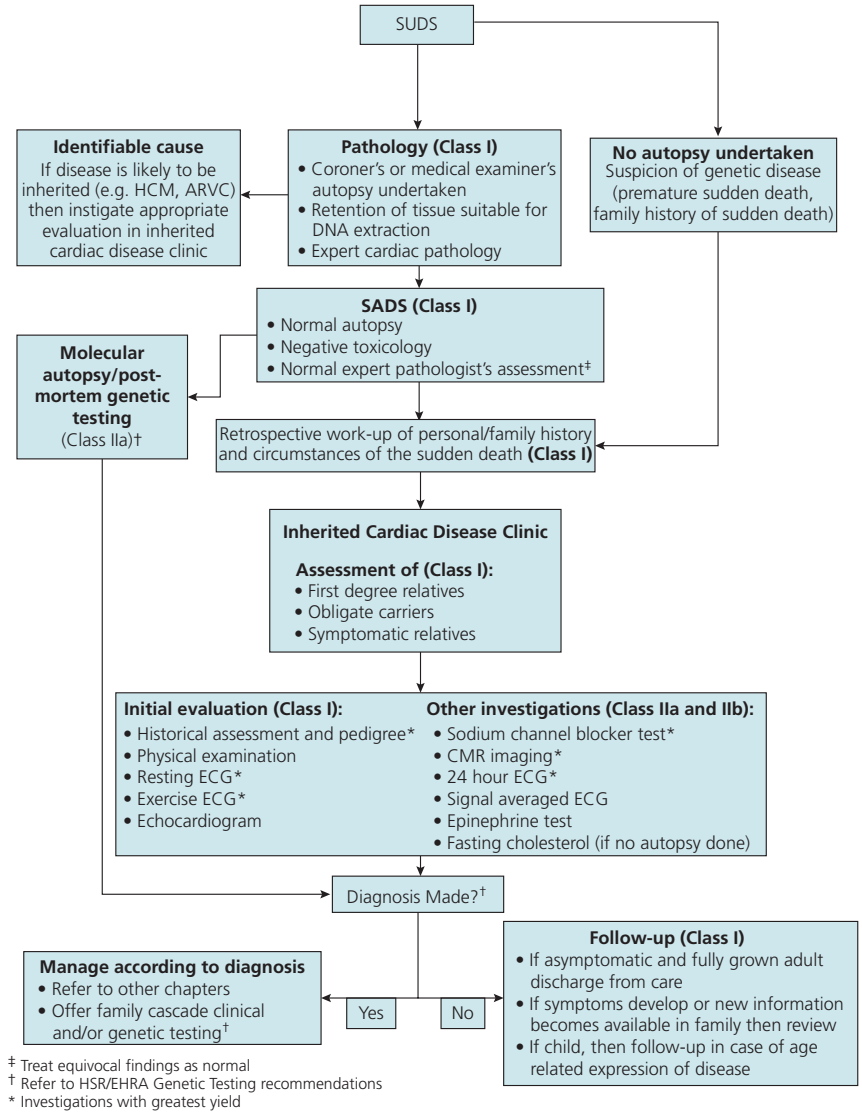

Figure 68.3 Algorithm to describe the investigative strategy for the identification of inherited heart disease in families that have suffered a SUDS event.

HRS/EHRA/APHRS 2013 Expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Europace*. 2013;**15**:1389–406 with permission from Oxford University Press.

Table 68.2 HRS/EHRA/APHRS 2013 expert consensus statement on inherited arrhythmia

Recommendations on idiopathic ventricular fibrillation	
Evaluation	
Genetic testing in IVF when there is a suspicion of a specific genetic disease following clinical evaluation of the IVF patient and/or family members.	IIa
Genetic screening of a large panel of genes in IVF patients in whom there is no suspicion of an inherited arrhythmogenic disease after clinical evaluation.	III
Therapeutic interventions	
ICD implantation in patients with the diagnosis of IVF.	I
Antiarrhythmic therapy with quinidine in patients with a diagnosis of IVF in conjunction with ICD implantation or when ICD implantation is contraindicated or refused.	IIb
Ablation of Purkinje potentials in patients with a diagnosis of IVF presenting with uniform morphology PVCs in conjunction with ICD implantation or when ICD implantation is contraindicated or refused.	IIb
If a first degree relative of an IVF victim presents with unexplained syncope and no identifiable phenotype following thorough investigation then, after careful counselling, an ICD may be considered.	IIb
Evaluation of family members	
Evaluation of first degree relatives of all IVF victims with resting ECG exercise stress testing and echocardiography. Assessment of first degree relatives with history of palpitations arrhythmias or syncope should be prioritized.	I
Follow up clinical assessment in young family members of IVF victims who may manifest symptoms and /or signs of the disease at an older age and in all family members whenever additional SUDS or SUDI events occur.	I
Evaluation of first degree relatives of IVF victims with Holter and signal averaged ECGs, cardiac MRI, and provocative testing with Class Ic antiarrhythmic drugs.	IIa
Evaluation of first degree relatives of IVF victims with epinephrine infusion	IIb
Recommendations on sudden unexplained death in infancy (SUDI)	
Evaluation	
For all SUDS victims:	
Personal/family history and circumstances of the sudden death are collected.	I
Collection of blood and/or suitable tissue for molecular autopsy.	I
An arrhythmia syndrome-focused molecular autopsy/postmortem genetic testing.	IIa
Expert cardiac pathology to rule out the presence of microscopic indicators of structural heart disease.	IIb
Therapeutic interventions	
Genetic screening of the first-degree relatives of a SUDI victim whenever a pathogenic mutation in a gene associated with an increased risk of sudden death is identified by molecular autopsy in the SUDI victim. Obligate mutation carriers should be prioritized.	I
Evaluation of first-degree relatives of SUDI victims with a family history of inherited heart disease or other SUDS or SUDI deaths with resting ECG and exercise stress testing and additional tests as indicated. Assessment of first-degree relatives with the history of arrhythmias or syncope should be prioritized.	IIa
Follow-up clinical assessment in young family members of SUDI victims with a family history of inherited heart disease or other SUDS or SUDI death who may manifest symptoms and/or signs of the disease at an older age and in all family members whenever additional SUDS or SUDI events occur.	IIa
Evaluation of first-degree relatives of SUDI victims with resting ECG and exercise stress testing.	IIb

HRS/EHRA APHRS 2013 Expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Heart Rhythm*. 2013;**10**:1932–63 with permission from Elsevier.

Recommendations on sudden unexplained death syndrome (SUDS)	
Evaluation	
For all SUDS victims:	
Personal/family history and circumstances of the sudden death are collected.	I
Expert cardiac pathology to rule out the presence of microscopic indicators of structural heart disease.	I
Collection of blood and/or suitable tissue for molecular autopsy/postmortem genetic testing.	I
An arrhythmia syndrome-focused molecular autopsy/postmortem genetic testing.	IIa

(*continued*)

Table 68.2 Continued

Therapeutic interventions	
Genetic screening of the first-degree relatives of a SUDS victim whenever a pathogenic mutation in a gene associated with an increased risk of sudden death is identified by molecular autopsy in the SUDS victim.	I
Evaluation of first-degree blood relatives of all SUDS victims with resting ECG with high right ventricular leads, exercise stress testing, and echocardiography. Assessment of obligate carriers and relatives with a history of palpitations, arrhythmias, or syncope should be prioritized.	I
Follow-up clinical assessment in young family members of SUDS victims who may manifest symptoms and/or sign of the disease at an older age and in all family members whenever additional SUDS or SUDI events occur	I
Evaluation of first-degree relatives of SUDS victims with ambulatory and signal-averaged ECGs, cardiac MRI, and provocative testing with Class Ic antiarrhythmic drugs.	IIa
Evaluation of first-degree relatives of SUDS victims with epinephrine infusion.	IIb

HRS/EHRA/APHRS 2013 Expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Europace*. 2013;**15**:1389–406 with permission from Oxford University Press.

A molecular autopsy may also be considered as part of the community forensic investigation to enhance prevention for other family members. (Table 68.3) Thus, in cases of documented sudden cardiac death without an obvious cause, collection of postmortem blood (in EDTA, to enable DNA extraction) for subsequent DNA analysis may identify a cause of death in up to 30% of cases.[65] A forensic examination, including a toxicology screen, may establish the diagnosis in cases of traumatic, toxic, or cardiac causes, whereas a negative pathological examination suggests a genetic channelopathy.[66] Postmortem MRI is also a valuable tool to non-invasively document pathological findings such as myocardial infarction or severe myocardial hypertrophy,[67] and post-mortem computed tomography coronary angiography is now possible.[68] However, despite every effort nearly half of the causes of cardiac arrest will remain unexplained.[30]

Management of cardiac arrest

Specific recommendations for management are presented in Chapter 56 on tachyarrhythmias. A population-based cohort study on out-of-hospital cardiac arrest survivors in Ontario, Canada, detected an improved 30-day survival from 9.4% in 2002 to 13.6% in 2011.[69] Survival is better in places with facilities for bystander resuscitation.[15] Defibrillators in public locations (Table 68.4), such as train stations,[13] may reduce the incidence of sudden cardiac death only when they are accompanied by training programmes of the local population.[70] Recent data from the US Cardiac Arrest Registry to Enhance Survival (CARES) suggest that rates of survival from out-of-hospital cardiac arrest have improved among sites participating in a performance improvement registry.[71] Improved survival rates are more prominent in patients 18–80 years of age.[72]

Table 68.3 ESC 2015 GL on VA and SCD. Indications for autopsy and molecular autopsy in sudden death victims

An autopsy to investigate the causes of sudden death and to define whether SCD is secondary to arrhythmic or non-arrhythmic mechanisms (e.g. rupture of an aortic aneurysm).	I-C
A standard histological examination of the heart including mapped labelled blocks of myocardium from representative transverse slices of both ventricles, whenever an autopsy is performed.	I-C
Analysis of blood and other adequately collected body fluids for toxicology and molecular pathology in all victims of unexplained sudden death.	I-C
Targeted post-mortem genetic analysis of potentially disease-causing genes in all sudden death victims in whom a specific inheritable channelopathy or cardiomyopathy is suspected.	IIa-C

ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015; **36**:2793–867 with permission from Oxford University Press.

Table 68.4 ESC 2015 GL on VA and SCD. Public access defibrillation

Public access defibrillation should be established at sites where cardiac arrest is relatively common and suitable storage is available (e.g. schools, sports stadiums, large stations, casinos, etc.) or at sites where no other access to defibrillation is available (e.g. trains, cruise ships, airplanes, etc.).	I-B
Teach basic life support to the families of patients at high risk of SCD	IIb-C

ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015; **36**:2793–867 with permission from Oxford University Press.

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Part XIII

Implantable devices

Relevant guidelines

AHA 2010 Scientific statement on cardiovascular implantable electronic device infections

Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. *Circulation*. 2010;**121**:458–77.

ESC 2015 Guidelines on infective endocarditis

2015 ESC Guidelines for the management of infective endocarditis. *Eur Heart J.* 2015;**36**:3075–128.

HRS/ASA 2011 Expert consensus statement on the perioperative management of patients with implantable devices

The Heart Rhythm Society (HRS)/American Society of Anesthesiologists (ASA) Expert Consensus Statement on the perioperative management of patients with implantable defibrillators, pacemakers and arrhythmia monitors: facilities and patient management. *Heart Rhythm*. 2011;**8**:1114–54.

EHRA 2009 Recommendations for driving by patients with ICDs

Consensus statement of the European Heart Rhythm Association: updated recommendations for driving by patients with implantable cardioverter defibrillators. *Europace*. 2009;**11**:1097–107.

ACC/AHA/HRS 2012 Guidelines for device-based therapy of cardiac rhythm abnormalities

2012 ACCF/AHA/HRS Focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2013;**61**:e6–75.

ESC 2013 Guidelines on pacing and cardiac resynchronization

2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J*. **34**:2281–329.

AHA/ESC 2013 Consensus document on sexual counselling.

Sexual counselling for individuals with cardiovascular disease and their partners: A consensus document from the American Heart Association and the ESC Council on Cardiovascular Nursing and Allied Professions (CCNAP). *Eur Heart J*. 2013;**34**:3217–3235

HRS 2015 Consensus statement on remote monitoring

HRS Expert consensus statement on remote interrogation and monitoring for cardiovascular electronic implantable devices. *Heart Rhythm* 2015;**12**:e69–e100.

Chapter 69

Technical issues

Permanent pacemakers

Pacemaker modes

A 5-letter code is used to describe the pacemaker mode. The first letter refers to the chamber that is paced (**a**trium, **v**entricle, **d**ual); the second letter refers to the chamber sensed (**a**trium, **v**entricle, **d**ual); the third letter refers to the response to sensing (**i**nhibit, **t**rigger, **d**ual); the fourth letter indicates the presence or absence of rate modulation, and the fifth letter indicates multisite pacing (Table 69.1).[1] Thus, a VVI pacemaker is a ventricular-only pacemaker, a DDDR a dual-chamber pacemaker with rate response ability, a DDI pacemaker is a non-tracking dual-chamber pacemaker that paces both the atrium and the ventricle but does not respond to intrinsic sinus or atrial rate changes (no atrial synchronous pacing), that can be useful to avoid tracking atrial tachyarrhythmias. Single-chamber atrial or ventricular pacemakers sense myocardial signals emanating from the corresponding cardiac chamber and deliver a pacing stimulus if no signal is sensed at the programmed lower rate. Dual-chamber pacemakers sense and pace both the atrium and the ventricle. Depending on the particular clinical situation and programming, sensed events trigger or inhibit pacing. For example, in the DDD pacing mode and during atrioventricular sequential pacing, atrial pacing takes place at the lower rate limit. Atrial pacing triggers ventricular pacing once the programmed AV delay has timed out. If the atrial rate is faster than the programmed lower rate, atrial pacing is inhibited. After the sensed atrial signal, ventricular pacing would occur only if no ventricular event is sensed by the end of the programmed sensed AV delay.[2]

Rate response

In the presence of chronotropic incompetence, rate-adaptive pacemakers are useful.[3] These devices have special sensor(s) that, when triggered during exercise, increase the pacing rate. Most commonly used sensors monitor body movement by detecting vibration (activity sensor or accelerometer) (Table 69.2). More physiologic sensors detect changes in minute ventilation by measuring changes in thoracic impedance with ventilation or changes in QT interval that reflect sympathetic drive. Some pacemakers incorporate more than one sensor to limit disadvantages of individual sensors and enhance specificity without compromising sensitivity. A commonly used combination is an activity sensor combined with a QT interval sensor or a minute ventilation sensor. Careful programming by considering a short walk or exercise is often required to achieve optimal clinical results.[3]

Table 69.1 The revised North American Society of Pacing and Electrophysiology (NASPE)/British Pacing and Electrophysiology Group (BPEG) generic code for antibradycardia, adaptive-rate, and multisite pacing

	I	II	III	IV	V
Category	Chamber(s) paced	Chamber(s) sensed	Response to sensing	Rate modulation	Multisite pacing
	O = None	O = None	O = None	O = None	O = None
	A = Atrium	A = Atrium	T = Triggered	R = Rate modulation	A = Atrium
	V = Ventricle	V = Ventricle	I = Inhibited		V = Ventricle
	D = Dual (A + V)	D = Dual (A + V)	D = Dual (T + I)		D = Dual (A + V)
Manufacturers' designation only	S = Single (A or V)		S = Single (A or V)		

Bernstein AD, *et al*. The revised NASPE/BPEG generic code for antibradycardia, adaptive-rate, and multisite pacing. *Pacing Clin Electrophysiol*. 2002;**25**:260–4 with permission from John Wiley and Sons.

Table 69.2 Commonly used sensors for heart rate modulation

	Technology	Advantage	Disadvantage
Activity sensor	Measures mechanical stress to piezoelectric material as a result of motion or acceleration	Simple; compatible with any device or lead; small energy requirement	Non-physiological estimate of exercise level and non-proportional response to exercise; environmental/external source interference
Minute ventilation sensor	Measures transthoracic impedance change between pacemaker lead and pulse generator	Compatible with any lead; measures physiological changes related to exercise; proportional response to exercise	Slow change at the beginning of exercise; has limitations in children or those with severe lung disease; subject to interference from certain medical equipment
QT interval-based sensors	Measures evoked QT interval changes as estimate of adrenergic tone	Measures physiological changes related to exercise; responds to mental stress	Interindividual variability; T wave sensing may vary; false response during ischaemia or presence of QT-prolonging medications; requires ventricular lead
Contractility sensors, impedance-based	Measures intracardiac impedance change during early ejection period as estimate of local contractility	Measures physiological changes related to exercise; proportional response to exercise; responds to mental stress	Requires ventricular lead; false response if local myocardial properties change (i.e. MI)
Contractility sensors, activity sensor-based	Measures peak endocardial acceleration as estimate of contractility and global LV function	Measures physiological changes related to exercise	Proprietary lead is required; limited long-term safety data

Kaszala K, Ellenbogen KA. Device sensing: sensors and algorithms for pacemakers and implantable cardioverter defibrillators. *Circulation*. 2010;**122**:1328–40 with permission from Wolters Kluwer.

Choice of pacemaker mode

Recommendations by HRS/ACCF and ESC are presented in Chapters 64 and 65.

Interrogation monitoring

Modern pacemakers are able to capture and store a wealth of information that may be helpful in clinical management, follow-up, and troubleshooting. Interrogation of the pacemaker will reveal recorded arrhythmias and programmed parameters, such as pacing mode and pacing rates, as well as battery and lead parameters. Recommendations on the frequency of in-office or remote monitoring of patients with implanted devices is provided in Table 69.3. However, incorporation of remote monitoring into follow-up practice, integrating this technology with a modified frequency of conventional in-person evaluation, ensures greater patient retention and improves adherence to scheduled evaluations. Thus, HRS now recommend that remote monitoring represents the new standard of care for patients with cardiac devices, with alert-driven in-person evaluation replacing most routine office interrogations.[4]

Pacemaker syndrome

Ventricular pacing without proper atrial synchronization (as happens with VVI pacing in the absence of AF) results

Table 69.3 ACC/AHA/HRS 2012 update on device therapy. Minimum frequency of CIED in person or remote monitoring*

Type and frequency	Method
Pacemaker/ICD/CRT	
Within 72 h of CIED implantation	In person
2–12 wk post-implantation	In person
Every 3–12 mo for pacemaker/CRT-pacemaker	In person or remote
Every 3–6 mo for ICD/CRT-D	In person or remote
Annually until battery depletion	In person
Every 1–3 mo at signs of battery depletion	In person or remote
Implantable loop recorder	
Every 1–6 mo, depending on patient symptoms and indication	In person or remote
Implantable haemodynamic monitor	
Every 1–6 mo, depending on indication	In person or remote
More frequent assessment as clinically indicated	In person or remote

* More frequent in-person or remote monitoring may be required for all the above devices as clinically indicated.
CIED indicates cardiovascular implantable electronic device; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy defibrillator; CRT-pacemaker, cardiac resynchronization therapy pacemaker; and ICD, implantable cardioverter-defibrillator.
ACCF/AHA/HRS 2012 Focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol*. 2013;**61**:e6–75 with permission from Elsevier.

in loss of the atrial contribution to ventricular filling, and atrial contraction may occur against closed AV valves. Thus, pacemaker syndrome develops in 5–25% of patients with VVI pacing, and usually manifests itself by prominent V waves in the jugular vein. Pacemaker syndrome can lead to symptoms such dizziness, weakness, heart failure, and presyncope or syncope, and predisposes the patient to the development of atrial fibrillation and increased incidence of stroke (see Chapter 65).

Endless loop (ELT) or pacemaker-mediated tachycardia (PMT)

PMT is initiated by a premature ventricular stimulus that is conducted retrograde via the AV node to the atrium. The retrograde atrial signal then is sensed by the atrial channel and triggers pacing in the ventricle. Ventricular pacing causes retrograde conduction to the atria, and the PMT circuit is established. Most pacemakers have algorithms to recognize and terminate PMT. Alternatively, adjustment of AV delays or post-ventricular pacing atrial refractory periods (PVARP) are necessary. Pacemaker component failures are responsible for other unusual, but dangerous, causes of high pacing rate, such as runaway pacemaker and sensor-driven tachycardia.[2] Figure 69.1 presents an algorithm for evaluation of suspected pacemaker malfunction, and Table 69.4 presents an approach to common problems related to electromagnetic interference.

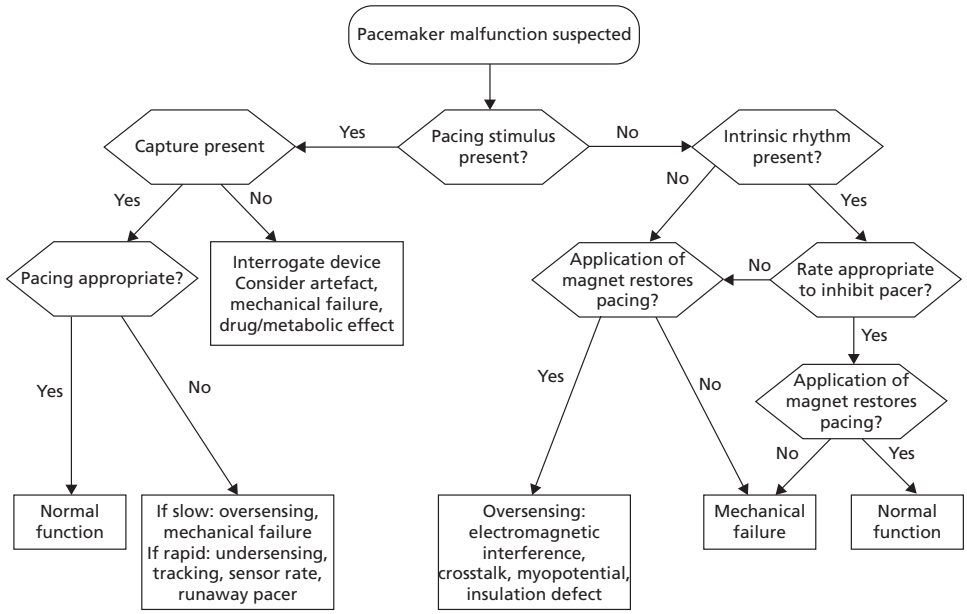

Figure 69.1 A guide for evaluating suspected pacemaker malfunction.

Kaszala K, *et al*. Contemporary pacemakers: what the primary care physician needs to know. *Mayo Clin Proc*. 2008;**83**:1170–86 with permission from Elsevier.

Table 69.4 Approach to common problems related to electromagnetic interference in patients with pacemakers

Problem	Solution
Cellular telephones	Keep telephone in contralateral pocket Place telephone over contralateral ear when talking
Household appliances (e.g. microwave oven, television, stereo, toaster, electric blanket)	No specific concerns
Dental office	No specific concerns
Theft detection equipment at stores	Do not loiter when passing through device
Magnetic resonance imaging	Absolute/relative contraindication, except when special precautions are used
Surgery (electrocautery)	Program device to asynchronous mode Alternative: place magnet over device during surgery. Place grounding pad away from the device. Monitor pulse pressure on telemetry. Check device after surgery
Transcutaneous electrical nerve stimulation	May need to programme pacemaker in asynchronous mode in some patients
Radiation therapy	Discuss with radiotherapist May need to move device in pacemaker-dependent patients
Direct current cardioversion	Place pads in anteroposterior position, at least 5 cm from the pulse generator Have programmer present; check device for increased pacing thresholds after cardioversion

Kaszala K, *et al*. Contemporary pacemakers: what the primary care physician needs to know. *Mayo Clin Proc.* 2008;**83**:1170–86 with permission from Elsevier.

Novel therapeutic approaches

Leadless pacing by means of implantation of a self-contained, very small VVIR unit within the right ventricle (Micra and Nanostim devices),[5,6] and genetic therapies and biological pacemakers are exciting therapeutic developments.[7,8]

Biventricular pacing

Cardiac resynchronization therapy (CRT) is an integral component of modern heart failure therapy for patients with severe symptoms, LVEF ≤35%, and a wide QRS complex (>150 ms) in the context of LBBB (see Chapter 32). Biventricular pacing by atrial-synchronized pacing of the RV and the LV via the coronary sinus to the basal or mid-ventricular but not apical LV region,[9] accomplishes reverse remodelling of the LV. The use of the posterior or lateral LV regions is also associated with decreased risk of arrhythmic events in comparison with anterior lead location and ICD-only patients.[10] A non-apical positioning of the RV lead has not been considered important to influence outcome,[11] and might even be proarrhythmic.[12] However, in a recent meta-analysis, both a non-apical and an apical RV lead position were equally effective in CRT.[13]

Specific problems of biventricular pacing are implant failure due to inability to obtain LV pacing (7–10%), lead dislodgement (5–10%), and coronary sinus dissection (<1%).[14,15] Adverse events, such as failure to implant, pneumothorax, pocket haematoma, and infection, are significantly higher among patients subjected to CRT than ICD alone.[14,15] There are no significant differences in clinical outcomes or complication rates between upgrades of existing devices and *de novo* CRT procedures.[16] Recommendations on indications, as well as on lead placement and follow-up of devices, have been published.[17,18]

Patients with CRT-D who achieve LVEF normalization (>50%) have a very low risk of ventricular arrhythmias, but the risk of inappropriate ICD therapy is still present. Thus, these patients could be considered for downgrade from CRT-D to CRT-P at time of battery depletion if no ventricular arrhythmias have occurred.[19]

Implantable cardioverter-defibrillators

Secondary and primary prevention randomized trials to assess the impact of ICD are presented in Tables 69.5 and 69.6. Recommendations for ICD implantation are presented in relevant chapters.

ICD are the only means for preventing sudden cardiac death in certain clinical settings, and the development of leadless devices for pacing and defibrillation is a novel possibility.[20] It avoids intracardiac leads but at the expense of lack of bradycardia support or antitachycardia pacing. Repeated shocks may lead to worsening of heart failure and a decline in survival.[21,22] Several important points should be noted:

- In patients with documented sustained ventricular arrhythmias and/or cardiac arrest, implantable cardioverter-defibrillators (ICD) confer a survival benefit (secondary prevention of sudden cardiac death). In several clinical settings, this might be lost

when modern medical therapy, including beta blockers, is implemented.[23]

- In patients without sustained ventricular arrhythmias or cardiac arrest, ICD confers a survival benefit (primary prevention of sudden cardiac death) only in high-risk patients with ischaemic cardiomyopathy and LVEF ≤35% due to a remote MI at least >40 days and especially >18 months, although this is debatable.[23]
- The benefits of ICD in the elderly as well as in women are not established, and ICDs are underused in the elderly.[24] Rates of appropriate shocks are similar across age groups,[25] but data from Medicare and Medicaid indicate that one-third of 66,974 ICD recipients die within 3 years, reflecting a population with more advanced age and progressed heart failure than seen in trial populations for primary prevention ICD.[26] While high-risk patients may show the greatest short-term benefit, it is the lower risk patients, e.g. primary prevention ICD implantation, who gain the most life-years over their lifetime.[27]
- With current prices, ICDs are definitely cost-effective only when used in high-risk patients without associated co-morbidities that limit the life expectancy to <10 years.[23]
- Implant failure rates are 0.1%.
- Mean battery longevity of an ICD is approximately 5 years. In a recent study, ICD devices implanted by Medtronic lasted longer than all other manufacturers,[28] but with CRT-ICD devices Medtronic had the lowest survival, compared to other manufacturers.[29]

Table 69.5 Major implantable cardioverter-defibrillator trials for primary prevention of sudden cardiac death

Study		Patients (n)	Inclusion criteria	Therapy	Hazard ratio	95% CI	P-value
AMIOVIRT	Amiodarone versus implantable cardioverter-defibrillator	103	NYHA I-III, DCM, asymptomatic NSVT, LVEF ≤0.35	ICD vs amiodarone	0.87	0.31–2.42	NS
CABG-Patch	Coronary artery bypass graft patch	900	Scheduled for CABG, LVEF ≤0.35, positive SAECG	ICD vs standard medical therapy	1.07[1]	0.81–1.42	NS
CAT	Cardiomyopathy trial	104	NYHA II or III, DCM ≤ 9 months, LVEF ≤0.30	ICD vs standard medical therapy	0.83	0.45–1.82	NS
DEFINITE	Defibrillators in non-ischaemic cardiomyopathy treatment evaluation	458	DCM, LVEF ≤0.35, PVCs or NSVT	ICD vs standard medical therapy	0.65[1] 0.20[2]	0.40–1.06 0.06–0.71	0.08 0.006
DINAMIT	Defibrillator in acute myocardial infarction trial	674	Recent MI, LVEF ≤0.35, impaired cardiac autonomic function	ICD vs standard medical therapy	1.08[1] 0.42[2]	0.76–1.55 0.22–0.83	NS 0.009
IRIS	Immediate risk stratification improves survival	898	Recent MI, LVEF ≤0.40, or NSVT	ICD vs standard medical therapy	1.04	0.81–1.35	NS
MADIT	Multicentre automatic defibrillator implantation trial	196	NYHA I–III, prior MI, LVEF ≤0.35, NSVT, and positive EPS	ICD vs standard medical therapy	0.46[1]	0.26–0.82	0.009
MADIT-II	Multicentre automatic defibrillator implantation trial-II	1232	Prior MI, LVEF ≤0.30	ICD vs standard medical therapy	0.69[1]	0.51–0.93	0.016
MUSTT	Multicentre unsustained tachycardia trial	351[3]	CAD, LVEF ≤0.40, NSVT, and positive EPS	ICD vs conventional antiarrhythmic therapy	0.40[1] 0.24[4]	0.27–0.59 0.13–0.45	<0.001 <0.001
SCD-HeFT	Sudden cardiac death in heart failure trial	1676[5]	NYHA II or III, LVEF ≤0.35, ischaemic and non-ischaemic cardiomyopathy	ICD plus standard medical therapy vs placebo plus standard medical therapy	0.77[1]	0.62–0.96	0.007

1: overall mortality; 2: death from arrhythmia; 3: group randomized to EPS-guided therapy with antiarrhythmic medications or ICDs (out of 704 patients in total); 4: cardiac arrest or death from arrhythmia; 5: ICD and placebo arms only (excluding amiodarone arm).
CI, confidence interval; NYHA, New York Heart Association; DCM, dilated cardiomyopathy; NSVT, non-sustained ventricular tachycardia; NS, non-significant (p >0.05); CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; SAECG, signal-averaged electrocardiogram; PVC, premature ventricular complex; MI, myocardial infarction; EPS, electrophysiologic study; CAD, coronary artery disease.
Katritsis DG, Josephson ME. Sudden cardiac death and implantable cardioverter defibrillators: two modern epidemics? *Europace*. 2012;**14**:787–94 with permission from Oxford University Press.

Table 69.6 Major implantable cardioverter-defibrillator trials for secondary prevention of sudden cardiac death

Study		Patients (n)	Inclusion criteria	Therapy	Hazard ratio	95% CI	P-value
AVID	Antiarrhythmics versus implantable defibrillators	1016	VF or symptomatic SVT	ICD vs antiarrhythmic medical therapy	0.62[1]	0.43–0.82	<0.02
CASH	Cardiac arrest study Hamburg	288	Cardiac arrest survivors	ICD vs antiarrhythmic medical therapy	0.77[1] 0.42[2]	1.112[3] 0.721[3]	0.081[4] 0.005[4]
CIDS	Canadian implantable defibrillator study	659	Cardiac arrest, VF, or symptomatic VT	ICD vs amiodarone	0.82[1]	0.60–1.10	NS
DEBUT	Defibrillator vs beta blockers for unexplained death in Thailand	86	Cardiac arrest survivors	ICD vs beta blocker therapy	NA (0 vs 4 deaths)	NA	0.02
DUTCH		60	Prior MI, cardiac arrest survivors	ICD as first choice vs conventional strategy	0.27[5]	0.09–0.85	0.02

1: overall mortality; 2: sudden death 3: upper bound of 97.5% confidence interval; 4: one-tailed; 5: death, recurrent cardiac arrest, cardiac transplantation.
CI, confidence interval; VF, ventricular fibrillation; SVT, sustained ventricular tachycardia; VT, ventricular tachycardia; NA, not available; NS, non-significant ($p > 0.05$); MI, myocardial infarction.
Recommendations for ICD implantation are presented in relevant chapters.
Katritsis DG, Josephson ME. Sudden cardiac death and implantable cardioverter defibrillators: two modern epidemics? *Europace*. 2012;**14**:787–94 with permission from Oxford University Press.

Practical points regarding the choice and programming of ICD devices

- Single-coil integrated bipolar (or true bipolar) leads are recommended for primary prevention ICDs in order to reduce the odds of failure.[30, 31]
- Dual-chamber ICDs are associated with a higher risk of complications than single-chamber ICDs,[32] and discrimination of ventricular arrhythmias alone is not a valid reason to implant a dual-chamber device. Atrial or ventricular pacing, as well as rate-responsive pacing, should be avoided, to increase generator longevity and avoid disruption of normal ventricular conduction.
- Defibrillation testing is not necessary with current technologies.[33] It might be considered in secondary prevention and conditions associated with higher defibrillation thresholds (DFT), such as right-sided implants and amiodarone therapy.
- Inappropriate ICD shocks may cause myocardial damage and have been associated with increased mortality.[22] Strategies to avoid inappropriate shocks should be considered.[34] Carvedilol is superior to metoprolol in preventing inappropriate shocks.[35] Extension of detection duration to prevent treatment of self-terminating tachycardia (30–40 intervals) is the most useful strategy to avoid unnecessary shocks. Higher cutoff rates for arrhythmia therapy should be used, ie > 170 bpm for VT monitoring, antitachycardia pacing for VT with CL < 300 ms (> 200 bpm) unless a clinical slower VT had been recorded, and shocks for VF with CL < 200 ms (> 300 bpm) or CL < 300 ms (200 bpm) after failed antitachycardia pacing and a 2.5 s monitoring delay. The application of SVT-VT discrimination (onset, stability, and morphology algorithms) measures is also useful. These measures have been found useful for both primary,[36–38] and secondary prevention.[39]
- ICD patients often die in the hospital, and one third have ventricular tachyarrhythmia events with shocks close to death. Deactivation of the ICD should be considered when a DNR order is decided to avoid unnecessary painful shocks.[40]
- Approximately 25% of patients who receive primary prevention ICDs may no longer meet guideline indications for ICD use at time of generator replacement. These patients receive subsequent ICD therapies at a significantly lower but not negligible rate (5% vs 12%).[41]
- The HRS now recommend remote monitoring as the new standard of care for patients with cardiac devices, with alert-driven in-person evaluation replacing most routine office interrogations.[4]

Magnetic resonance imaging

Up to 75% of patients with implanted devices may need an MRI in the future, and this can now be performed in scanners with up to 1.5 T under certain circumstances.[42–44] The ESC has recently published the following recommendations (Table 69.7 and Figure 69.2):[42]

- Exclude patients with leads that have not matured (<6 weeks since implantation, during which the leads are prone to spontaneous dislodgement) and those with epicardial and abandoned leads (which are prone to heating).
- Programme an asynchronous pacing mode in pacemaker-dependent patients to avoid inappropriate inhibition of pacing due to detection of electromagnetic interference.
- Use an inhibited pacing mode for patients without pacemaker dependence, to avoid inappropriate pacing due to tracking of electromagnetic interference.

Table 69.7 ESC 2013 GL on cardiac pacing and CRT

Magnetic resonance in patients with implanted cardiac devices	
In patients with **conventional cardiac devices**, MR at 1.5 T can be performed with a low risk of complications if appropriate precautions are taken.	IIb-B
In patients with **MR-conditional PM systems**, MR at 1.5 T can be done safely following manufacturer instructions.	IIa-B

MRI: magnetic resonance imaging; PM: pacemaker.
ESC 2013 Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J.* 2013;**34**:2281–329, with permission from Oxford University Press.

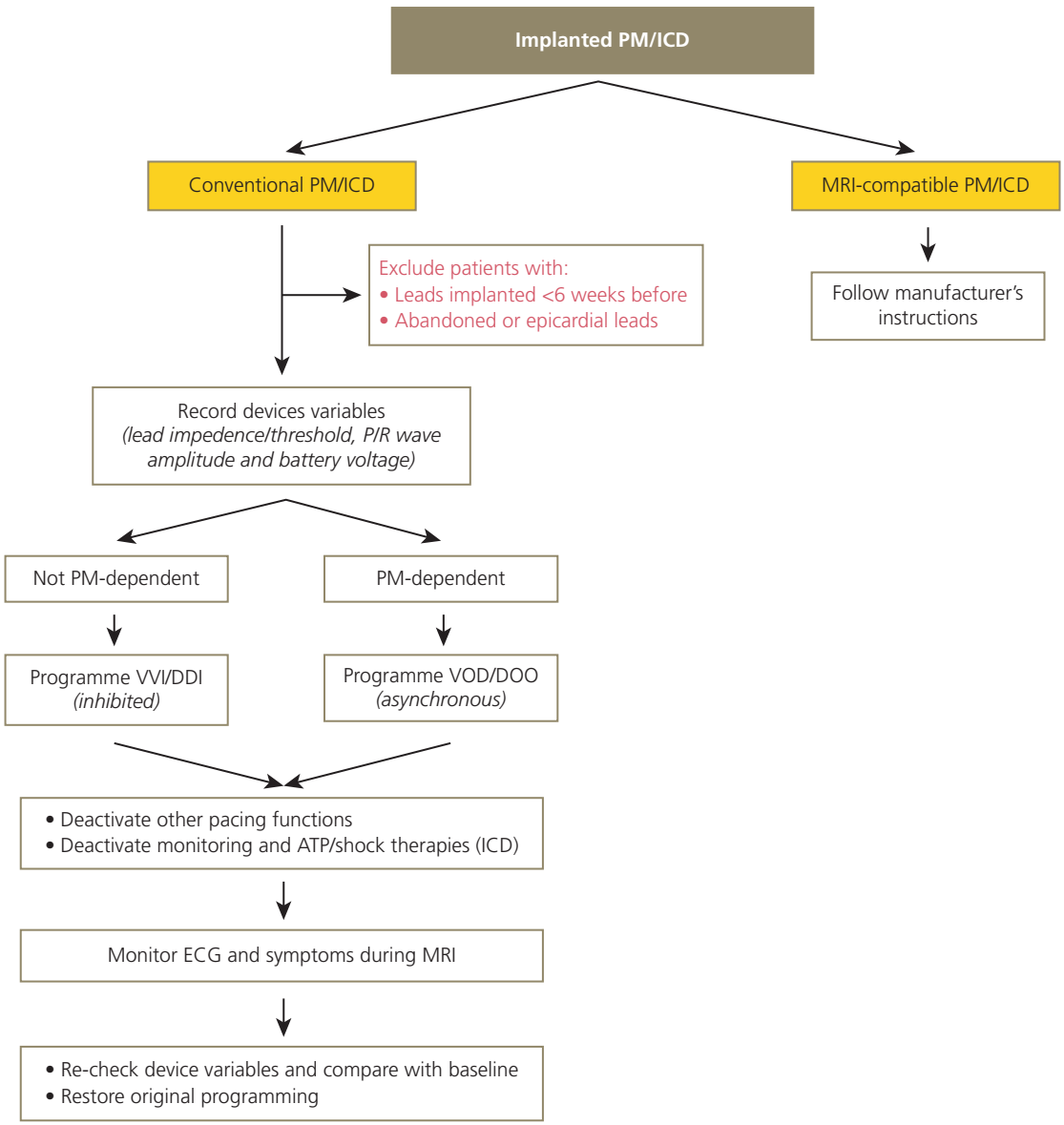

Figure 69.2 ESC 2013 GL on cardiac pacing and CRT.

Safety precautions for magnetic resonance imaging (MRI) in patients with conventional cardiac devices.
ATP, antitachycardic pacing; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; PM, pacemaker.
ESC 2013 Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J.* 2013;**34**:2281–329, with permission from Oxford University Press.

- Deactivate other pacing functions (magnet, rate, noise, PVC, ventricular sense, AF response) in order to ensure that sensing of electromagnetic interference does not lead to unwarranted pacing.
- Deactivate tachyarrhythmia monitoring and therapies (ATP/shock) to avoid delivery of unwarranted therapies.

In addition, MRI with devices implanted before 2000 should be better avoided.[43]

Electromagnetic interference

Daily life electromagnetic interferences of low frequency do not disturb sensing capabilities of ICDs, especially in patients with true bipolar leads.[45] Strong interference (≥50 Hz), present in certain occupational environments, such as high voltage power lines and installations, may cause inappropriate sensing, potentially leading to false detection of atrial/ventricular arrhythmic events.[46]

Radiotherapy

The use of non-neutron-producing RT (up to 5.4 Gy) is recommended. In a recent study comparing neutron-producing radiotherapy with 15- or 18-MV photons and non–neutron-producing with electrons, GammaKnife, or 6-MV photons, all cases of single-event upset malfunction occurred in the setting of notable neutron production.[47]

Driving, sports, and sexual activity

Driving is allowed 4 weeks after permanent pacemaker implantation.[48] Following ICD implantation, professional driving is not allowed.[48,49] Private driving is allowed, as indicated in Table 69.8. Similar recommendations were offered by a recent study.[50] Current recommendations do not allow intensive or competitive sports in patients with ICDs. However, a more liberal policy may be considered in some competitive athletes and in those who want to perform mild-to-moderate recreational activities.[51] Sexual activity is reasonable for patients with an ICD used for secondary prevention in whom moderate physical activity (>3–5 METS) does not precipitate ventricular tachycardia or fibrillation (AHA/ESC 2013 consensus on sexual counselling, IIa-C).[52]

Table 69.8 Private driving with ICD

AHA/HRS	
Primary prevention	**Secondary prevention (or shock from ICD implanted for primary prevention)**
Until recovery from implantation	6 months (at least 1 week)
EHRA	
	Restriction for private driving
ICD implantation for secondary prevention	3 months
ICD implantation for primary prevention	4 weeks
After appropriate ICD therapy	3 months
After inappropriate ICD therapy	Until measures to prevent inappropriate therapy are taken
After replacement of the ICD	1 week
After replacement of the lead system	4 weeks
Patients refusing ICD for primary prevention	No restriction
Patients refusing ICD implantation for secondary prevention	7 months

HRS/ASA 2011 Expert Consensus Statement on the perioperative management of patients with implantable defibrillators, pacemakers and arrhythmia monitors: facilities and patient management. *Heart Rhythm*. 2011;**8**:1114–54 with permission from Elsevier.
Consensus statement of the European Heart Rhythm Association: updated recommendations for driving by patients with implantable cardioverter defibrillators. *Europace*. 2009;**11**:1097–107 with permission from Oxford University Press.

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Chapter 70

Procedural issues and complications of implantable devices

Device implantation in the anticoagulated patient

In patients on chronic anticoagulation, bridging is not required, especially in patients at low risk of thrombosis.[1–6] In the continued-warfarin group, the INR on the day of surgery should be ≤3, except for patients with one or more mechanical valves, for whom an INR ≤3.5 or less is permitted.[1] In patients with AF, invasive procedures can be safely accomplished with an INR <1.8.[6] It has been postulated that, during minor surgery, haemostasis is primarily dependent on capillary and platelet function as opposed to the coagulation cascade itself, and antithrombotics that interfere with the former (e.g. heparin and antiplatelet drugs) are less well tolerated than those that do not. Another explanation is the concept of an 'anticoagulant stress test.' That is, if patients undergo surgery while receiving full-dose anticoagulation therapy, any excessive bleeding will be detectable and appropriately managed while the wound is still open.[1] Data on new oral anticoagulants are limited. A 24 h discontinuation[4,7] with reinitiation 48 h after implantation (24 h in patients with a $CHADS_2DS_2VASC$ score >4, i.e. >5% annual risk of stroke)[4] is recommended.

Table 70.1 Differential diagnosis of pace-sense lead failure

Electrogram	Impedance*	Condition
Abnormal		
Lead-system noise	High; abrupt increase	Fracture or connector
Lead-system noise	Normal	Fracture, insulation breach†
Spikes, myopotentials on true bipolar electrograms	Normal or low	Insulation breach
Other rapid oversensing	Normal	Normal lead
Normal	High; abrupt increase	Fracture or connector
	High; gradual increase	Normal lead
	Low	Insulation breach

* High impedance = 75% > baseline. Abrupt increase indicates the maximum value for 1 week exceeds baseline of past 3 weeks by 75%. Gradual increase does not meet abrupt criterion. Impedance <200Ω is considered low, but data correlating insulation breach with impedance changes are limited, and most insulation failures have impedance within normal range.

† Data supporting correlation between insulation breach and lead-system noise are limited.

Swerdlow CD, Ellenbogen KA. Implantable cardioverter-defibrillator leads. Design, diagnostics, and management. *Circulation*. 2013:**128**:2062–71 with permission from Wolters Kluwer.

Reimplantation

Lead complications are the main reason for reoperation after implantation of pacemakers or cardiac resynchronization therapy devices (Table 70.1).[8–10] Sprint Fidelis (Medtronic) and Riata (St Jude Medical) defibrillator leads have a failure rate at 2.6–2.7% per year and have been removed from the market. Fracture of a pace-sense conductor is the most widely studied failure mode of the Sprint Fidelis. Fractures of high voltage conductors are much less common but, unlike pace-sense conductor fractures, may result in failed defibrillation.[11] Patients with an ICD-CRT have a significantly higher Fidelis fracture rate than patients with an ICD.[12]

The Riata ST and Riata (especially) ICD leads are prone to high-voltage failures that have resulted in death. These failures appeared to have been caused by insulation defects that resulted in short-circuiting between high-voltage components.[13] Early extraction of Riata leads with externalized conductors has been proposed to avoid the potential for large organized thrombus formation that has been recently described.[14] However, fluoroscopic detection of externalized conductors does not necessarily imply electrical dysfunction, and an individualized approach is probably reasonable.[15]

Lead dislodgement for primary implantation is approximately 0.8–1% per procedure-year for pacemakers and ICDs, and 3% for CRT.[16]

Lead extraction, more than 4–6 months after implantation, requires extensive experience and can be accomplished in 90% of cases with the use of various dedicated devices. It is associated with potential complications including a 2.2% mortality, especially in women and with infected devices.[17]

Pacemaker and ICD generator replacements are associated with a notable complication risk (1–2% and 4–6%, respectively), particularly those with lead additions.[18] Pacemaker reuse, although not allowed in most countries, is an interesting opportunity for elimination of resources waste.[19] Pacemaker reuse has an overall low rate of infection and device malfunction, but there is a higher rate of device malfunction as compared with new device implantation.[20] Admission for heart failure within the prior 12 months, NYHA III or IV, antiarrhythmic drug use, chronic kidney disease, and cerebrovascular disease are independently associated with 6-month mortality after replacement (REPLACE DARE Score).[21]

Strategies for avoiding complications, as well as the optimum management of patients with electronic devices during and after medical and surgical procedures, have been described.[22]

Perioperative management of patients with devices

The HRS has recently published a statement on the issue.[23] The main points are presented in Tables 70.2 to 70.5.

Table 70.2 HRS/ASA 2011 consensus statement on the perioperative management of patients with implantable devices

Problems that can occur during medical procedures
• Bipolar electrosurgery does not cause EMI, unless it is applied directly to a CIED
• EMI from monopolar electrosurgery is the most common problem incurred during surgical procedures
- Pacemakers may have oversensing and be inhibited when exposed to EMI
- ICDs and pacemakers with anti-tachycardia function may be inhibited or may falsely detect arrhythmias when exposed to EMI
- Device reset occurs infrequently with electrosurgery
- Electrosurgery applied below the umbilicus is much less likely to cause PM or ICD interference than when applied above the umbilicus
- Pulse generator damage from electrosurgery can occur but is uncommon
- Impedance-based rate-responsive systems may go to upper rate behaviour with electrosurgery exposure
- Risk mitigation strategies can be effective
- Keeping the current path away from CIED diminishes the potential for adverse interaction with the CIED
- Using bipolar electrosurgery whenever possible
- Minimizing the length of monopolar electrosurgery bursts to 5 s or less
• Lead tissue interface damage from external current is considered an unlikely risk
• Cardioversion can cause reset of the CIED
• RF ablation can cause all of the interactions that monopolar electrosurgery can cause but may have a more significant risk profile due to the prolonged exposure to current
• Therapeutic radiation is the most likely source of EMI to result in CIED reset
• ECT has rarely been reported to cause EMI during the stimulus, but the more common problem with EMI may be the extreme sinus tachycardia that occurs with the seizure, prompting a need to review tachycardia therapy zones in ICDs
• GI procedures that use electrosurgery may result in interference
• TENS units can result in EMI

ICD, implantable cardioverter defibrillator; EMI, electromagnetic interference; CIED, cardiovascular implantable electronic device; RF, radio frequency; ECT, electroconvulsive therapy; TUNA, transurethral needle ablation; TURP, transurethral resection of the prostate; TENS, transcutaneous electrical nerve stimulation; CRT-P, cardiac resynchronization therapy pacemaker; CRT-D, cardiac resynchronization therapy defibrillator.
HRS/ASA 2011 Expert consensus statement on the perioperative management of patients with implantable defibrillators, pacemakers and arrhythmia monitors: facilities and patient management. *Heart Rhythm*. 2011;**8**:1114–54 with permission from Elsevier.

Table 70.3 HRS/ASA 2011 consensus statement on the perioperative management of patients with implantable devices

Preoperative recommendations
• The procedure team must advise the CIED team about the nature of the planned procedure.
• The CIED team will provide guidance in the form of a prescription to the procedure team for the management of the CIED.
• General principles guiding this prescription include the acknowledgement that:
- Inactivation of ICD detection is not a universal requirement for all procedures.
- Rendering pacemakers asynchronous in pacemaker-dependent patients is not a universal requirement of all procedures.
- Pacemakers that need to be protected from inhibition may be made asynchronous by programming or by placement of a magnet applied over the pulse generator, provided the pulse generator is accessible.
- ICD arrhythmia detection can be suspended by placement of a magnet over the pulse generator, provided the pulse generator is accessible.
- A magnet placed over an ICD generator will not render pacemaker function in an ICD asynchronous.
- Inactivation of ICD detection is recommended for all procedures using monopolar electrosurgery or RF ablation above the umbilicus.
- Rendering a pacemaker asynchronous in a pacemaker-dependent patient is preferable for most procedures above the umbilicus.
- In pacemaker patients, no reprogramming is usually needed if the electrosurgery is applied below the level of the umbilicus.
• All patients with pacemakers undergoing elective surgery should have had a device check as part of routine care within the past 12 months that identifies the required elements specified below.
• All patients with ICDs undergoing elective surgery should have had a device check as part of routine care within the past 6 months.

HRS/ASA 2011 Expert consensus statement on the perioperative management of patients with implantable defibrillators, pacemakers and arrhythmia monitors: facilities and patient management. *Heart Rhythm*. 2011;**8**:1114–54 with permission from Elsevier.

Table 70.4 HRS/ASA 2011 consensus statement on the perioperative management of patients with implantable devices

Approach to emergent/urgent procedures
Identify the type of device
• ICD, pacemaker, CRT-ICD, or CRT-pacemaker. Options for help in identification are:
- Evaluate the medical record
- Examine the patient registration card
- Telephone the company to clarify device type
- Examine the chest radiograph
Determine if the patient is pacing
• Obtain a 12-lead electrocardiogram or rhythm strip documentation
• If there are pacemaker spikes in front of all, or most, P waves and/or QRS complexes, assume pacemaker dependency
Pacemaker dependent?#
—**Yes:** pacemaker (not ICD): Use short electrosurgical bursts; place magnet over device for procedures above umbilicus or extensive electrosurgery, and have magnet immediately available for procedures below umbilicus
— Monitor patient with plethysmography or arterial line
— Transcutaneous pacing and defibrillation pads placed anterior/posterior
— Evaluate the pacemaker before leaving a cardiac-monitored environment
— **Yes:** ICD or CRT-D*: Place magnet over device to suspend tachyarrhythmia detection; use short electrosurgical bursts†
— Monitor patient with plethysmography or arterial line
— Transcutaneous pacing and defibrillation pads placed anterior/posterior
— Evaluate the ICD before leaving a cardiac-monitored environment
— **No:** pacemaker (not ICD): Have magnet immediately available
— Monitor patient with plethysmography or arterial line
— Transcutaneous pacing and defibrillation pads placed anterior/posterior
— Evaluate the pacemaker before leaving a cardiac-monitored environment
—**No:** ICD or CRT-D: Place magnet over device to suspend tachyarrhythmia detection; use short electrosurgery bursts†
— Monitor patient with plethysmography or arterial line
— Transcutaneous pacing and defibrillation pads placed anterior/posterior
— Evaluate the ICD before leaving a cardiac-monitored environment
Contact CIED team
• A member of the CIED team should be contacted as soon as feasible
- Provide preoperative recommendations for CIED management if time allows
- Contact manufacturer representative to assist in interrogation of device pre- and/or post-operatively (under the direction of a physician knowledgeable in CIED function and programming)
- Perform or review post-operative interrogation

* A magnet placed over an ICD (or CRT-ICD) will not result in asynchronous pacemaker function. This can only be accomplished by reprogramming of ICDs (or CRT-ICDs) capable of this feature (majority of newer devices implanted).
† Long electrosurgery application (>5 s and/or frequent close spaced bursts) may result in pacemaker inhibition, causing haemodynamic risk in a pacemaker-dependent patient. Long electrosurgery application in close proximity to the device generator may rarely result in power on reset or Safety Core™ programming.
# Pacemaker dependency is defined as absence of a life-sustaining rhythm without the pacing system.
HRS/ASA 2011 Expert consensus statement on the perioperative management of patients with implantable defibrillators, pacemakers and arrhythmia monitors: facilities and patient management. *Heart Rhythm*. 2011;**8**:1114–54 with permission from Elsevier.

Table 70.5 HRS/ASA 2011 consensus statement on the perioperative management of patients with implantable devices

Recommendations for the intraoperative monitoring of patients with CIEDs
• External defibrillation equipment is required in the operating room and immediately available for all patients with pacemakers or ICDs having surgical and sedation procedures or procedures where EMI may occur
• All patients with ICDs deactivated should be on a cardiac monitor and, during surgery, should have immediate availability of defibrillation
• Some patients may need to have pads placed prophylactically during surgery (e.g. high-risk patients and patients in whom pad placement will be difficult due to surgical site)
• All patients with pacemakers or ICDs require plethysmographic or arterial pressure monitoring for all surgical and sedation procedures
• Use an ECG monitor with a pacing mode set to recognize pacing stimuli
• Pacemakers may be made asynchronous, as needed, with either a magnet application or reprogramming, provided that the pulse generator is accessible
• ICD detection may be suspended by either magnet application, as needed, or reprogramming, provided that the pulse generator is accessible
• During the placement of central lines using the Seldinger technique from the upper body, caution should be exercised to avoid causing false detections and/or shorting the RV coil to the SVC coil
• Because of interactions with monitoring, ventilation, and other impedance monitoring operative devices, inactivating minute ventilation sensors can be considered
• Keep a magnet immediately available for all patients with a CIED who are undergoing a procedure that may involve EMI

HRS/ASA 2011 Expert consensus statement on the perioperative management of patients with implantable defibrillators, pacemakers and arrhythmia monitors: facilities and patient management. *Heart Rhythm*. 2011;**8**:1114–54 with permission from Elsevier.

Implantation-related complications

The incidence of complications following implantation of permanent pacemakers and ICD is 3–12%, and ICD or biventricular pacemakers implantation carries an in-hospital mortality of 0.05%.[24-26] Chronic heart failure as an indication, inexperienced operators, CRT or DDD devices, and passive-fixation atrial leads are independent risk factors for lead complications.[9]

Pneumothorax occurs in 1.5% after subclavian puncture.

Haematomas of the pocket requiring evacuation occur in 1–2% of implants. Pocket haematoma is, after lead dislodgement, the second most frequent complication of device implantation.[27]

Deep venous thrombosis/venous occlusion, air embolism, and perforation of cardiac chambers are rare complications. Venous thrombosis leading to SVC syndrome may be seen in 0–6% of patients, but asymptomatic pulmonary embolism may be detected in up to 20% of patients. Mobile thrombi on device leads can be detected in up to 30% of patients with intracardiac echocardiography, but their clinical significance is not known.[28] Increasing age predicts worsening outcomes in the elderly, but the absolute rates are modest, even in nonagenarians, and comorbidity is a stronger predictor of complications following implantation of permanent pacemakers.[29] A clinical model that predicts risks for in-hospital events in patients undergoing ICD implantation has been proposed.[30]

Device-related infections

They now occur in <1% of implants but the rate is higher with ICD than pacemakers.[31–34] In a recent report from the US ICD registry, the infection rate was 1.4%, 1.5%, and 2.0% for single, dual, and biventricular ICDs, respectively. Peri-ICD implant complications requiring early reintervention, previous valve surgery, device replacement for reasons other than battery depletion, and increased comorbidity such as renal failure, chronic lung disease and CVA were predisposing factors for infection that was associated with a twice as high 6-month mortality rate (12 vs 6.5%).[36] The 6-month mortality was 12.0% in patients with ICD infection and 6.5% in those without.[35] In general, one-year mortality in patients with device infections is 17–24%.[33,36] The majority of patients (up to 60%) present with localized infection involving the device pocket, and the rest with bloodstream infection with or without evidence of inflammation of the device pocket.[33,37] A negative transoesophageal echo does not rule out lead infection. Intracardiac echocardiography is superior to transoesophageal echocardiography in detecting intracardiac vegetations, especially around the tricuspid valve, in this respect.[38] Renal failure, haematoma formation, poor wound healing, and implantation of devices with multiple leads are risk factors. Several studies have identified device revision or replacement as a risk factor for infection,[35] although the REPLACE registry showed a low rate of major infection (0.8%).[34] Perioperative antibiotic prophylaxis (i.e. cefazolin) reduces the risk of device-related infections.[31] Main causes are staphylococci (60–80% and up to half of them methicillin-resistant). Gram-positive cocci (15%), Gram-negative, and polymicrobial infections are rare. Infections due to coagulase-negative staphylococci usually have an indolent presentation, whereas *S. aureus* infections, particularly those complicated by bloodstream infection or infective endocarditis, develop more rapidly,

Table 70.6 Management of device-related infections

AHA 2010 scientific statement on cardiovascular implantable electronic device (CIED) infections	
Recommendations for diagnosis of CIED infection and associated complications	
All patients should have at least 2 sets of blood cultures drawn at the initial evaluation before prompt initiation of antimicrobial therapy for CIED infection.	I-C
Generator-pocket tissue Gram stain and culture and lead-tip culture should be obtained when the CIED is explanted.	I-C
Patients with suspected CIED infection who either have positive blood cultures or who have negative blood cultures but have had recent antimicrobial therapy before blood cultures were obtained should undergo TOE for CIED infection or valvular endocarditis.	I-C
All adults suspected of having CIED-related endocarditis should undergo TOE to evaluate the left-sided heart valves, even if transthoracic views have demonstrated lead-adherent masses. In paediatric patients with good views, transthoracic echocardiography may be sufficient.	I-B
Patients should seek evaluation for CIED infection by cardiologists or infectious disease specialists if they develop fever or bloodstream infection for which there is no initial explanation.	IIa-C
Percutaneous aspiration of the generator pocket should not be performed as part of the diagnostic evaluation of CIED infection.	III-C
Recommendations for antimicrobial management of CIED infection	
Choice of antimicrobial therapy should be based on the identification and in vitro susceptibility results of the infecting pathogen.	I-B
Duration of antimicrobial therapy should be 10 to 14 days after CIED removal for pocket-site infection.	I-C
Duration of antimicrobial therapy should be at least 14 days after CIED removal for bloodstream infection.	I-C
Duration of antimicrobial therapy should be at least 4 to 6 weeks for complicated infection (ie, endocarditis, septic thrombophlebitis, or osteomyelitis or if bloodstream infection persists despite device removal and appropriate initial antimicrobial therapy).	I-C
Recommendations for removal of infected CIED	
Complete device and lead removal for all patients with definite CIED infection, as evidenced by valvular and/or lead endocarditis or sepsis.	I-A
Complete device and lead removal is recommended for all patients with CIED pocket infection as evidenced by abscess formation, device erosion, skin adherence, or chronic draining sinus without clinically evident involvement of the transvenous portion of the lead system.	I-B
Complete device and lead removal is recommended for all patients with valvular endocarditis without definite involvement of the lead(s) and/or device.	I-B
Complete device and lead removal is recommended for patients with occult staphylococcal bacteraemia.	I-B
Complete device and lead removal is reasonable in patients with persistent occult Gram-negative bacteraemia despite appropriate antibiotic therapy.	IIa-B
CIED removal is not indicated for a superficial or incisional infection without involvement of the device and/or leads.	III-C
CIED removal is not indicated for relapsing bloodstream infection due to a source other than a CIED and for which long-term suppressive antimicrobials are required.	III-C
Recommendations for new CIED implantation after removal of an infected CIED	
Each patient should be evaluated carefully to determine whether there is a continued need for a new CIED.	I-C
The replacement device implantation should not be ipsilateral to the extraction site. Preferred alternative locations include the contralateral side, the iliac vein, and epicardial implantation.	I-C
When positive before extraction, blood cultures should be drawn after device removal and should be negative for at least 72 hours before new device placement is performed.	IIa-C
New transvenous lead placement should be delayed for at least 14 days after CIED system removal when there is evidence of valvular infection.	IIa-C
Recommendations for use of long-term suppressive antimicrobial therapy	
Long-term suppressive therapy should be considered for patients who have CIED infection and who are not candidates for complete device removal.	IIb-C
Long-term suppressive therapy should not be administered to patients who are candidates for infected CIED removal.	III-C
Recommendations for antimicrobial prophylaxis at the time of CIED placement	
Prophylaxis with an antibiotic that has in vitro activity against staphylococci should be administered. If cefazolin is selected for use, then it should be administered IV within 1 hour before incision; if vancomycin is given, then it should be administered IV within 2 hours before incision.	I-A
Recommendations for antimicrobial prophylaxis for invasive procedures in patients with CIEDs	
Antimicrobial prophylaxis is not recommended for dental or other invasive procedures not directly related to device manipulation to prevent CIED infection.	III-C
Recommendations to avoid microbiological studies in cases of CIED removal for noninfectious reasons	
Routine microbiological studies should not be conducted on CIEDs that have been removed for noninfectious reasons.	III-B

(*Continued*)

Table 70.6 (Continued)

ESC 2015 GL on infective endocarditis. Cardiac device-related infective endocarditis: diagnosis, treatment and prevention	
A. Diagnosis	
Three or more sets of blood cultures before prompt initiation of antimicrobial therapy for CIED infection	I-C
Lead-tip culture when the CIED is explanted	I-C
TOE in patients with suspected CDRIE with positive or negative blood cultures, independent of the results of TTE, to evaluate lead-related endocarditis and heart valve infection	I-C
Intracardiac echocardiography in patients with suspected CDRIE, positive blood cultures and negative TTE and TOE results	IIb-C
Radiolabelled leucocyte scintigraphy and 18F-FDG PET/CT scanning as additive tools in patients with suspected CDRIE, positive blood cultures and negative echocardiography	IIb-C
B. Principles of treatment	
Prolonged (i.e. before and after extraction) antibiotic therapy and complete hardware (device and leads) removal in definite CDRIE, as well as in presumably isolated pocket infection	I-C
Complete hardware removal on the basis of occult infection without another apparent source of infection	IIa-C
In patients with NVE or PVE and an intracardiac device with no evidence of associated device infection, complete hardware extraction	IIb-C
C. Mode of device removal	
Percutaneous extraction in most patients with CDRIE, even those with vegetations >10 mm	I-B
Surgical extraction if percutaneous extraction is incomplete or impossible or when there is associated severe destructive tricuspid IE	IIa-C
Surgical extraction in patients with large vegetations (>20 mm)	IIb-C
D. Reimplantation	
After device extraction, reassessment of the need for reimplantation	I-C
When indicated, definite postpone reimplantation if possible, to allow a few days or weeks of antibiotic therapy	IIa-C
A 'temporary' ipsilateral active fixation strategy in pacemaker-dependent patients requiring appropriate antibiotic treatment before reimplantation	IIb-C
Temporary pacing is not routinely recommended	III-C
E. Prophylaxis	
Routine antibiotic prophylaxis before device implantation	I-B
Potential sources of sepsis should be eliminated ≥2 weeks before implantation of an intravascular/cardiac foreign material, except in urgent procedures	IIa-C

CDRIE, cardiac device-related infective endocarditis; CIED, cardiac implantable electronic device; FDG, fluorodeoxyglucose; IE, infective endocarditis; NVE, native valve endocarditis; PET, positron emission tomography; PVE, prosthetic valve endocarditis; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. *Circulation*. 2010;**121**:458–77.

ESC 2015 Guidelines for the management of infective endocarditis. *Eur Heart J*. 2015;**36**:3075–128 with permission from Oxford University Press.

with more severe systemic manifestations. Device infection will be confirmed in 35% or more of patients with bacteraemia due to staphylococcal species, whereas its likelihood is lower (20% or less) in patients with bacteraemia caused by non-staphylococcal Gram-positive cocci or by Gram-negative bacilli. A single blood culture that is positive for coagulase-negative staphylococci usually represents contamination rather than infection; multiple blood cultures that are positive for coagulase-negative staphylococci should prompt consideration of a device-related infection, even if there are no other suggestive symptoms or signs.[31] In patients with left ventricular assist devices, device infection occurs in 22% of patients per year despite the use of newer, smaller devices, and affects mortality. Staphylococci are the most common pathogen (approximately 50%), but Pseudomonas or other Gram-negative bacteria cause up to 30% of infections.[39]

Therapy

Aspiration of the pocket should be avoided because it could result in infection. If the pocket has to be surgically explored, deep tissue and lead tip, rather than swab, cultures are obtained. Device removal is not required for superficial or incisional-only infection at the pocket site if there is no involvement of the device. Seven to ten days of oral antibiotic therapy with anti-staphylococcal activity is recommended. However, if localized pocket infection is established or blood cultures become positive, early and complete removal of the device and leads is necessary.[31,40] Biofilm formation on the leads without obvious vegetations is a distinct possibility and precludes eradication of the infection without system extraction. The high frequency of leads extracted in patients with findings limited to the pocket indicates that the spread of the infection from

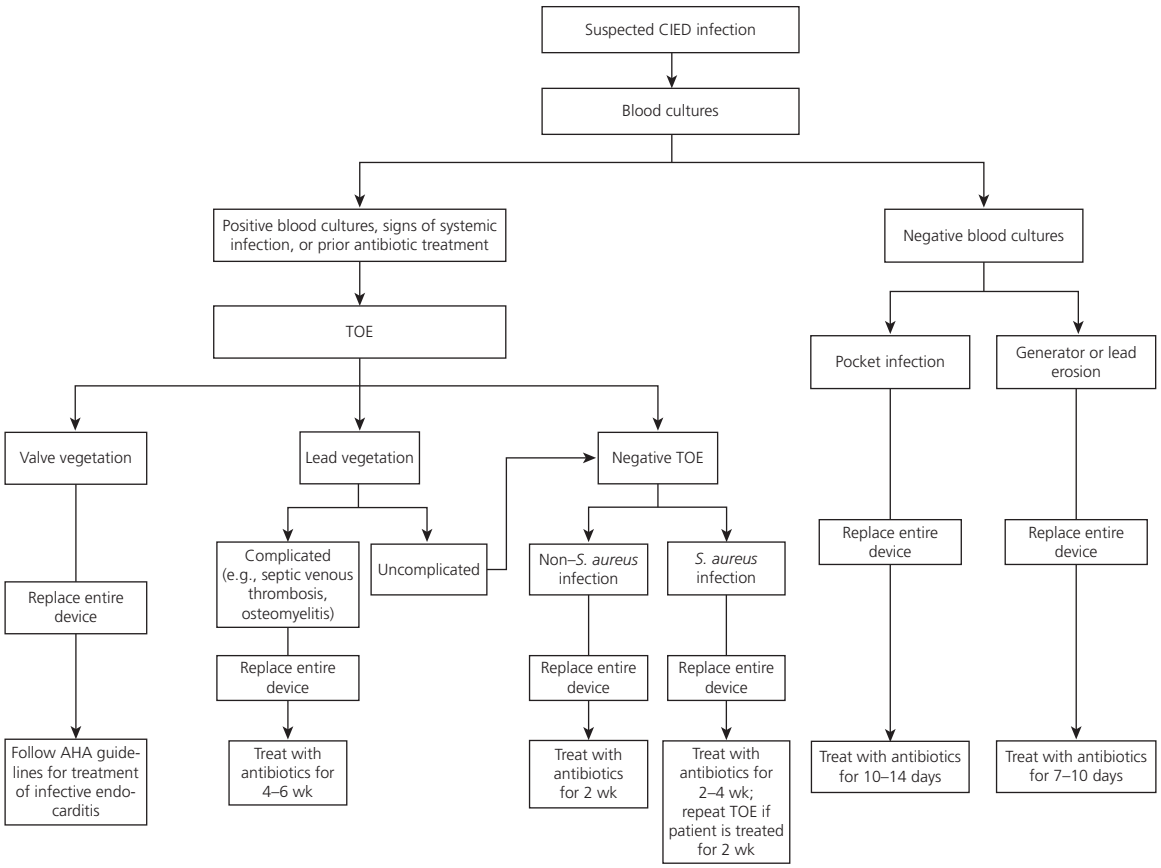

Figure 70.1 Algorithm for management of an infected cardiovascular implantable electronic device (CIED) in adults.

AHA, American Heart Association; TOE, transoesophageal echocardiography.

Baddour LM, *et al*. Clinical practice. Infections of cardiovascular implantable electronic devices. *N Engl J Med*. 2012;**367**:842–9 with permission from Massachusetts Medical Society.

the pocket site is common, and complete removal of the device is usually necessary to prevent relapse. Most pacemaker leads implanted within a year can be explanted without the use of any specialized equipment. For older leads, teflon, polypropylene, and stainless steel sheaths were initially used for removal, but have largely been replaced by laser sheaths and rotating mechanical sheaths, which are easier and safer to use. Postextraction wound management is crucial to eradication of infection and timely healing. Complete debridement of the infected and avascular tissue or foreign materials can be accomplished by surgical dissection and electrocautery. Vacuum-assisted closure therapy may also be useful.[41]

In established pocket infection, IV vancomycin should be given, pending culture results, and therapy should last up to 14 days if there is no evidence of infective endocarditis. A new device should be implanted in the contralateral side at least 72 hours after the infected device has been removed. Clinical manifestations of pocket infection are present in the majority of patients with early lead-associated endocarditis. However, late lead-associated endocarditis (> 6 months after device implantation) should be considered in any patient who presents with fever, bloodstream infection, or signs of sepsis, even if the device pocket appears uninfected. Prompt recognition and management may improve outcomes.[17] Development of lead vegetations > 2 cm in diameter may require surgical removal to avoid pulmonary embolism. In patients too sick to be subjected to lead extraction, a conservative approach may be adopted by extensive resection of infected and non-viable tissue, mechanical and chemical sterilization of all remaining hardware and local antibiotics by a closed irrigation system, and oral antibiotics upon discharge.[42,43] Recommendations for management of infections are presented in Table 70.6 and a management algorithm in Figure 70.1. Recommendations by the ESC and AHA/ACC about cardiac device-related endocarditis are also provided in Chapter 81 on infective endocarditis (Tables 81.7 and 81.8).

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Part XIV

Diseases of the aorta

Relevant guidelines

ESC 2014 Guidelines on aortic diseases

2014 ESC Guidelines on the diagnosis and treatment of aortic diseases. *Eur Heart J*. 2014;**35**:2873–926.

ACC/AHA 2010 Guidelines on thoracic aortic disease (specific issues on pre- and post-operative care have not been included. The reader should consult with the actual text for this purpose)

2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease. *J Am Coll Cardiol*. 2010;**55**:e27–129.

ESC 2010 Guidelines on GUCH

ESC guidelines for the management of grown-up congenital heart disease. *Eur Heart J*. 2010;**31**:2915–57.

AHA 2010 Statement on surgical management thoracic aortic disease

Surgical management of descending thoracic aortic disease: open and endovascular approaches: a scientific statement from the American Heart Association. *Circulation*. 2010;**121**:2780–804.

EACTS/ESC/EAPCI 2012 on TEVAR

Thoracic Endovascular Aortic Repair (TEVAR) for the treatment of aortic diseases: a position statement from the European Association for Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2012;**33**:1558–63.

ESC 2011 Guidelines on pregnancy

ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**:3147–97

Chapter 71

Acute aortic syndromes

Definitions and classification

The segments of the ascending and descending aorta are indicated in Figure 71.1. The term acute aortic syndrome includes the classic aortic dissection and conditions with a similar clinical profile, such as intramural aortic haematoma and penetrating atherosclerotic aortic ulcer.[1–4]

Aortic dissection (AoD) denotes disruption of the medial layer of the aorta, with bleeding within and along the wall, resulting in separation of the layers of the aorta (Figure 71.2). The outer part of the aortic media forms with the adventitia the false channel outside wall whereas the rest of the media and the intima constitute the inner wall, i.e. the intimomedial flap (also called intimal flap). An intimal disruption is usually present (90% of cases) that results in tracking of the blood in a dissection plane within the media. This may rupture through the adventitia or back through the intima into the aortic lumen. Dissection may, and often does, occur without an aneurysm being present. The term 'dissecting aortic aneurysm' is often used incorrectly and should be reserved only for those cases where a dissection occurs in an aneurysmal aorta.[4]

Acute dissection is defined as occurring within 2 weeks of onset of pain.

Subacute dissection Between 2 and 6 weeks from onset of pain.

Chronic dissection More than 6 weeks from onset of pain.

Intramural haematoma (IMH) is characterized by the absence of an entrance tear (Figure 71.2). The false lumen is created by a haemorrhage into the aortic media, most likely after rhexis of the vasa vasorum that penetrates the outer half of the aortic media from the adventitia. An entrance tear is not visualized by the current imaging

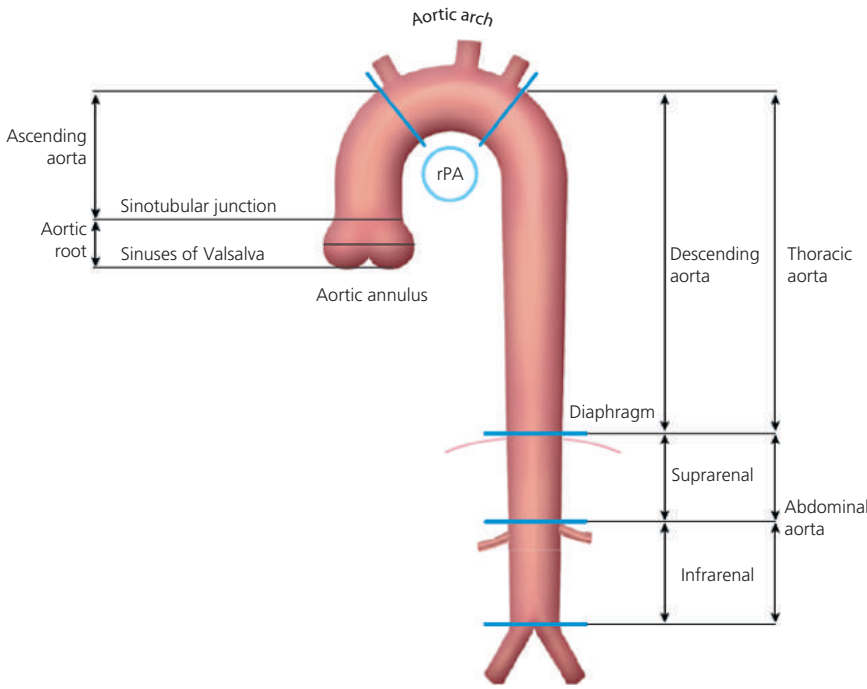


Figure 71.1 ESC 2014 GL on aortic diseases. Segments of the ascending and descending aorta. rPA = right pulmonary artery.

ESC 2014 Guidelines on the diagnosis and treatment of aortic diseases. *Eur Heart J.* 2014;**35**:2873–926 with permission from Oxford University Press.

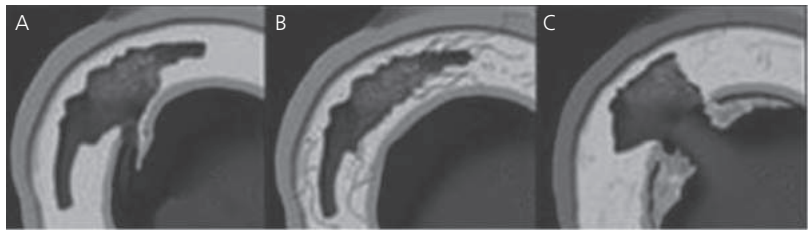


Figure 71.2 Classification of acute aortic syndrome. A, Aortic dissection; B, Intramural haematoma; C, Penetrating atheromatous ulcer.

Sheikh AS, *et al*. Acute aortic syndrome. *Circulation*. 2013;**128**:1122–7 with permission from Wolters Kluwer.

techniques but is usually found at surgery or autopsy.[4] IMH is difficult to distinguish from classic dissection, and carries a higher rate of complications.[5] Involvement of the ascending aorta and aortic diameter ≥5 cm are the most important predictors of mortality.

Penetrating atherosclerotic ulcer (PAU) denotes ulceration of an aortic atherosclerotic lesion penetrating the internal elastic lamina into the media. It is usually found in the descending aorta and may precipitate IMH or classic dissection. However, the natural history of PAU is virtually unknown.[2]

Incomplete dissection refers to that situation in which there is laceration of the intima and subjacent media (dissection tear) without significant intramural (separation of the medial layers) dissection. Patients are at high risk of aortic rupture.

Classifications of aortic dissection

The **De Bakey classification** is based on the origin of the tear and the extent of the dissection (Figure 71.3):

Type I: dissection originates in the ascending aorta and propagates distally to include, at least, the aortic arch and typically the descending aorta (surgery usually recommended).

Type II: dissection originates in and is confined to the ascending aorta (surgery usually recommended).

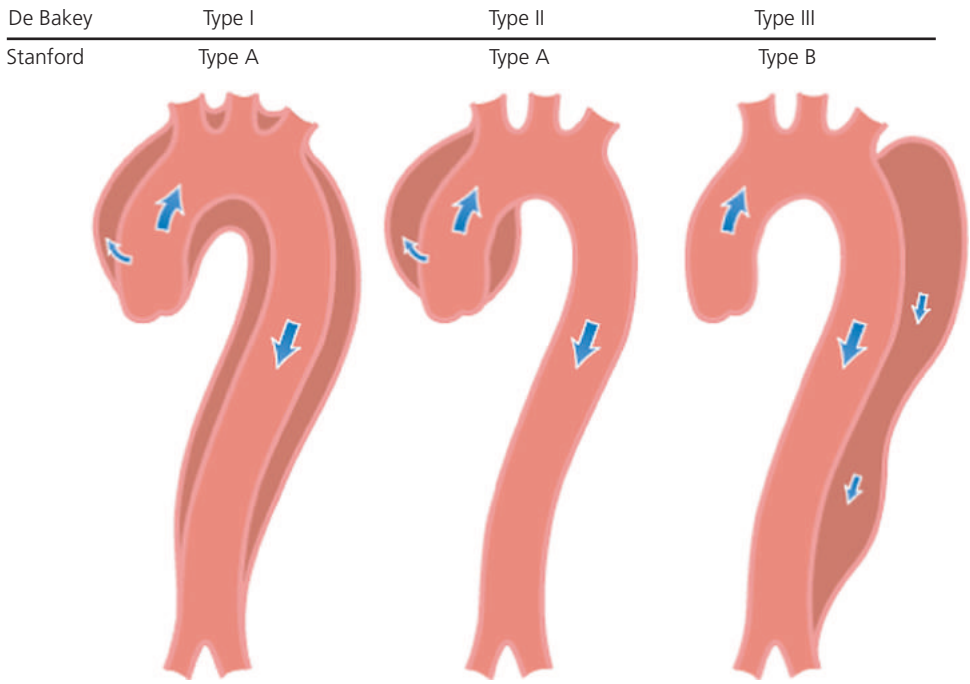


Figure 71.3 ESC 2014 GL on aortic diseases. Classification of aortic dissection localization.

ESC 2014 Guidelines on the diagnosis and treatment of aortic diseases. *Eur Heart J*. 2014;**35**:2873–926 with permission from Oxford University Press.

Type III: dissection originates in the descending aorta and propagates most often distally (non-surgical treatment usually recommended). In type ***IIIa***, the dissection is limited to the descending thoracic aorta, and, in type ***IIIb***, it extends below the diaphragm.

The **Stanford classification** is based on the involvement of the ascending aorta vs the arch and/or descending aorta:

Type A: all dissections involving the ascending aorta, regardless of the site of origin (surgery usually recommended).

Type B: all dissections that do not involve the ascending aorta (non-surgical treatment usually recommended). Involvement of the aortic arch without involvement of the ascending aorta in the Stanford classification is labelled as type B.

Anatomy of the aorta

Aortic root includes the aortic valve annulus, the aortic valve cusps, and the sinuses of Valsalva.[1]

Ascending aorta includes the tubular portion of the ascending aorta, beginning at the sinotubular junction and extending to the origin of the brachiocephalic artery.

Aortic arch from the origin of the brachiocephalic artery to the isthmus between the origin of the left subclavian artery and the ligamentum arteriosum, coursing in front of the trachea, and to the left of the oesophagus and the trachea.

Descending aorta from the isthmus and through the diaphragm to the abdomen.

Epidemiology

The true incidence of AoD is difficult to define since it leads to immediate death in 40% of patients. Estimates range from 3 to 16 cases per 100 000 persons per year, being higher in men (>40 years old) than in women.[1,4,6] The mortality from thoracic aortic aneurysm and aortic dissection has been found in decline over the last decades.[7]

Aetiology and pathophysiology

Mechanisms that weaken the media layers of the aorta lead to higher wall stress, can induce aortic dilatation and aneurysm formation, eventually resulting in intramural haemorrhage, aortic dissection, or rupture. Acute aortic dissection requires a tear in the aortic intima that commonly is preceded by medial wall degeneration or cystic medial necrosis.[3]

Risk factors for AoD include conditions that result in aortic medial degeneration or place extreme stress on the aortic wall (Table 71.1). The main risk factor is uncontrolled arterial hypertension.[8] Traumatic rupture of the aorta is seen in 20% of fatal motor vehicle accidents.[4] Non-aortic cardiac surgery is associated with a 0.15% incidence of type A aortic dissection, and is mainly seen in patients with dilated (>4 cm) and thin ascending aortas.[9] Certain genetic conditions, such as mutations in the gene **FBN1** that encodes the extracellular matrix protein fibrillin-1 and causes Marfan's syndrome, also weaken the media layers of the aorta and predispose to dissection. In addition, mutations in TGFBR1/2, ACTA2, MHY11, and S11A12 encoding transforming growth factor-beta receptors, smooth muscle a-actin, myosin heavy chain, and the pro-inflammatory protein S100A12, respectively, predispose humans to aortic diseases.[10]

Table 71.1 Risk factors for development of thoracic aortic dissection

Conditions associated with increased aortic wall stress
Hypertension, particularly if uncontrolled
Phaeochromocytoma
Cocaine or other stimulant use
Weightlifting or other Valsalva manoeuvre
Trauma
Deceleration or torsional injury (e.g. motor vehicle crash, fall)
Coarctation of the aorta
Conditions associated with aortic media abnormalities
Genetic
Marfan's syndrome
Ehlers–Danlos syndrome, vascular form
Bicuspid aortic valve (including prior aortic valve replacement)
Turner syndrome
Loeys–Dietz syndrome
Familial thoracic aortic aneurysm and dissection syndrome
Inflammatory vasculitides
Takayasu arteritis
Giant cell arteritis
Behçet arteritis
Ormond's disease (retroperitoneal fibrosis)
Other
Pregnancy
Polycystic kidney disease
Chronic corticosteroid or immunosuppression agent administration
Infections involving the aortic wall, either from bacteraemia or extension of adjacent infection
Iatrogenic factors
Catheter/instrument intervention
Valvular/aortic surgery
Side or cross-clamping/aortotomy
Graft anastomosis
Patch aortoplasty

Presentation

Patients with acute aortic syndromes often present in a similar fashion, regardless of whether the underlying condition is AoD, IMH, PAU, or contained aortic rupture. **Acute chest pain** is the most common symptoms, but dissection may also occur without any symptoms or signs (6% of cases).[4] In contrast with the more gradual increasing intensity of pain due to coronary syndromes, pain from aortic dissection has a sudden onset with maximal intensity, often at the time of onset. However, coronary compression by the false lumen or extension of the dissection flap into the coronary ostium may cause **coronary ischaemia** in up 19% of cases.[4] The classic characteristics of pain are its tearing or ripping quality, and, most of the time, pain is described as sharp or stabbing, but the description can be highly variable. Chest pain irradiating to the neck, throat, or jaw indicates that the aortic segment involved is the ascending aorta, whereas pain located in the back or the abdomen suggests that the diseased segment is most probably the descending aorta (Table 71.2). **Fever** may be present. **Cerebrovascular accidents** occur in up to 40% of cases and may be transient but are suggestive of arch vessel involvement. **Syncope** (13%) is an ominous sign; it may be caused by severe AR or tamponade, impaired cerebral flow, false lumen rupture into the pleural space, and vasovagal responses. Approximately 6–13% of patients present with **cardiac failure** or **shock**. **Death** is usually due to rupture of the false lumen. Perfusion deficits and end-organ ischaemia as a result of dissection-related obstruction of aortic branch vessels are presented in Table 71.3.

Table 71.2 Differential diagnosis for high-risk pain or examination features

Chest pain
Acute myocardial infarction
Pulmonary embolism
Spontaneous pneumothorax
Oesophageal rupture
Abdominal pain
Renal/biliary colic
Bowel obstruction/perforation
Non-dissection-related mesenteric ischaemia
Back pain
Renal colic
Musculoskeletal pain
Intervertebral disc herniation
Pulse deficit
Non-dissection-related embolic phenomena
Non-dissection-related arterial occlusion
Focal neurologic deficit
Primary ischaemic cerebrovascular accident
Cauda equina syndrome

ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM 2010 Guidelines for the diagnosis and management of patients with thoracic aortic disease. *J Am Coll Cardiol.* 2010;**55**:e27–129 with permission from Elsevier.

Table 71.3 Complications of acute aortic dissection

ACC/AHA 2010 GL on thoracic aortic disease

End-organ complications of acute aortic dissection

Type	End-organ complication
Cardiovascular	Aortic insufficiency
	Syncope
	Pericardial tamponade
	Myocardial ischaemia or infarction
	Congestive heart failure
Neurologic	Ischaemic stroke or transient ischaemic attack
	Peripheral neuropathy
	Paraplegia/paraparesis
	Spinal ischaemia
Pulmonary	Pleural effusion
	Aortopulmonary fistula with haemorrhage
Gastrointestinal	Mesenteric ischaemia or infarction
	Aortoenteric fistula with haemorrhage
Renal	Renal failure
	Renal ischaemia or infarction
Extremities	Limb ischaemia

ESC 2014 GL on aortic diseases

Main clinical presentations and complications of patients with acute aortic dissection

	Type A	Type B
Chest pain	80%	70%
Back pain	40%	70%
Abrupt onset of pain	85%	85%
Migrating pain	<15%	20%
Aortic regurgitation	40–75%	N/A

(*Continued*)

Table 71.3 (Continued)

Cardiac tamponade	<20%	N/A
Myocardial ischaemia or infarction	10–15%	10%
Heart failiure	<10%	<5%
Pleural effusion	15%	20%
Syncope	15%	<5%
Major neurological deficit (coma/stroke)	<10%	<5%
Spinal cord injury	<1%	NR
Mesenteric ischaemia	<5%	NR
Acute renal failure	<20%	10%
Lower limb ischaemia	<10%	<10%

Predictors of intramural haematoma complications
Persistent and recurrent pain despite aggressive medical treatment
Difficult blood pressure control
Ascending aortic involvement
Maximum aortic diameter >50 mm
Progressive maximum aortic wall thickness (>11 mm)
Enlarging aortic diameter
Recurrent pleural effusion
Penetrating ulcer or ulcer-like projection secondary to localized dissections in the involved segment
Detection of organ ischaemia (brain, myocardium, bowels, kidneys, etc)

ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM 2010 Guidelines for the diagnosis and management of patients with thoracic aortic disease. *J Am Coll Cardiol*. 2010;**55**:e27–129 with permission from Elsevier.

Physical findings

A complete search for arterial perfusion differentials in both upper and lower extremities, evidence of visceral ischaemia, focal neurologic deficits, a murmur of aortic regurgitation, bruits, and findings compatible with possible cardiac tamponade is essential. Findings depend upon the extension of the dissection, as previously described, and the rapidity of the process.

Aortic regurgitation (45–75% of cases) may be due to dilatation of the aortic root, disruption of the aortic valve by extension of the dissection or by the prolapsing flap. **Pulse differentials** may be present (30%). The majority of patients with acute type A aortic dissection present with **aortic diameters <5.5 cm**. Although up to 75% of patients may be hypertensive,[4] on presentation, >50% patients with type A dissection may be found **normotensive or hypotensive** (IRAD data).[11] **Ischaemic lower extremities** (30%) and **tamponade** (5–10% in proximal dissections) may also be present. **Paraplegia** and other **neurological signs** may be present in 10–40% of patients and, in half of the cases, may be transient.[12]

Diagnosis

AoD should be suspected in any patient presenting with acute chest pain, especially in the context of a wide mediastinum, and usually without ECG evidence of STEMI. A patient with thickening of the aortic walls and pericardial effusion or AR should be evaluated for an acute aortic syndrome. Recommendations for the initial evaluation of patients are presented in Figures 71.4 and 71.5 and Tables 71.4 and 71.5.

Chest X-ray has low sensitivity in excluding AoD in patients with widened mediastinum or abnormal aortic contour (especially in patients with chest trauma), but a completely normal chest X-ray lowers the likelihood of AoD.

Transoesophageal echocardiography has 80% sensitivity and 95% specificity for proximal AoD (Figure 71.4). For distal AoD, sensitivity is lower, and mid-portion ascending dissections may be missed. Another disadvantage is the interference of reverberation artefacts that are produced by the echocardiography that may obscure the picture.

Multidetector helical CT with contrast (305 mL/s up to 150 mL) has excellent sensitivity and specificity (100 and 98%, respectively) in diagnosing AoD, even in trauma patients. ECG-gated tomographic images limit motion artefacts.

Magnetic resonance angiography with gadolinium is currently the imaging modality of choice. MRI or CT should be combined with TOE for optimum results. Standards for measurements are presented in Table 71.5.

Angiography has lower sensitivity and specificity than the other techniques.

D-dimers elevation is very sensitive for aortic dissection but not a specific finding, since D-dimers may rise in several other conditions (see Chapter 76 on PE). A negative test (cut-off value of 500 ng/mL) performed within the first 24 hours of symptoms excludes dissection.[13] Other biomarkers are promising but have no definitive role as yet.

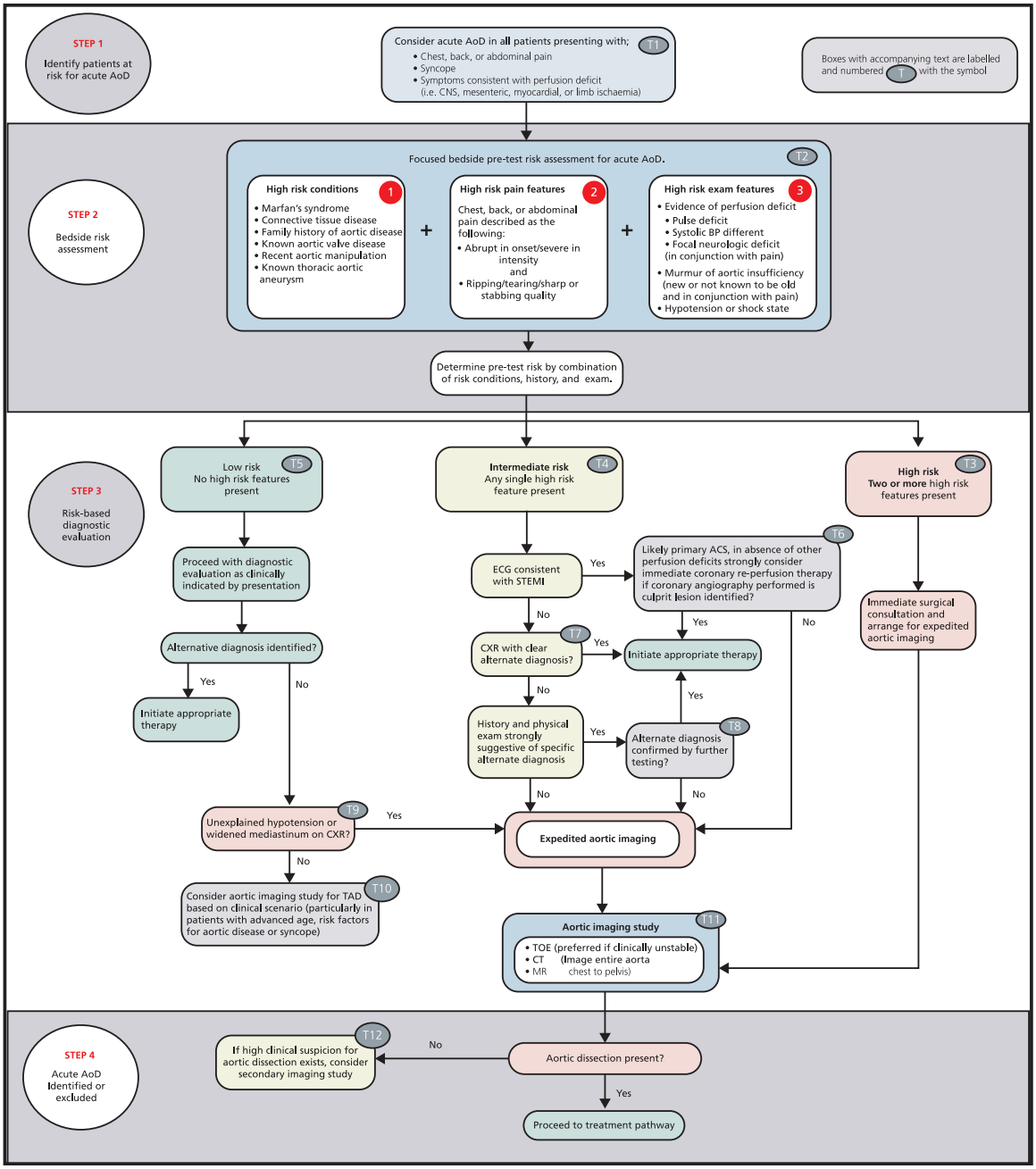
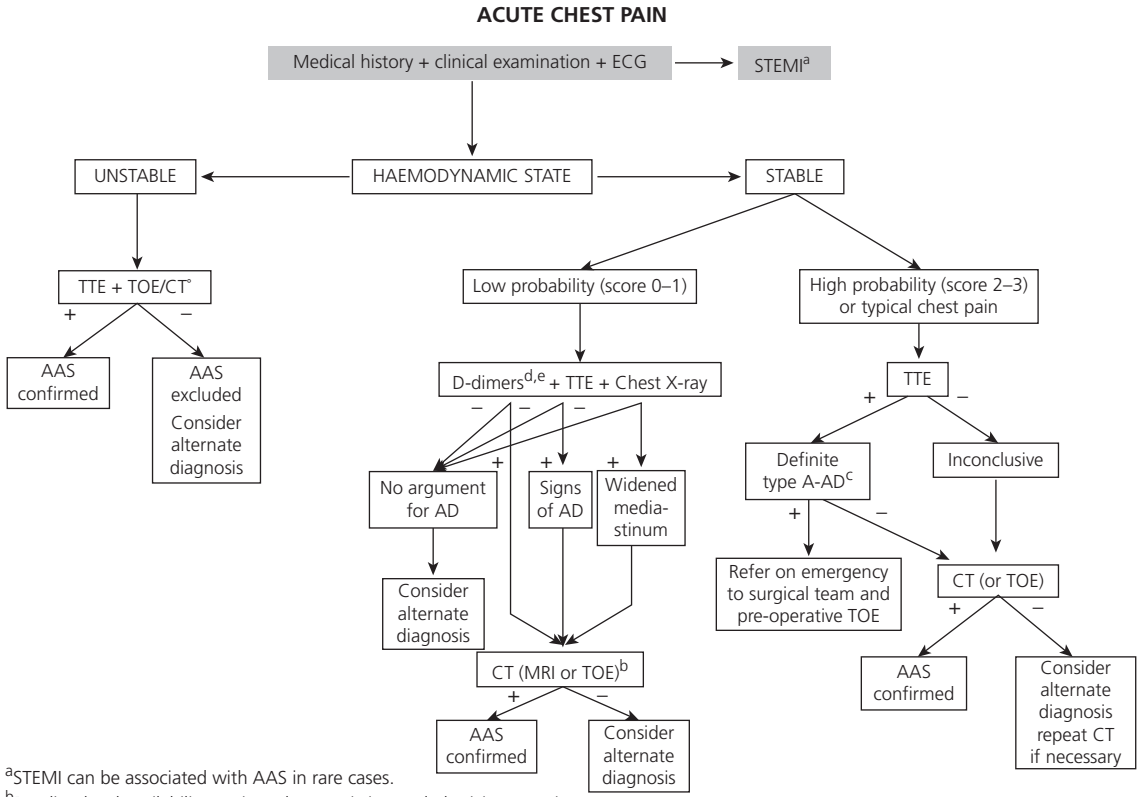


Figure 71.4 ACCF/AHA 2010 GL on thoracic aortic disease. AoD evaluation pathway.

ACS indicates acute coronary syndrome; AoD, aortic dissection; BP, blood pressure; CNS, central nervous system; CT, computed tomographic imaging; CXR, chest X-ray; ECG, electrocardiogram; MR, magnetic resonance imaging; STEMI, ST elevation myocardial infarction; TAD; thoracic aortic disease; and TOE, transoesophageal echocardiogram.

ACCF /AHA /AATS/ACR /ASA /SCA /SCA I/SIR/STS /SVM 2010 Guidelines for the diagnosis and management of patients with thoracic aortic disease. *Circulation*. 2010;**121**:e266–e369 with permission from Wolters Kluwer.



[a]STEMI can be associated with AAS in rare cases.
[b]Pending local availability, patient characteristics, and physician experience.
[c]Proof of type-A AD by the presence of flap, aortic regurgitiation, and/or pericardial effusion
[d]Preferably point-of-care, otherwise classical.
[e]Also troponin to detect non–ST-segment elevation myocardial Infarction.

Figure 71.5 ESC 2014 GL on aortic diseases. Flowchart for decision-making based on pre-test sensitivity of acute aortic syndrome.

AAS, acute aortic syndrome; AD, aortic dissection; CT, computed tomography; MRI, magnetic resonance imaging; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography.
ESC 2014 Guidelines on the diagnosis and treatment of aortic diseases. *Eur Heart J*. 2014;**35**:2873–926 with permission from Oxford University Press.

Table 71.4 ACCF/AHA 2010 GL on thoracic aortic disease. Recommendations for estimation of pretest risk of thoracic aortic dissection

High-risk conditions and historical features	I-B
• Marfan's syndrome, Loeys–Dietz syndrome, vascular Ehler–Danlos syndrome, Turner syndrome, or other connective tissue disease.	
• Patients with mutations in genes known to predispose to thoracic aortic aneurysms and dissection, such as FBN1, TGFBR1, TGFBR2, ACTA2, and MYH11.	
• Family history of aortic dissection or thoracic aortic aneurysm.	
• Known aortic valve disease.	
• Recent aortic manipulation (surgical or catheter-based).	
• Known thoracic aortic aneurysm.	
High-risk chest, back, or abdominal pain features	I-B
• Pain that is abrupt or instantaneous in onset.	

(*Continued*)

Table 71.4 (Continued)

• Pain that is severe in intensity.	
• Pain that has a ripping, tearing, stabbing, or sharp quality.	
High-risk examination features	I-B
• Pulse deficit.	
• Systolic blood pressure limb differential greater than 20 mmHg.	
• Focal neurologic deficit.	
• Murmur of aortic regurgitation (new).	
Patients presenting with sudden onset of severe chest, back, and/or abdominal pain,particularly < 40 years of age, should be examined for Marfan syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, Turner syndrome, or other connective tissue disorder associated with thoracic aortic disease and should be questioned about a history of aortic pathology in immediate family members.	I-B/C
Recent aortic manipulation (surgical or catheter-based) or a known history of aortic valvular disease.	I-C
In patients with suspected or confirmed aortic dissection and a syncopal episode, examination to identify neurologic injury or the presence of pericardial tamponade.	I-C
Patients with acute neurologic complaints should be questioned about the presence of chest, back, and/or abdominal pain and checked for peripheral pulse deficits, as patients with dissection-related neurologic pathology are less likely to report thoracic pain than the typical aortic dissection patient.	I-C

ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM 2010 Guidelines for the diagnosis and management of patients with thoracic aortic disease. *J Am Coll Cardiol*. 2010;**55**:e27–129 with permission from Elsevier.

Table 71.5 Diagnosis of aortic dissection

ACCF/AHA 2010 GL on thoracic aortic disease. Recommendations for screening tests	
ECG Given the relative infrequency of dissection-related coronary artery occlusion, the presence of ST segment elevation suggestive of myocardial infarction should be treated as a primary cardiac event without delay for definitive aortic imaging, unless the patient is at high risk for aortic dissection.	I-B
Chest X-ray	I-C
A negative chest X-ray should not delay definitive aortic imaging in patients determined to be high-risk for aortic dissection.	III-C
Transoesophageal echocardiogram, computed tomographic imaging, or magnetic resonance imaging in patients at high risk for the disease.	I-B
Measurements of aortic diameter should be taken at reproducible anatomic landmarks, perpendicular to the axis of blood flow. For aortic root measurements, the widest diameter, typically at the mid-sinus level, should be used.	I-C
For computed tomographic imaging or magnetic resonance imaging, the external diameter should be measured perpendicular to the axis of blood flow.	I-C
For echocardiography, the internal diameter should be measured perpendicular to the axis of blood flow.	I-C
ESC 2014 GL on aortic diseases	
Details required from imaging in acute aortic dissection	
Extent of the disease according to the aortic anatomic segmentation	
Visualization of intimal flap	
Identification, grading, and mechanism of aortic valve regurgitation	
Identification of the false and true lumens (if present)	
Localization of entry and re-entry tears (if present)	
Identification of antegrade and/or retrograde aortic dissection	
Involvement of side branches	
Detection of malperfusion (low flow or no flow)	
Detection of organ ischaemia (brain, myocardium, bowels, kidneys, etc.)	
Detection of pericardial effusion and its severity	

(*Continued*)

Table 71.5 (Continued)

Detection and extent of pleural effusion		
Detection of peri-aortic bleeding		
Signs of mediastinal bleeding		
Intramural haematoma		
Localization and extent of aortic wall thickening		
Co-existence of atheromatous disease (calcium shift)		
Presence of small intimal tears		
Penetrating aortic ulcer		
Localization of the lesion (length and depth)		
Co-existence of intramural haematoma		
Involvement of the peri-aortic tissue and bleeding		
Thickness of the residual wall		
In all cases		
Co-existence of other aortic lesions: aneurysms, plaques, signs of inflammatory disease, etc.		
Recommendations on imaging of the aorta		
Diameters to be measured at pre-specified anatomical landmarks, perpendicular to the longitudinal axis.		I-C
In repetitive imaging use the imaging modality with the lowest iatrogenic risk		I-C
In repetitive imaging to assess change in diameter, use the same imaging modality with a similar method of measurement.		I-C
All relevant aortic diameters and abnormalities to be reported according to the aortic segmentation.		I-C
Assessment of renal function, pregnancy, and history of allergy to contrast media to select the optimal imaging modality of the aorta with minimal radiation exposure, except for emergency cases.		I-C
Assess the risk of radiation exposure, especially in younger adults and in those undergoing repetitive imaging.		IIa-B
Aortic diameters to be indexed to the body surface area, especially for the outliers in body size.		IIb-B
Recommendations on diagnostic work-up of acute aortic syndrome		
History and clinical assessment		
In all patients with suspected AAS, pre-test probability assessment according to the patient's condition, symptoms, and clinical features.		I-B
Laboratory testing		
In suspicion of AAS, the interpretation of biomarkers should always be considered along with the pretest clinical probability.		IIa-C
In case of low clinical probability of AAS, negative D-dimer levels rule out the diagnosis.		IIa-B
In case of intermediate clinical probability of AAS with a positive (point-of-care) D-dimer test, further imaging testing recommended.		IIa-B
In patients with high probability (risk score 2 or 3) of aortic dissection, testing of D-dimers is not recommended.		III-C
Imaging		
TTE as an initial imaging investigation.		I-C
In unstable* patients with a suspicion of AAS:		
TOE		I-C
CT		I-C
In stable patients with a suspicion of AAS:		
CT		I-C
MRI		I-C
TOE		IIa-C
In initially negative imaging with persistence of suspicion of AAS, repetitive imaging (CT or MRI) recommended.	I-C	

(*Continued*)

Table 71.5 (Continued)

Chest X-ray in cases of low clinical probability of AAS.	IIb-C
In case of uncomplicated Type B AD treated medically, repeated imaging (CT or MRI)** during the first days recommended.	I-C

Laboratory tests required for patients with acute aortic dissection

Laboratory tests	To detect signs of
Red blood cell count	Blood loss, bleeding, anaemia
White blood cell count	Infection, inflammation (systemic inflammatory response syndrome)
C-reactive protein	Inflammatory response
Procalcitonin	Differential diagnosis between systemic inflammatory response syndrome and sepsis
Creatine kinase	Reperfusion injury, rhabdomyolysis
Troponin I or T	Myocardial ischaemia, myocardial infarction
D-dimer thrombosis	Aortic dissection, pulmonary embolism,
Creatinine	Renal failure (existing or developing)
Aspartate transaminase/alanine aminotransferase	Liver ischaemia, liver disease
Lactate	Bowel ischaemia, metabolic disorder
Glucose	Diabetes mellitus
Blood gases	Metabolic disorder, oxygenation

* Unstable means very severe pain, tachycardia, tachypnoea, hypotension, cyanosis, and/or shock.
* Preferably MRI in young patients, to limit radiation exposure.
ESC 2014 Guidelines on the diagnosis and treatment of aortic diseases. *Eur Heart J*. 2014;**35**:2873–926 with permission from Oxford University Press.
ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM 2010 Guidelines for the diagnosis and management of patients with thoracic aortic disease. *J Am Coll Cardiol*. 2010;**55**:e27–129 with permission from Elsevier.

Therapy

Acute aortic dissection of the ascending aorta (type A) is highly lethal, with a mortality of 1–2% per hour after symptom onset. Without surgery, mortality exceeds 50% at 1 month. Analysis of inpatient Medicare data from 2000 to 2011 indicated that, for patients undergoing surgical repair for type A dissections, the observed 30-day mortality has decreased from 30.7% to 21.4% and the observed 1-year mortality from 39.9% to 31.6%. For surgical repair of type B dissection, the 30-day mortality has shown a modest decrease from 24.9% to 21%.[14] Data from the International Registry of Acute Aortic Dissection (IRAD) indicate that in the recent years, patients with type A dissection have been more frequently managed surgically with decreasing mortality, and endovascular repair is increasingly used at referral centers for patients with complicated type B dissection.[15] Uncomplicated (type B) descending dissections have a 30-day mortality of 10% and may be managed medically or by stent grafting in the future. In complicated acute type B aortic dissections, open surgery may be considered, but thoracic endovascular aortic repair (TEVAR) is the treatment of choice.[16] In survivors of type B dissection, thoracic endovascular aortic repair is associated with improved 5-year aorta-specific survival and delayed disease progression, and should be considered to avoid late complications.[17]

Intramural haematomas and penetrating ulcers are treated in the same manner as classic dissection.[3,4] The rate of aortic rupture is much higher for intramural haematoma (35%) and penetrating atheromatous ulcer (42%) in comparison with aortic dissection (type A 7.5%, type B 4.1%).[12] Aortic dissection with persistent patent false lumen carries a high risk of complications. Marfan's syndrome, aorta diameter, and a large entry tear located in the proximal part of the dissection indicate a high risk of complications, particularly in type B dissections.[18]

Initial management

Decreasing wall stress by lowering blood pressure and heart rate is the first step in haemodynamically stable patients (Figure 71.6 and Table 71.6). IV propranolol, metoprolol, esmolol, and especially labetalol (an alpha and beta blocker) are used.[19] If beta blockers are not tolerated or contraindicated, verapamil or diltiazem are a less well-established alternative. Initial targets are a heart rate <60 bpm and a systolic blood pressure between 100 and 120 mmHg. Vasodilators, such as sodium nitroprusside, nicardipine, or nitroglycerin, may be needed after initiation of beta blockade to avoid reflex tachycardia and increase in the force of left ventricular ejection leading to increased aortic wall stress. Pain control with opiates is essential.

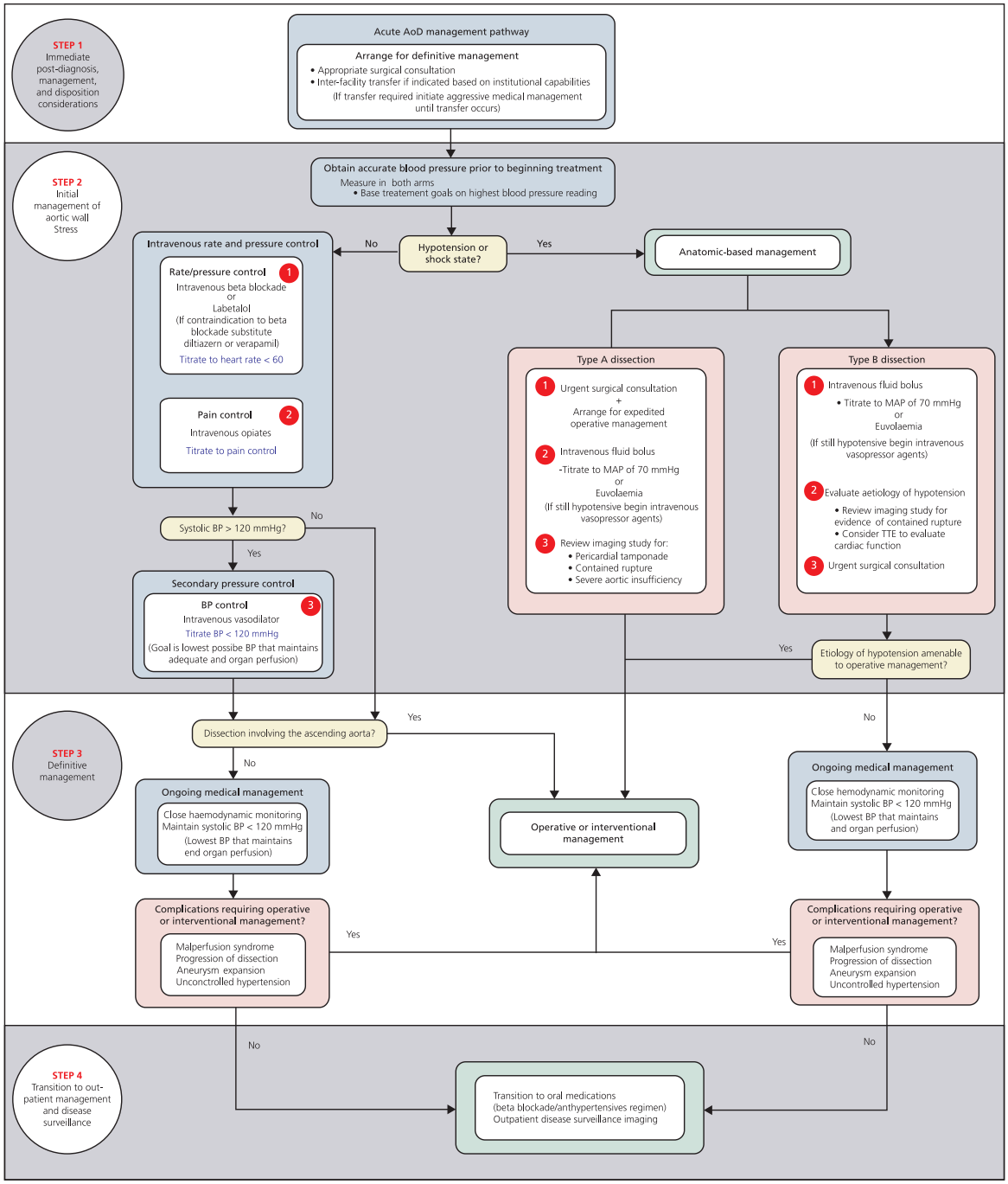


Figure 71.6 ACCF/AHA 2010 GL on thoracic aortic disease. AoD management pathway.

AoD indicates aortic dissection; BP, blood pressure; MAP, mean arterial pressure; TTE, transthoracic echocardiogram.
ACCF /AHA /AATS/ACR /ASA /SCA /SCA I/SIR/STS /SVM 2010 Guidelines for the diagnosis and management of patients with thoracic aortic disease. *Circulation*. 2010;**121**:e266–e369 with permission from Wolters Kluwer.

Table 71.6 Management of aortic dissection

ACCF/AHA 2010 GL on thoracic aortic disease	
Recommendations for initial management of aortic dissection	
In the absence of contraindications, IV beta blockade titrated to a target heart rate ≤60 bpm.	I-C
Non-dihydropyridine calcium channel blocking agents in patients with clear contraindications to beta blockade.	I-C
If systolic blood pressures remain >120 mmHg after adequate heart rate control, ACEI and/or other vasodilators should be administered IV.	I-C
Beta blockers should be used cautiously in the setting of acute aortic regurgitation.	I-C
Vasodilator therapy should not be initiated prior to rate control so as to avoid associated reflex tachycardia that may increase aortic wall stress.	III-C
Urgent surgical consultation should be obtained, regardless of the anatomic location (ascending versus descending).	I-C
Dissection involving the ascending aorta should be urgently evaluated for emergent surgical repair.	I-B
In ascending thoracic aortic dissection, all of the aneurysmal aorta and the proximal extent of the dissection should be resected. A partially dissected aortic root may be repaired with aortic valve resuspension. Extensive dissection of the aortic root should be treated with aortic root replacement with a composite graft or with a valve sparing root replacement. If a De Bakey type II dissection is present, the entire dissected aorta should be replaced.	I-C
Dissection involving the descending aorta should be managed medically, unless life-threatening complications develop (e.g. malperfusion syndrome, progression of dissection, enlarging aneurysm, inability to control blood pressure or symptoms).	I-B
Recommendations for surgical intervention for acute thoracic aortic dissection	
For patients with ascending thoracic aortic dissection, all of the aneurysmal aorta and the proximal extent of the dissection should be resected. A partially dissected aortic root may be repaired with aortic valve resuspension. Extensive dissection of the aortic root should be treated with aortic root replacement with a composite graft or with a valve sparing root replacement. If a De Bakey Type II dissection is present, the entire dissected aorta should be replaced.	I-C
Treat intramural haematoma similar to aortic dissection in the corresponding segment of the aorta.	IIa-C
ESC 2014 Guidelines on aortic diseases	
Treatment of aortic dissection	
Medical therapy including pain relief and blood pressure control in all patients	I-C
Urgent surgery in Type A aortic dissection	I-B
A hybrid approach (i.e. ascending aorta and/or arch replacement associated with any percutaneous aortic or branch artery procedure) in acute type A dissection and organ malperfusion	IIa-B
Medical therapy in uncomplicated Type B dissection	I-C
TEVAR in uncomplicated Type B dissection	IIa-B
TEVAR in complicated Type B dissection	I-C
Surgery in complicated Type B dissection	IIb-C
Management of intramural haematoma (IMH) or penetrating ulcer (PAU)	
Medical therapy including pain relief and blood pressure in all patients	I-C
Urgent surgery in type A IMH	I-C
Urgent surgery in type A PAU	IIa-C
Initial medical therapy under careful surveillance in Type B IMH or PAU	I-C
Repetitive imaging (MRI or CT) in uncomplicated Type B IMH,* or PAU	I-C
TEVAR in complicated Type B IMH,* or PAU	IIa-C
Surgery in complicated Type B IMH,* or PAU	IIb-C
Contained rupture of thoracic aortic aneurysm	
Emergency CT angiography in suspected rupture of thoracic aneurysm for diagnosis confirmation	I-C
Urgent repair in acute contained rupture of thoracic aneurysm.	I-C
TEVAR preferred to surgery if the anatomy is favourable and the expertise available.	I-C
Traumatic aortic injury	
CT in suspicion of traumatic aortic injury	I-C
TOE if CT is not available	IIa-C

(*Continued*)

Table 71.6 (Continued)

TEVAR preferred to surgery if suitable anatomy requiring intervention	IIa-C
Surgical techniques in aortic disease	
Cerebrospinal fluid drainage in surgery of the thoraco-abdominal aorta, to reduce the risk of paraplegia.	I-B
Aortic valve repair, using the re-implantation technique or remodelling with aortic annuloplasty, recommended in young patients with aortic root dilation and tricuspid aortic valves.	I-C
An open distal anastomotic technique avoiding aortic clamping (hemiarch/complete arch) for repair of acute Type A dissection	I-C
In patients with connective tissue disorders* requiring aortic surgery, the replacement of aortic sinuses is indicated.	I-C
Selective antegrade cerebral perfusion in aortic arch surgery, to reduce the risk of stroke.	IIa-B
The axillary artery as first choice for cannulation for surgery of the aortic arch and in aortic dissection.	IIa-C
Left heart bypass during repair of the descending aorta or the thoraco-abdominal aorta, to ensure distal organ perfusion.	IIa-C
(Thoracic) endovascular aortic repair ((T)EVAR)	
The indication for TEVAR or EVAR should be decided on an individual basis, according to anatomy, pathology, comorbidity and anticipated durability of any repair, using a multidisciplinary approach.	I-C
A sufficient proximal and distal landing zone of at least 2 cm recommended for the safe deployment and durable fixation of TEVAR.	I-C
In case of aortic aneurysm, select a stent-graft with a diameter exceeding the diameter of the landing zones by at least 10–15% of the reference aorta.	I-C
During stent graft placement, invasive blood pressure monitoring and control (either pharmacologically or by rapid pacing).	I-C
Preventive cerebrospinal fluid (CSF) drainage in high-risk patients.	IIa-C

* Uncomplicated/complicated IMH means absent or present recurrent pain, expansion of the IMH, periaortic haematoma, intimal disruption
* Ehlers-Danlos IV -, Marfan- or Loeys-Dietz syndromes.
ESC 2014 Guidelines on the diagnosis and treatment of aortic diseases. *Eur Heart J*. 2014;**35**:2873–926 with permission from Oxford University Press.
ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM 2010 Guidelines for the diagnosis and management of patients with thoracic aortic disease. *J Am Coll Cardiol*. 2010;**55**:e27–129 with permission from Elsevier.

Surgery and TEVAR

Urgent surgical consultation is vital (Table 71.6). Type A dissections are operated with implantation of a composite graft in the ascending aorta, with or without reimplantation of coronary arteries. Resecting or closing any significant communication between true and false lumina in the distal ascending aorta or aortic arch is important.[18] Because cardiac tamponade and haemodynamic instability are rare (1%), patients with previous cardiac surgery in stable condition should undergo preoperative native coronary and graft status assessment and appropriate operative planning, including aggressive revascularization and the use of deep hypothermic cardiac arrest.[9] Patients with uncomplicated aortic dissections confined to the descending aorta are treated with medical therapy. Indications for endovascular interventions in type B dissections have been recently reviewed by an expert multidisciplinary panel (Figure 71.7).[20] For acute (first 2 weeks) type B aortic dissection, the pooled early mortality rate is approximately 6.4% with medical treatment, 10.2% with transthoracic endovascular repair (TEVAR), and 17.5% with open surgery.[20] TEVAR involves implantation of a membrane-covered stent graft across the lesion, taking care to avoid vessels supplying the major spinal cord. Paraplegia and stroke range between 0.8–1.9% and 2.1–3.5%, respectively, and appear to be lower than with open surgery. In the first randomized study on elective stent graft placement in survivors of uncomplicated type B aortic dissection, TEVAR failed to improve the 2-year survival and adverse event rates.[21] However, in a retrospective analysis of the International Registry of Acute Aortic Dissection, TEVAR was associated with lower mortality over a 5-year period, compared to medical therapy alone.[22]

The management of **intramural haematoma** and penetrating aortic ulcer is almost similar to that for aortic dissection. There has been some evidence that the intramural haematoma type B may have a slightly more benign course than the classic acute type B aortic dissection (i.e. with an intimal flap) in the acute setting and can often be treated medically.[23] Urgent surgical repair is recommended in traumatic aortic rupture.[4] The International Aortic Arch Surgery Study Group has published a guide for standardizing the reporting system for surgical complications in aortic arch surgery.[24]

Iatrogenic catheter dissection of the aorta is a rare complication that usually carries an excellent short- and long-term prognosis with the adoption of a conservative approach. When a coronary artery is involved as an entry point, it usually can be sealed safely with a stent with good results.[25]

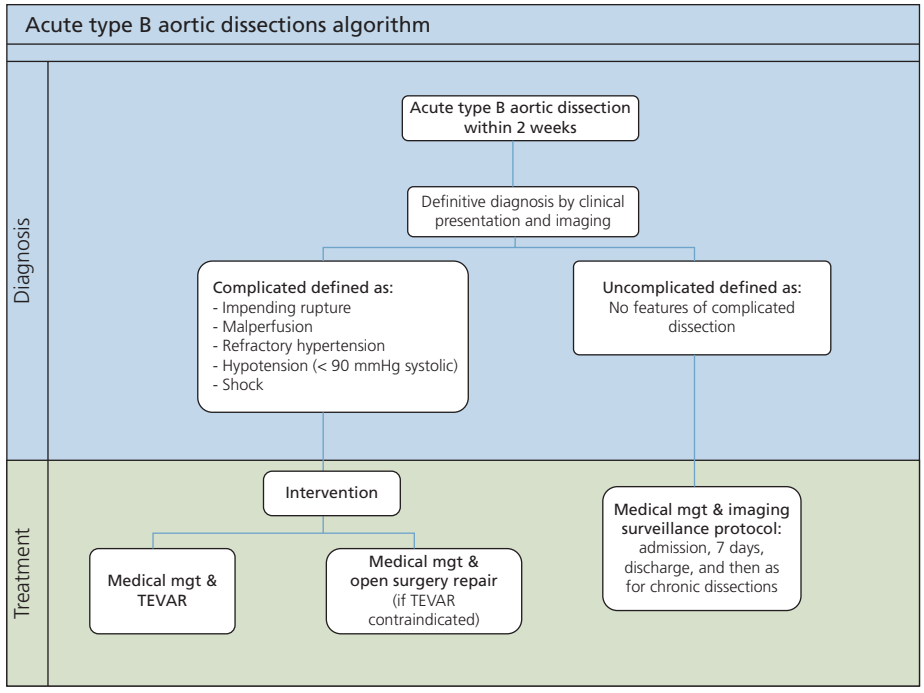


Figure 71.7 Interdisciplinary expert consensus document. Algorithms for management of acute, subacute, and chronic type B aortic dissections. TEVAR indicates transthoracic endovascular repair.

Fattori R, *et al*. Interdisciplinary expert consensus document on management of type B aortic dissection. *J Am Coll Cardiol*. 2013;**61**:1661–78 with permission from Elsevier.

Follow-up

Excellent control of blood pressure and regular imaging are essential. The 10-year actuarial survival rate of patients with an aortic dissection who leave the hospital is 30–60%.[10]

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Chapter 72

Thoracic aortic aneurysms and other conditions

Thoracic aortic aneurysms

Definitions and classification

Thoracic aortic aneurysms are classified into four general anatomical categories: ascending aortic aneurysms (60%), aortic arch aneurysms (10%), descending aortic aneurysms (40%), and thoracoabdominal aneurysms (10%).[1] The ascending aorta, and/or root, is most commonly involved while involvement of the aortic arch occurs in <10%.

Aneurysm (or true aneurysm) A permanent localized dilatation of an artery, having at least a 50% increase in diameter compared with the expected normal diameter of the artery in question. Although all three layers (intima, media, and adventitia) may be present, the intima and media in large aneurysms may be so attenuated that, in some sections of the wall, they are undetectable.[2] Normal adult thoracic aortic diameters depend on age, sex, and body surface area (BSA). Average diameters in the adult (although the aorta is not a perfect cylinder) are indicated in Figure 72.1.[3] MRI and CT measure the external aortic diameter which is expected to be 0.2–0.4 cm larger than the internal one as measured at echocardiography.

Annuloaortic ectasia is often used to describe root aneurysms associated with genetic conditions and usually Marfan's syndrome.

Pseudoaneurysm (or false aneurysm) contains blood resulting from disruption of the arterial wall, with extravasation of blood contained by periarterial connective tissue and not by the arterial wall layers. Such an extravascular haematoma that freely communicates with the intravascular space is also known as a pulsating haematoma.

Ectasia is an arterial dilatation <150% of normal arterial diameter.

Arteriomegaly denotes diffuse arterial dilatation involving several arterial segments with an increase in diameter greater than 50% by comparison to the expected normal arterial diameter.

Mycotic aneurysm is defined by a combination of clinical presentation (pain, fever, sepsis, and/or concomitant infection), laboratory tests (elevation of inflammatory markers like C-reactive protein and white blood cells, and/or positive cultures), and radiological findings on computed tomography (CT) or magnetic resonance imaging (MRI) (rapid expansion of aneurysm, saccular aneurysm, multilobular aneurysms, eccentric aneurysms, periaortic gas, and periaortic soft tissue mass).[4]

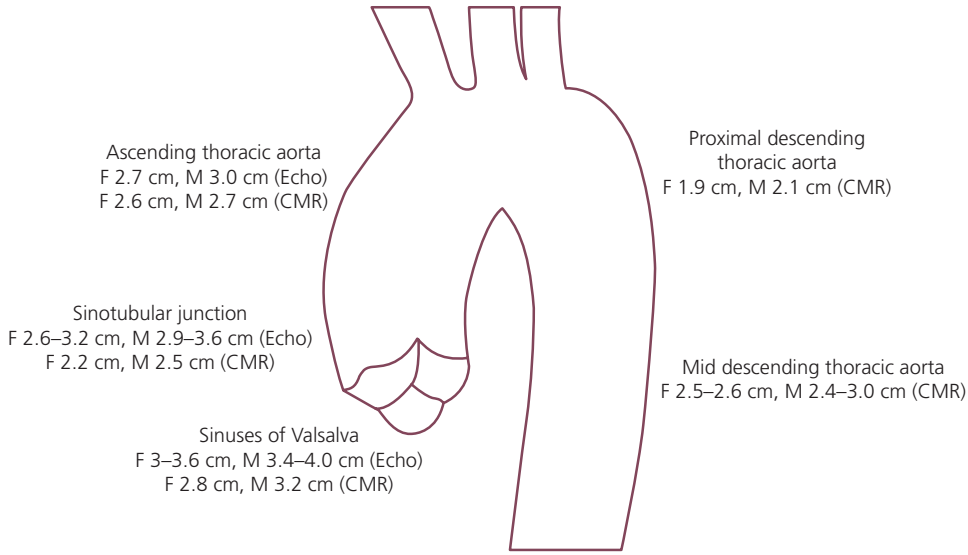

Figure 72.1 Normal sizes for aortic segments by sex and imaging modality.

CMR, cardiac magnetic resonance; Echo, echocardiography; F, female; M, male.
Goldfinger JZ, *et al*. Thoracic aortic aneurysm and dissection. *J Am Coll Cardiol*. 2014;**64**:1725–39 with permission from Elsevier.

Epidemiology

The incidence of thoracic aortic aneurysms is estimated to be increasing, and there are around 10.4 cases per 100 000 person-years.[5] Aneurysm disease is the 18th most common cause of death in all individuals, and the 15th most common in individuals >65 years.[6] Mycotic aneurysm has an incidence of about 0.65–2% of all aortic aneurysms in western countries, and reportedly higher in east Asia.[4] The mortality from thoracic aortic aneurysm and aortic dissection has been found in decline over the period 1994–2010, with a positive linear relationship between trends in systolic blood pressure, cholesterol, and mortality from thoracic aneurysm.[7]

Aetiology and pathophysiology

Smoking, hypertension, dyslipidaemia, chronic obstructive pulmonary disease, and **advanced age** are the most important risk factors. Patients with abdominal aortic aneurysms have higher concentrations of circulating interleukin-6, suggesting that pro-inflammatory signaling via interleukin-6 plays a causal role in aneurysm formation.[8] A variant in low-density lipoprotein receptor is also associated with abdominal aortic aneurysm.[9] Approximately 50% of patients with a bicuspid aortic valve have dilated aortic root and ascending aorta.[10] In addition, conditions that are associated with aortic medial abnormalities (Table 71.1 of Chapter 71) may also lead to aneurysm formation. Potentially clinically significant ascending aorta (but not aortic root) dilation is present in a large proportion of paediatric patients with **isolated congenital complete heart block**, probably due to fetal exposure to maternal autoantibodies.[11] The development and expansion of an aortic aneurysm is an indolent process. The diameter of the aorta grows slowly with age at 0.12 cm/year, with the descending growing faster than the ascending aorta.[1] The average rate of expansion of thoracic aortic aneurysms is estimated to be 0.10 to 0.42 cm/y.[2] Mutations in genes encoding components of the TGF-β signalling pathway, that are responsible for the Loeys–Dietz syndrome (Chapter 73), can cause aortic and arterial aneurysm and dissection.[12]

Presentation

Many patients with a thoracic aortic aneurysm are asymptomatic and diagnosed by chest X-ray or CT scan obtained for other reasons. With large aneurysms, compressive symptoms on adjacent structures may develop: **hoarseness** from left recurrent laryngeal nerve stretching, **stridor** from tracheal or bronchial compression, **dyspnoea** from lung compression, **dysphagia** from oesophageal compression, and **plethora and oedema** from superior vena cava compression. **AR** may develop due to aortic root or ascending aortic dilatation and result in heart failure. **Neck and jaw pain** may occur with aortic arch aneurysms whereas **back, interscapular, and/or left shoulder pain** may occur with descending thoracic aortic aneurysms. **Embolization** of atherosclerotic debris to the kidneys, mesenteric arteries, and limbs may be seen. Finally, acute syndromes, including **dissection** or **rupture without dissection**, may occur. **Chest pain and hypotension** may occur due to haemorrhage into the pleural or pericardial space. **Aorto-oesophageal fistula** and **haemoptysis** can also be seen.[1] Atherosclerotic coronary artery disease may coexist.

Diagnosis

When an aortic aneurysm is identified at any location, assessment of the entire aorta and aortic valve should be performed at baseline and follow-up (ESC 2014 GL on aortic diseases, I-C). Duplex ultrasound for screening of peripheral artery disease and peripheral aneurysms should also be carried out in cases of aneurysm of the abdominal aorta (IIa-C). **CT or MRI** is used for estimation of the external aortic diameter. All imaging modalities, including MRA, have limitations. Apart from absolute size, temporal changes and shape loss of the normal waist of the aorta at the sinotubular junction) are of importance.[6]

Therapy

Recommendations for medical management are presented in Table 72.1. Cessation of **smoking** is strongly recommended, and exertion at maximal capacity and competitive, contact, and isometric sports are avoided.[13] **Beta blockers, and especially ACEI/ARBs**, have been shown to inhibit aneurysm expansion.[14,15] However, a study on the effectiveness of perindopril,[14] was retracted in November 2015. **Statins** are also used, especially in the presence of aortic atheroma. Doxycycline, macrolide antibiotics, and antioxidant agents are under study.

In the ascending aorta, there is a steep increase in complication rates once the aneurysm exceeds 6 cm in diameter. Above that diameter, the rate of aortic dissection and rupture increases to >30% a year. In descending aortic aneurysms, this happens when the diameter reaches 7 cm.[1] **Surgical treatment** of **ascending aortic** aneurysms is contemplated when the diameter exceeds 5.5 cm or when the growth rate exceeds 0.5 cm/year or when the diameter is >4.5 cm, but aortic valve disease or genetic syndromes associated with aneurysm are present or pregnancy is planned (Table 72.2). Operational risk should be <5%.[2] Valve-sparing aortic root replacements are becoming more popular. Therapy of **descending aortic** aneurysms is still unsatisfactory but continues to evolve with the development of new technologies and management strategies.[16,17] Both surgery and endovascular stent grafts have increased mortality and morbidity, including the risk of spinal cord ischaemic injury. Open surgical repair has a surgical mortality rate of 5–10% for elective repair and up to twice as high for non-elective operations, with a risk of spinal cord ischaemia causing paraplegia in 5–10%.[1,2] The value of fenestrated endografts

Table 72.1 Medical management of patients with aortic aneurysms

ACCF/AHA 2010 GL on thoracic aortic disease	
Recommendation for medical treatment of patients with thoracic aortic diseases	
Stringent control of hypertension, lipid profile optimization, smoking cessation, and other atherosclerosis risk reduction measures.	I-C
Recommendations for blood pressure control	
Antihypertensive therapy to a goal of <140/90 mmHg (patients without diabetes) or less than 130/80 mmHg (patients with diabetes or chronic renal disease).	I-B
Beta blockers to all patients with Marfan's syndrome and aortic aneurysm to reduce the rate of aortic dilatation unless contraindicated.	I-B
For patients with thoracic aortic aneurysm, reduce blood pressure with beta blockers and ACEI or ARBs to the lowest point patients can tolerate without adverse effects.	IIa-B
An angiotensin receptor blocker (losartan) is reasonable for patients with Marfan's syndrome to reduce the rate of aortic dilatation unless contraindicated.	IIa-B
Recommendation for dyslipidaemia	
Treatment with a statin to achieve a target LDL cholesterol <70 mg/dL for patients with a coronary heart disease risk equivalent, such as non-coronary atherosclerotic disease, atherosclerotic aortic aneurysm, and coexistent coronary heart disease at high risk for coronary ischaemic events.	IIa-A
Recommendation for smoking cessation	
Smoking cessation and avoidance of exposure to environmental tobacco smoke at work and home. Follow-up, referral to special programmes, and/or pharmacotherapy (including nicotine replacement, buproprion, or varenicline) are useful as is adopting a stepwise strategy aimed at smoking cessation (the 5 As are Ask, Advise, Assess, Assist, and Arrange).	I-B

ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM 2010 Guidelines for the diagnosis and management of patients with thoracic aortic disease. *J Am Coll Cardiol*. 2010;**55**:e27–129 with permission from Elsevier.

Table 72.2 Therapy

ACCF/AHA 2010 GL on thoracic aortic disease. Surgical and endovascular treatment by location of disease	
Recommendations for asymptomatic patients with ascending aortic aneurysm	
Surgical repair in asymptomatic patients with degenerative thoracic aneurysm, chronic aortic dissection, intramural haematoma, penetrating atherosclerotic ulcer, mycotic aneurysm, or pseudoaneurysm, with ascending aorta or aortic sinus diameter ≥5.5 cm.	I-C
In Marfan's syndrome or other genetically mediated disorders (vascular Ehlers–Danlos syndrome, Turner's syndrome, bicuspid aortic valve, or familial thoracic aortic aneurysm and dissection), operation is recommended at smaller diameters (4.0–5.0 cm, depending on the condition).	I-C
Patients with a growth rate of >0.5 cm/y in an aorta that is <5.5 cm in diameter should be considered for operation.	I-C
Patients undergoing aortic valve repair or replacement and who have an ascending aorta or aortic root >4.5 cm should be considered for concomitant repair of the aortic root or replacement of the ascending aorta.	I-C
Separate valve and ascending aortic replacement are recommended in patients without significant aortic root dilatation, in elderly patients, or in young patients with minimal dilatation who have aortic valve disease.	I-C
Patients with Marfan's, Loeys–Dietz, and Ehlers–Danlos syndromes and other patients with dilatation of the aortic root and sinuses of Valsalva should undergo excision of the sinuses in combination with a modified David reimplantation operation, if technically feasible, or, if not, root replacement with valved graft conduit.	I-B
Elective aortic replacement in Marfan's syndrome, other genetic diseases, or bicuspid aortic valves when the ratio of maximal ascending or aortic root area (πr^2) in cm^2 divided by the patient's height in metres exceeds 10.	IIa-C
Patients with Loeys–Dietz syndrome or a confirmed TGFBR1 or TGFBR2 mutation undergo aortic repair when the aortic diameter is ≥4.2 cm by transoesophageal echocardiogram (internal diameter) or ≥4.4–4.6 cm by computed tomographic imaging and/or magnetic resonance imaging (external diameter).	IIa-C
Recommendations for aortic arch aneurysms	
For thoracic aortic aneurysms also involving the proximal aortic arch, partial arch replacement, together with ascending aorta repair, using right subclavian/axillary artery inflow and hypothermic circulatory arrest.	IIa-B
Replacement of the entire aortic arch for acute dissection when the arch is aneurysmal or there is extensive aortic arch destruction and leakage.	IIa-B
Replacement of the entire aortic arch for aneurysms of the entire arch, for chronic dissection when the arch is enlarged, and for distal arch aneurysms that also involve the proximal descending thoracic aorta, usually with the elephant trunk procedure.	IIa-B
For patients with low operative risk in whom an isolated degenerative or atherosclerotic aneurysm of the aortic arch is present, operative treatment is reasonable for asymptomatic patients when the diameter of the arch is >5.5 cm.	IIa-B
In isolated aortic arch aneurysms <4.0 cm in diameter, reimage using computed tomographic imaging or magnetic resonance imaging at 12-month intervals.	IIa-C
In isolated aortic arch aneurysms ≥4.0 cm in diameter, reimage using computed tomographic imaging or MRI at 6-month intervals.	IIa-C
Recommendations for descending thoracic aorta and thoracoabdominal aortic aneurysms	
For chronic dissection, particularly if associated with a connective tissue disorder, but without significant co-morbid disease, and a descending thoracic aortic diameter >5.5 cm, open repair is recommended.	I-B
For degenerative or traumatic aneurysms of the descending thoracic aorta exceeding 5.5 cm, saccular aneurysms, or post-operative pseudoaneurysms, endovascular stent grafting should be strongly considered when feasible.	I-B
For thoracoabdominal aneurysms, in whom endovascular stent graft options are limited and surgical morbidity is elevated, elective surgery if the aortic diameter is >6.0 cm or less if a connective tissue disorder, such as Marfan's or Loeys–Dietz syndrome, is present.	I-C
For thoracoabdominal aneurysms and with end-organ ischaemia or significant stenosis from atherosclerotic visceral artery disease, an additional revascularization procedure is recommended.	I-B
ESC 2014 GL on aortic diseases. Recommendations on interventions on ascending aortic aneurysms	
Aortic root aneurysms	
Surgery in maximal aortic diameter ≥50 mm for patients with Marfan syndrome.[a]	I-C
Surgery in maximal ascending aortic diameters: ≥45 mm for patients with Marfan syndrome with risk factors.[b] ≥50 mm for patients with bicuspid valve with risk factors.[c,d] ≥55 mm for other patients with no elastopathy.[e,f]	IIa-C
Lower thresholds for intervention according to body surface area in patients of small stature or in the case of rapid progression, aortic valve regurgitation, planned pregnancy, and patient's preference.	IIb-C
Aortic arch aneurysms	
Surgery in isolated aortic arch aneurysm with maximal diameter ≥55 mm.	IIa-C
Aortic arch repair in patients with aortic arch aneurysm who already have an indication for surgery of an adjacent aneurysm located in the ascending or descending aorta.	IIb-C

(*Continued*)

Table 72.2 (Continued)

Descending aortic aneurysms	
TEVAR rather than surgery, when anatomy is suitable.	IIa-C
TEVAR in descending aortic aneurysm with maximal diameter ≥55 mm.	IIa-C
When TEVAR is not technically possible, surgery in descending aortic aneurysm with maximal diameter ≥60 mm.	IIa-C
Surgery rather than TEVAR in Marfan syndrome or other elastopathies.	IIa-C

a: Decision should also take into account the shape of the different parts of the aorta. Lower thresholds can be used for combining surgery on the ascending aorta for patients who have an indication for surgery on the aortic valve.
b: Family history of AD and/or aortic size increase >3 mm/year (on repeated measurements using the same imaging technique, at the same aorta level, with side-by-side comparison and confirmed by another technique), severe aortic or mitral regurgitation, or desire for pregnancy.
c: Coarctation of the aorta, systemic hypertension, family history of dissection, or increase in aortic diameter >3 mm/year (on repeated measurements using the same imaging technique, measured at the same aorta level, with side-by-side comparison and confirmed by another technique).
d: Pending comorbidities in the elderly.
e: Elastopathies are genetic conditions like Marfan's.
f: For patients with Loeys-Dietz syndrome or vascular type IV Ehlers-Danlos syndrome, lower thresholds should be considered, possibly even lower than in Marfan syndrome. There are no data to provide figures and a sensible case-by-case approach is the only option.
ESC 2014 Guidelines on the diagnosis and treatment of aortic diseases. *Eur Heart J*. 2014;**35**:2873–926 with permission from Oxford University Press.
ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM 2010 Guidelines for the diagnosis and management of patients with thoracic aortic disease. *J Am Coll Cardiol*. 2010;**55**:e27–129 with permission from Elsevier.

is not yet proven. Long-term treatment with beta-blockers reduces the progression of aortic dilatation.[18] In general, repair is recommended for a descending thoracic aortic aneurysm at 6 cm if repaired with open surgical technique and 5.5 cm if repaired with endovascular technique (5.5 cm for Marfan's patients) or if the rate of growth is >1 cm/y. A scheme for standardizing clinical end-points in aortic arch surgery has been proposed.[19] Abdominal aortic aneurysms are treated with either EVAR or surgery when the diameter exceeds 55 mm (or >50 mm in women) or expands more than 10 mm/year (ESC 2014 GL on aortic diseases, I-B), or symptoms develop.[20]

Endovascular treatment of mycotic aneurysms is now feasible and, for most patients, a durable treatment option. Late infections do occur, are often lethal, and warrant long-term antibiotic treatment and follow-up. Patients with non-*Salmonella*-positive blood cultures were more likely to die from late infection.[4]

Follow-up

Computed tomographic imaging or magnetic resonance imaging of the aorta is reasonable at 1, 3, 6, and 12 months post-dissection and, if stable, annually thereafter so that any threatening enlargement can be detected (ACC/AHA 2010 I-C). Surveillance imaging is similar in patients with intramural haematoma. The ESC recommendations are presented in Table 72.3.

Pregnancy

Recommendations for pregnancy are presented in Tables 72.4 and 72.5.

Table 72.3 ESC 2014 GL on aortic diseases. Recommendations for follow-up and management of chronic aortic diseases

Chronic aortic dissection	
Contrast CT or MRI to confirm the diagnosis of chronic aortic dissection.	I-C
Initial close imaging surveillance of patients with chronic aortic dissection to detect signs of complications as soon as possible.	I-C
Elective surgery in asymptomatic patients with chronic dissection of the ascending aorta, depending on comorbidities and perioperative risk	IIa-C
Tight blood pressure control <130/80 patients with chronic aortic dissection	I-C
Surgical repair or TEVAR for complicated Type B dissection (aortic diameter >60 mm, >10 mm/year growth, malperfusion or recurrent pain).	I-C
Follow-up after endovascular treatment for aortic diseases	
After TEVAR or EVAR, surveillance after 1 month, 6 months, 12 months, and then yearly. Shorter intervals in the event of abnormal findings requiring closer surveillance.	I-C
CT as the first choice imaging technique for follow up after TEVAR or EVAR.	I-C
If neither endoleak nor AAA sac enlargement is documented during first year after EVAR, then duplex colour ultrasonography, with or without contrast agents, for annual postoperative surveillance, with noncontrast CT imaging every 5 years.	IIa-C
For patients with thoracic aneurysm <45 mm, annual imaging is recommended; while in patients with < 45 mm and <55 mm, imaging every 6 months, unless the stability of the lesions is confirmed by serial imaging	I-C
For follow-up after (T)EVAR in young patients, MRI preferred to CT for magnetic resonance-compatible stent grafts, to reduce radiation exposure.	IIa-C
Long-term surveillance of open abdominal aortic repair at loose (5-year) intervals using colour ultrasonography or CT imaging.	IIb-C

(T) EVAR : (thoracic) endovascular aortic repair.
ESC 2014 Guidelines on the diagnosis and treatment of aortic diseases. *Eur Heart J*. 2014;**35**:2873–926 with permission from Oxford University Press.

Table 72.4 ACCF/AHA 2010 GL on thoracic aortic disease. Recommendations for counselling and management of chronic aortic diseases in pregnancy

Women with Marfan's syndrome and aortic dilatation, as well as without Marfan's syndrome but with aortic disease, should be counselled about the risk of aortic dissection, as well as the heritable nature of the disease, prior to pregnancy.	I-C
Strict blood pressure control, specifically to prevent stage II hypertension, with known thoracic aortic dilatation or a familial or genetic predisposition for aortic dissection.	I-C
Monthly or bimonthly echocardiographic measurements of the ascending aortic dimensions until birth.	I-C
MRI (without gadolinium) is recommended over computed tomographic imaging.	I-C
Transoesophageal echocardiogram is an option for imaging of the thoracic aorta.	I-C
Pregnant women with aortic aneurysms should deliver where cardiothoracic surgery is available.	I-C
Fetal delivery via Caesarean section for patients with significant aortic enlargement, dissection, or severe aortic valve regurgitation.	IIa-C
Prophylactic surgery for progressive aortic dilatation and/or advancing aortic valve regurgitation.	IIb-C

ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM 2010 Guidelines for the diagnosis and management of patients with thoracic aortic disease. *J Am Coll Cardiol*. 2010;**55**:e27–129 with permission from Elsevier.

Table 72.5 ESC 2011 GL on pregnancy. Recommendations for pregnancy. Recommendations for the management of aortic disease

Women with Marfan's syndrome or other known aortic disease should be counselled about the risk of aortic dissection during pregnancy and the recurrence risk for the offspring.	I-C
Imaging of the entire aorta (CT/MRI) before pregnancy in patients with Marfan's syndrome or other known aortic disease.	I-C
Women with Marfan's syndrome and an ascending aorta >45 mm should be treated surgically pre-pregnancy.	I-C
Strict blood pressure control in pregnant women with known aortic dilatation, (history of) type B dissection, or genetic predisposition for dissection.	I-C
Repeated echocardiographic imaging every 4 weeks during pregnancy in patients with ascending aorta dilatation.	I-C
For imaging of pregnant women with dilatation of the distal ascending aorta, aortic arch, or descending aorta, MRI (without gadolinium) is recommended.	I-C
Imaging of the ascending aorta in women with a bicuspid aortic valve.	I-C
In patients with an ascending aorta <40 mm, vaginal delivery is favoured.	I-C
Women with aortic dilatation or (history of) aortic dissection should deliver in a centre where cardiothoracic surgery is available.	I-C
In patients with an ascending aorta >45 mm, Caesarean delivery should be considered.	I-C
Surgical treatment pre-pregnancy in women with aortic disease associated with a bicuspid aortic valve when the aortic diameter is >50 mm (or >27 mm/m^2 BSA).	IIa-C
Prophylactic surgery during pregnancy if the aortic diameter is ≥50 mm and increasing rapidly.	IIa-C
In Marfan's and other patients with an aorta 40–45 mm, vaginal delivery with epidural anaesthesia and expedited second stage should be considered.	IIa-C
In Marfan's and other patients with an aorta 40–45 mm, Caesarean section may be considered.	IIb-C
Patients with (or history of) type B dissection should be advised against pregnancy.	III-C

ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**:3147–97 with permission from Oxford University Press.

Aortic arch and thoracic aortic atheroma and atheroembolic disease

Aortic arch atheroma and, in particular, plaques 4 mm or greater in thickness proximal to the origin of the left subclavian artery are associated with stroke and constitute one-third of patients with otherwise unexplained stroke.[21,22] In patients with stroke, especially cryptogenic stroke, large aortic plaques remain associated with an increased risk of recurrent stroke and death at 2 years despite treatment with warfarin or aspirin. Complex plaque morphology confers a slight additional increase in risk.[23] Non-calcified plaques also convey a higher risk for recurrent vascular events.[24] Statins may result in regression of atheroma and are recommended (ACC/AHA 2010 GL on thoracic aortic disease, IIa-C).[25,26] They are probably more effective in combination

with bisphosphonates such as etidronate.[27] Anticoagulation or antiplatelet therapy may be administered (ESC 2014 GL on aortic diseases, IIa-C). Anticoagulation may also be beneficial, especially in patients with mobile lesions or aortic arch atheroma >4 mm (ACC/AHA 2010 GL on thoracic aortic disease, IIb-C).[28] However, in a recent randomized trial that compared aspirin plus clopidogrel with warfarin in stroke patients who had aortic arch plaque, the incidence of recurrent stroke was not significantly different in the two treatment groups.[19] Surgical removal of high-risk plaques is not indicated (ESC 2014 GL on aortic diseases, III-C).

Cardiovascular conditions associated with thoracic aortic disease

Bicuspid aortic valve

This is discussed in the chapter on congenital conditions. Aortic aneurysms are found in 20% of patients undergoing surgery for a bicuspid valve, and 15% of patients with acute aortic dissection have a bicuspid valve.[2]

Aberrant right subclavian artery

Aberrant right subclavian artery, which arises as the fourth branch from the aorta, courses behind the oesophagus in approximately 80% of patients and causes dysphagia in many patients. Dysphagia usually occurs in adults as the artery enlarges (Kommerell diverticulum).[2]

Coarctation of the aorta

This is discussed in Chapter 1 on GUCH. Approximately 25% of patients with untreated coarctation die due to aortic rupture.[2]

Right aortic arch

A right-sided aortic arch is present in approximately 0.5% of the population and rarely requires surgical repair. However, some patients present with dysphagia or asthma-like symptoms with expiratory wheezing. Diagnosis is made by CT or MR demonstrating either tracheal compression or oesophageal compression with the oesophagus enlarged and filled with gas above the level of the arch.[2]

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Chapter 73

Genetic syndromes associated with thoracic aneurysm and dissection

Marfan's syndrome

Definition

Marfan's syndrome is a multisystem disease characterized by long bone overgrowth and other skeletal abnormalities, dislocation of the ocular lens, decreased skeletal muscle mass, pneumothorax, mitral valve prolapse, and dilatation of the aortic root.

Aetiology

Marfan's syndrome is an autosomal dominant condition with high penetrance, but variable expression, and represents one of the more common, potentially lethal Mendelian conditions, with an estimated prevalence of 1/3000–5000 individuals.[1] The most common mutations (>800) that cause classic Marfan's syndrome are in the gene **FBN**1 that encodes the extracellular matrix protein, fibrillin-1. Some families, or sporadic patients, in which some of the features of Marfan's syndrome occur, but usually without ectopia lentis and thus overlapping with the **Loeys–Dietz syndrome**, have mutations in the gene **TGFBR2** that encodes receptors for the cytokine transforming growth factor-β (TGF-β) (Table 73.1). Children of an affected parent have a 50% chance to develop the syndrome while one-third of cases represent *de novo* mutations. Approximately 25% of patients do not have a family history and represent new cases due to sporadic mutations for the condition.

Table 73.1 ACCF/AHA 2010 GL on thoracic aortic disease. Genetic syndromes associated with thoracic aortic aneurysm and dissection

Genetic syndrome	Common clinical features	Genetic defect	Diagnostic test	Comments on aortic disease
Marfan's syndrome	Skeletal features (see text), Ectopia lentis, Dural ectasia,	*FBN1* mutations*	Ghent diagnostic criteria DNA for sequencing	Surgical repair when the aorta reaches 5.0 cm, unless there is a family history of AoD at <5.0 cm, a rapidly expanding aneurysm, or presence of significant aortic valve regurgitation
Loeys–Dietz syndrome	Bifid uvula or cleft palate, Arterial tortuosity, Hypertelorism, Skeletal features similar to MFS, Craniosynostosis, Aneurysms and dissections of other arteries	*TGFBR2* or *TGFBR1* mutations	DNA for sequencing	Surgical repair recommended at an aortic diameter of ≥4.2 cm by TOE (internal diameter) or 4.4 to ≥4.6 cm by CT and/or MR (external diameter)

(*Continued*)

Table 73.1 (Continued)

Ehlers–Danlos syndrome, vascular form	Thin, translucent skin, Gastrointestinal rupture, Rupture of the gravid uterus Rupture of medium-sized to large arteries	*COL3A1* mutations	DNA for sequencing Dermal fibroblasts for analysis of type III collagen	Surgical repair is complicated by friable tissues Non-invasive imaging recommended
Turner's syndrome	Short stature, Primary amenorrhoea, Bicuspid aortic valve, Aortic coarctation, Webbed neck, low-set ears, low hairline, broad chest	45,X karyotype	Blood (cells) for karyotype analysis	AoD risk is increased in patients with bicuspid aortic valve, aortic coarctation, hypertension, or pregnancy

AoD indicates aortic dissection; *COL3A1*, type III collagen; CT, computed tomographic imaging; *FBN1*, fibrillin-1; MFS, Marfan's syndrome; MR, magnetic resonance imaging; TOE, transoesophageal echocardiogram; *TGFBR1*, transforming growth factor-beta receptor type I; *TGFBR2*, transforming growth factor-beta receptor type II.

* The defective gene at a second locus for MFS is *TGFBR2*, but the clinical phenotype as MFS is debated.

ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/ STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease: Executive summary. *J Am Coll Cardiol*. 2010;**55**:1509–44 with permission Elsevier.

Pathophysiology

Perturbation of fibrillin-1 results in degeneration of the medial layer, with disarray throughout the extracellular matrix, progressive fragmentation and loss of elastic lamellae, and excess activation of the cytokine transforming growth factor-β (TGF-β), a potent stimulator of inflammation and fibrosis. Ongoing destruction of the elastic and collagen lamellae and medial degeneration result in progressive dilatation of proximal aortic segments, as well as a predisposition to aortic dissection from the loss of elasticity and appropriate medial layer support. Superimposed on underlying Marfan's syndrome tissue abnormalities are the normal haemodynamic stressors on the proximal aorta throughout the cardiac cycle.[1]

Presentation and physical findings

Chest pain in a person with **tall, asthenic habitus, anterior chest deformity, or a family history of aortic dissection or sudden death** should always raise the suspicion of aortic dissection. Patients with Marfan's syndrome are predisposed to thoracic aojrtic aneurysm or type A or B, and every patient with the syndrome has evidence of aortic involvement at some point during their life. Cardiovascular, ocular, and skeletal features are presented in Table 73.1. Mitral valve prolapse, MR, and AR may also be seen. The ECG may show ST segment abnormalities, prolonged QT, and AV conduction disturbances.

Diagnosis

Major criteria for the diagnosis include aortic dilatation, family history, ectopic (dislocated) lens that differentiates Marfan's from Loeys–Dietz syndrome, identification of FBN1 mutation, and the presence of systemic features, such as wrist and thumb signs, pectus carinatum and hindfoot deformity, pneumothorax, and dural ectasia. The **revised Ghent criteria** are presented in Table 73.2.[2] They might have lower sensitivity, even in patients with aortic root >40 mmHg, due to the use of the Z-score (aortic size ratio based on gender- and body size-related norms in order to take into account that the diameter of the aorta is directly proportional to body size throughout normal

Table 73.2 Revised Ghent criteria

In the absence of family history
1. Ao (Z ≥2) and ectopia lentis
2. Ao (Z ≥2) and FBN1 mutation
3. Ao (Z ≥2) and systemic features (≥7 points), as presented below
4. Ectopia lentis and FBN1 mutation and aortic diameter at the sinuses of Valsalva above indicated Z-score or aortic root dissection
In the presence of family history
5. Ectopia lentis and family history of Marfan's
6. Systemic features (≥7 points) and family history of Marfan's
7. Ao (Z ≥2 above 20 years old, ≥3 below 20 years) and family history of Marfan's
Scoring of systemic features
Wrist and thumb sign—3 (wrist or thumb sign—1)
Pectus carinatum deformity—2 (pectus excavatum or chest asymmetry—1)
Hindfoot deformity—2 (plain pes planus—1)
Pneumothorax—2
Dural ectasia—2
Protrusio acetabuli—2
Reduced US/LS and increased arm/height and no severe scoliosis—1
Scoliosis or thoracolumbar kyphosis—1
Reduced elbow extension—1
Facial features (3/5)—1 (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)
Skin striae—1
Myopia >3 dioptres—1
Mitral valve prolapse (all types)—1

US: upper segment, LS: lower segment.

growth) that seems to underestimate aortic root dilatation.[3] Disorders that are often clinically difficult to distinguish from Marfan's syndrome, such as **familial ectopia lentis, MASS phenotype** (myopia, mitral valve prolapse, aortic root dilatation, striae, skeletal findings), and **familial aortic aneurysm**, may also be associated with mutations in FBN1. Thus, for the patient being evaluated for the first time who has some, but not enough, features for a clinical diagnosis and no, or an uncertain, family history, molecular analysis is of minimal help. DNA analysis is indicated when a pathological mutation is known in a family, and relatives at risk can be screened for this mutation. Recommendations for the management of patients are presented in Table 73.3.

Table 73.3 Genetic syndromes

ACCF/AHA 2010 GL on thoracic aortic disease. Recommendations for genetic syndromes	
Echocardiogram at the time of diagnosis of Marfan's syndrome to determine the aortic root and ascending aortic diameters and 6 months thereafter to determine the rate of enlargement of the aorta.	I-C
Annual imaging for patients with Marfan's syndrome if stability of the aortic diameter is documented. If the maximal aortic diameter is ≥4.5 cm or if the aortic diameter shows significant growth from baseline, more frequent imaging should be considered.	I-C
Patients with Loeys–Dietz syndrome or a confirmed genetic mutation known to predispose to aortic aneurysms and aortic dissections (TGFBR1, TGFBR2, FBN1, ACTA2, or MYH11) should undergo complete aortic imaging at initial diagnosis and 6 months thereafter.	I-C
Patients with Loeys–Dietz syndrome should have yearly MRI from the cerebrovascular circulation to the pelvis.	I-B
Patients with Turner's syndrome should undergo imaging of the heart and aorta for evidence of bicuspid aortic valve, coarctation of the aorta, or dilatation of the ascending thoracic aorta. If initial imaging is normal and there are no risk factors for aortic dissection, repeat imaging should be performed every 5 to 10 years or if otherwise clinically indicated. If abnormalities exist, annual imaging or follow-up imaging should be done.	I-C
Consider surgical repair of the aorta in all adult patients with Loeys–Dietz syndrome or a confirmed TGFBR1 or TGFBR2 mutation and an aortic diameter ≥4.2 cm by transoesophageal echocardiogram (internal diameter) or ≥4.4–4.6 cm by computed tomographic imaging and/or MRI (external diameter).	IIa-C
For women with Marfan's syndrome contemplating pregnancy, prophylactically replace the aortic root and ascending aorta if the diameter is > 4.0 cm.	IIa-C
If the maximal cross-sectional area in square centimetres of the ascending aorta or root divided by the patient's height in metres exceeds a ratio of 10, surgical repair is reasonable because shorter patients have dissection at a smaller size and 15% of patients with Marfan's syndrome have dissection at a size <5.0 cm.	IIa-C
In patients with Turner's syndrome with additional risk factors, including bicuspid aortic valve, coarctation of the aorta, and/or hypertension, and in patients who attempt to become pregnant or who become pregnant, perform imaging of the heart and aorta to help determine the risk of aortic dissection.	IIb-C
ESC 2014 GL on aortic diseases. Recommendations on interventions on ascending aortic aneurysms	
Surgery with aortic root aneurysm and maximal aortic diameter ≥50 mm for patients with Marfan's syndrome.[a]	I-C
ESC GL on GUCH 2010. Indications for surgery in Marfan's*	
Aortic root maximal diameter is:	
>50 mm	I-C
46–50 mm with - family history of dissection or - progressive dilation >2 mm/year as confirmed by repeated measurement or - severe AR or MR or - desire of pregnancy	I-C
Other parts of the aorta >50 mm or dilation is progressive	IIa-C

[a] Decision should also take into account the shape of the different parts of the aorta. Lower thresholds can be used for combining surgery on the ascending aorta for patients who have an indication for surgery on the aortic valve.

* Similar recommendations have been provided by the ESC 2012 GL on valve disease.

ESC 2014 Guidelines on the diagnosis and treatment of aortic diseases. *Eur Heart J*. 2014;**35**:2873–926 with permission from Oxford University Press.

ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM 2010 Guidelines for the diagnosis and management of patients with thoracic aortic disease. *J Am Coll Cardiol*. 2010;**55**:e27–129 with permission from Elsevier.

ESC Guidelines for the management of grown-up congenital heart disease. *Eur Heart J*. 2010;**31**:2915–57 with permission from Oxford University Press.

Risk stratification

Aortic size >5 cm, Z-score >3, proximal aortic ratio >1.3 (i.e. >30% enlargement of the aortic root above the mean for that patient's age and body surface area), rapid increase in aortic size (>0.5 cm/year), and family history are ominous prognostic factors.[1] Higher aortic stiffness, which can be assessed segmentally using CMR, is associated with higher rates of surgical aortic replacement and aortic root dilation.[4] Identification of a FBN1 mutation, in general, denotes increased risk.[5] Apart from aortic rupture, patients with Marfan's can die from severe MR or ventricular arrhythmias that may be seen in 20% of patients, conferring a long-term risk of arrhythmic sudden death of 4%.[6]

Therapy

Beta blockers (aiming at a resting heart rate <60 bpm) should be given to all patients and may reduce mortality.[7] In a recent study in children and young adults with Marfan's syndrome, losartan and atenolol in relatively high doses had a similar effect on the rate of aortic-root dilatation between the two treatment groups over a 3-year period.[8] **Angiotensin receptor blocks** such as losartanan inhibitor of the transformin factor-β (TGFβ) may also be used in combination with beta blockers, and delay aortic arch dilatation, pre- or post-operatively.[9,10] However, in the Marfan Sartan RCT, losartan did not limit aortic dilatation during a 3-year period in patients >10 years old.[11] Effects of therapy should be monitored regularly (Table 73.3). Isometric static exercise, competitive contact sports, involving bodily collisions, and marked changes in ambient air pressure (as in scuba diving or sudden changes in altitude in non-pressurized aircraft that may cause pneumothorax) are avoided. Aerobic exercise allowing a heart rate <100 bpm (110 for children) is permitted under beta blockade (see also http://www.Marfan.org).

Indications for surgery Surgery with a valve conduit is recommended in patients with aortic root diameter >5 cm or 4.5 cm in the presence of a family history of dissection, rapid diameter change (>0.5 cm/y), and significant AR (Table 73.3). Risk of sudden death or aortic dissection remains low in patients with Marfan's syndrome and aortic diameter between 45 and 49 mm.[12] Mortality with elective surgery is 1.5% and 11.7% with emergency root replacement. The David technique, with preservation of the native valve, is rather preferable to composite mechanical valve conduits (Bentall) but requires extended experience and patients with totally normal native valves.[13] Emergency surgery for Type A dissection in Marfan should be aimed at replacing the entire aortic arch rather than the hemi-arch. Aortic root replacement or repair is recommended since supracoronary ascending replacement is associated with a high need (>40%) for root re-intervention.[14] Type A dissection should be operated, whereas medical therapy is preferable in type B dissection, unless the aortic diameter exceeds 5–6 cm. Stents are not recommended. Elective root replacement by a prosthesis may constitute a risk factor for downstream type B aortic dissection (because of the loss of the elastic properties of the root or clamp injuries of the aorta), but in clinical practice this appears to be outweighed by the risk of type A dissection if timely proximal repair is performed.[15] Patients with prior prophylactic aortic surgery are at substantial risk for type B aortic dissection, even when the descending aorta is only slightly dilated.[10]

Genetic testing

Recommendations are provided in Table 73.4.

Table 73.4 Genetic testing

ACCF/AHA 2010 GL on thoracic aortic disease. Recommendations for familial thoracic aortic aneurysms and dissections	
Aortic imaging for first-degree relatives of patients with thoracic aortic aneurysm and/or dissection to identify those with asymptomatic disease.	I-B
If the mutant gene (FBN1, TGFBR1, TGFBR2, COL3A1, ACTA2, MYH11) associated with aortic aneurysm and/or dissection is identified in a patient, first-degree relatives should undergo counselling and testing. Then, only the relatives with the genetic mutation should undergo aortic imaging.	I-C
If one or more first-degree relatives of a patient with known thoracic aortic aneurysm and/or dissection are found to have thoracic aortic dilatation, aneurysm, or dissection, then imaging of second-degree relatives is reasonable.	IIa-B
Sequencing of the ACTA2 gene is reasonable in patients with a family history of thoracic aortic aneurysms and/or dissections to determine if ACTA2 mutations are responsible for the inherited predisposition.	IIa-B
Sequencing of other genes known to cause familial thoracic aortic aneurysms and/or dissection (TGFBR1, TGFBR2, MYH11) may be considered in patients with a family history and clinical features associated with mutations in these genes.	IIb-B
If one or more first-degree relatives of a patient with known thoracic aortic aneurysm and/or dissection are found to have thoracic aortic dilatation, aneurysm, or dissection, then referral to a geneticist may be considered.	IIb-C

(*Continued*)

Table 73.4 (Continued)

ESC 2014 GL on aortic diseases. Recommendations on genetic testing in aortic diseases	
Investigate first-degree relatives (siblings and parents) of a subject with TAAD to identify a familial form in which relatives all have a 50% chance of carrying the family mutation/disease.	I-C
Once a familial form of TAAD is highly suspected, refer the patient to a geneticist for family investigation and molecular testing.	I-C
Variability of age of onset warrants screening every 5 years of 'healthy' at-risk relatives until diagnosis (clinical or molecular) is established or ruled out.	I-C
In familial non-syndromic TAAD, screening for aneurysm not only in the thoracic aorta, but also throughout the arterial tree (including cerebral arteries).	IIa-C

TAAD: thoracic aortic aneurysms and dissection.
ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM 2010 Guidelines for the diagnosis and management of patients with thoracic aortic disease. *J Am Coll Cardiol*. 2010;**55**:e27–129 with permission from Elsevier.

Pregnancy

Pregnancy may be allowed under beta blockade, with a known small risk of small-for-dates babies, hyperbilirubinaemia, and hyperglycaemia. Pregnancy causes a slight increase in aortic root diameter and should be discouraged in women with previous aortic dissection. Dissection and rupture are more common in the third trimester, up to 2 days after uneventful delivery, and usually occurs in patients with aortic root diameters >4.5 cm. Recommendations for pregnancy are presented in Tables 72.3 and 72.4 of Chapter 72 on aortic aneurysms. AACF/AHA guidelines consider an aortic root diameter ≤40 mm to be considered safe, whereas both the European and Canadian guidelines accept a limit of 45 mm, and recent evidence supports this view.[16]

Other heritable syndromes and genetic defects associated with thoracic aortic disease

Heritable disorders associated with aortic dilatation are the Loeys-Dietz syndrome, the vascular form of Ehlers-Danlos syndrome, and the Turner syndrome. **Loeys-Dietz syndrome** is characterized by the triad of arterial tortuosity and aneurysms; orbital hypertelorism (widely-spaced eyes); and bifid uvula or cleft palate. It results from mutations in TGF-β receptors 1 or 2, and diagnosis is confirmed by genotyping. Mean age of death is usually 26 years due to aortic dissection.[17] The **vascular form of Ehlers-Danlos syndrome** is characterized by easy bruising; thin skin with visible veins; characteristic facial features; and rupture of arteries, uterus, or intestines. Diagnosis requires genetic testing to identify a defect in the COL3A1 gene, encoding type III collagen. Median survival is 48 years.[17] **Turner syndrome** (short stature and ovarian failure due to absence of one X chromosome) is associated with bicuspid aortic valve and coarctation. Clinical features and genetic causes are presented in Table 73.1. More rare conditions are the arterial tortuosity syndrome, the aneurysms-osteoarthritic syndrome, and non-syndromic familial thoracic aortic aneurysms and dissections due to mutations in various genes.[10] Most common genetic defects associated with **familial thoracic aortic aneurysm and dissection** that do not belong to any described syndrome are presented in Table 73.5. In addition to these, other genetic syndromes, such as **autosomal dominant polycystic kidney disease** and **Noonan's syndrome**, are also associated with aortic dissections. Not much data exist, but management in general is similar to that with Marfan's syndrome.

Table 73.5 Gene defects associated with familial thoracic aortic aneurysm and dissection

Gene	Associated clinical features and conditions
ACTA2	Livedo reticularis, iris floccule, patent ductus arteriosus, bicuspid aortic valve, coronary artery disease, stroke, Moyamoya disease
MHY11	Patent ductus arteriosus
TGFBR2	Thin, translucent skin resembling Marfan's
MYLK	Dissection with no or little aortic enlargement
PRKG1	Aneurysm and acute dissection at young age

Siblings and parents of patients should be followed with aortic imaging every 2 years.[18]

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Chapter 74

Inflammatory diseases associated with thoracic aortic disease

Introduction

Inflammation of large arteries, such as the aorta and its major branches, occurs in a number of disorders, including Kawasaki syndrome, Behçet's syndrome, rheumatoid arthritis, ankylosing spondylitis, syphilis, and tuberculosis. Infected thoracic aortic aneurysms due to bacterial infections may also be seen as a complication of endocarditis or cardiac surgery or due to contiguous spread from adjacent thoracic structures. Aortitis and large-vessel arteritis are characteristics of Takayasu's arteritis and giant cell (temporal) arteritis.[1,2]

Takayasu's arteritis

Definition

Takayasu's arteritis, also known as pulseless disease, is an idiopathic arteritis involving the aorta and its branches.

Epidemiology

It mainly affects women (ten times more than men) and is usually, but not invariably, diagnosed in the third decade of life. In the USA, its prevalence is 2.6 cases/million.[3]

Pathophysiology

Takayasu's is a T cell-mediated panarteritis, the pathogenesis of which remains poorly defined. The disease proceeds from adventitial vasa vasorum involvement inward, with resultant tissue destruction that yields aneurysms and inflammatory infiltrates that cause stenosis. Coronaries are affected in <10% with the development of aneurysms. In the Japanese type, the thoracic aorta and great vessels are most commonly affected. In the Indian type, the disease most commonly affects the abdominal aorta and the renal arteries.[1]

Presentation

Fatigue, night sweats, anorexia, malaise, and weight loss characterize the acute phase of the disease. Chronic symptoms are upper extremity claudication, cerebrovascular insufficiency (vision loss, light-headedness, stroke) and carotid artery pain, and hypertension in involvement of the renal arteries.

Diagnosis

The diagnosis of Takayasu's arteritis is made by identifying, at least, three of the 1990 American College of

Table 74.1 ACC/AHA 2010 GL on thoracic aortic disease. Inflammatory diseases associated with thoracic aortic aneurysm and dissection

Names	Criteria used in diagnosis/source	When is diagnosis established?
Takayasu's arteritis	Age of onset <40 years Intermittent claudication Diminished brachial artery pulse Subclavian artery or aortic bruit Systolic BP variation of >10 mmHg between arms Aortographic evidence of aorta or aortic branch stenosis	≥3 criteria are present (sensitivity 90.5%; specificity 97.8%)
Giant cell arteritis	Age >50 years Recent-onset localized headache Temporary artery tenderness or pulse attenuation Elevated erythrocyte sedimentation rate >50 mm/h Arterial biopsy shows necrotizing vasculitis	≥3 criteria are present (sensitivity greater than 90%; specificity >90%)
Behçet's disease	Oral ulceration Recurrent genital ulceration Uveitis or retinal vasculits Skin lesions—erythema nodosum, pseudofolliculitis, or pathergy	Oral ulceration plus two of the other three criteria
Ankylosing spondylitis	Onset of pain <40 years Back pain for >3 mo Morning stiffness Subtle symptom onset Improvement with exercise	Four of the diagnostic criteria are present

ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM 2010 Guidelines for the diagnosis and management of patients with thoracic aortic disease. *J Am Coll Cardiol*. 2010;**55**:e27–129 with permission from Elsevier.

Rheumatology criteria:[4] (1) age of onset younger than 40 years, (2) intermittent claudication, (3) diminished brachial artery pulse, (4) subclavian artery or aortic bruit, (5) systolic blood pressure variation of greater than 10 mmHg between arms, and (6) angiographic (CT, MR) evidence of aorta or aortic branch vessel stenosis. ESR and CRP are elevated in 50–70% of patients, depending on the disease phase (Table 74.1).

Therapy

Immunosuppression with steroids or agents, such as methotrexate, azathioprine, and anti-tumour necrosis factor-alpha agents, are used for 1–2 years (Table 74.2). Remissions occur in 40–60% of patients on steroids, and 40% of them respond to cytotoxic agents.[3,5] Markers of inflammation are not indicators of disease activity under treatment. Recently, TNF-α antagonists and tocilizumab (anti–IL-6 receptor), were found safe and effective in drug-refractory disease.[6] Surgical revascularization is implemented, when needed, in the non-acute phase, but at an increased risk of anastomotic aneurysms. Percutaneous intraluminal angioplasty of the carotid, subclavian, and renal arteries is feasible. Surgical or percutaneous revascularization is associated

Table 74.2 ACC/AHA 2010 GL on thoracic aortic disease. Recommendations for Takayasu's arteritis and giant cell arteritis

Corticosteroids at a high dose (prednisone 40 to 60 mg daily at initiation or its equivalent) to reduce the active inflammatory state.	I-B
The success of treatment should be periodically evaluated to determine disease activity by repeated physical examination and either an erythrocyte sedimentation rate or C-reactive protein level.	I-B
Elective revascularization should be delayed until the acute inflammatory state is treated and quiescent.	I-B
The initial evaluation should include thoracic aorta and branch vessel CT or MRI to investigate the possibility of aneurysm or occlusive disease.	I-C
Treat patients receiving corticosteroids with an additional anti-inflammatory agent if there is evidence of progression of vascular disease, recurrence of constitutional symptoms, or re-elevation of inflammatory marker.	IIa-C

ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM 2010 Guidelines for the diagnosis and management of patients with thoracic aortic disease. *J Am Coll Cardiol*. 2010;**55**:e27–129 with permission from Elsevier.

with a 44% 5-year rate of complications, particularly when it is performed at time of prominent biological inflammation.[7]

Giant cell (temporal) arteritis

Definition

Giant cell arteritis involves the aorta and its secondary and tertiary branches, and especially the external and internal carotids, and shares the same pathology with Takayasu's arteritis.

Epidemiology

It mainly affects patients above 50 years (with a peak at 75–85 years, women:men in a 3:2 ratio) and has a predilection for northern Europeans. Its incidence in the USA is 20/100 000.[2]

Pathophysiology

This is also a T cell-mediated arteritis that mainly involves the extracranial branches of the aorta and spares intracranial vessels. In medium-sized arteries, inflammation results in narrowing and obstruction of vessels, but, in the thoracic aorta, aneurysm formation and rupture may be caused.

Presentation

It is variable. Half of the patients report **malaise, fever, night sweats, weight loss, and depression. Headache, scalp tenderness, and abnormal temporal arteries** are present in most patients with biopsy-proven disease. Jaw claudication is common (50%), visual changes and/or neurologic symptoms and stroke develop in one-third of patients. Diplopia, amaurosis fugax, or blurriness are important to notice since, if left untreated, permanent blindness may occur. Up to 30% of patients develop large artery complications, such as aortic aneurysm/dissection and stenosis of the vertebral, subclavian, and brachial arteries.[8] Approximately 40% of patients also have polymyalgia rheumatica, which has the same genetic risk factors and acute-phase responses.[2]

Diagnosis

It is established by, at least, three of the 1990 American College of Rheumatology criteria: (1) age older than 50 years, (2) recent-onset localized headache, (3) temporal artery pulse attenuation or tenderness, (4) erythrocyte sedimentation rate greater than 50 mm/h, and (5) an arterial biopsy demonstrating necrotizing vasculitis. With intracranial disease, temporal artery biopsies (performed within 7 days of steroid initiation) are diagnostic in up to 80% of cases.[1]

Therapy

Immunosuppression with steroids and aspirin for 1 or 2 years is the treatment of choice. Steroids are essential to prevent blindness, although exacerbations of the disease may be seen in 30–59% of patients (Table 74.2).

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Part XV

Venous thromboembolism

Relevant guidelines

ESC 2014 Guidelines on pulmonary embolism

2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014;**35**:3033–69

ACCF/AHA 2009 Expert consensus document on pulmonary hypertension

ACCF/AHA 2009 Expert consensus document on pulmonary hypertension.*Circulation*.2009; **119**:2250–94.

AHA 2011 Scientific statement on pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension

Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation*. 2011;**123**:1788–830.

ACCP 2012 Guidelines on antithrombotic therapy

Antithrombotic therapy for VTE disease: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;**141**(2 Suppl):7S–47S.

ESC 2011 Guidelines on pregnancy

ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**:3147–97.

Chapter 75

Venous thromboembolism: epidemiology and aetiology

Definitions

Venous thromboembolism (VTE) denotes pulmonary embolism (PE) and deep venous thrombosis (DVT). PE refers to embolization of usually thrombotic material to pulmonary arteries, with complete or partial occlusion of one or more of their branches. VTE includes PE and DVT,[1] although whether these two conditions belong to the same disease entity is disputable.[2]

Epidemiology

The annual incidence of VTE is approximately 1–2 cases per 1000 adults.[1,3,4] The risk of a first venous thrombosis is twice as high in men as in women not exposed to the reproductive risk factors of oral contraception use, pregnancy/puerperium, and post-menopausal hormone therapy.[5] PE is a potentially life-threatening cardiopulmonary illness.[6] The mortality rate associated with PE is 15% in the first 3 months after diagnosis and, in nearly 25% of the cases, PE presents with sudden death.[1] Blacks have a 3-fold higher incidence for PE than whites, and blacks and hispanics suffer fatal PE at a significantly younger age than whites,[7] but this finding has not been confirmed in all epidemiological studies.[8] VTE confers an increased risk of death. The 30-day mortality risk for VTE patients was recently estimated as 3% for DVT and 31% for PE vs 0.4% for a comparison cohort.[9]

Aetiology

Venous stasis, hypercoagulability, and endothelial damage predispose to VTE. The pathogenesis of VTE after surgery is incompletely understood. Tissue factor exposed at the surgical site is thought be the major driver through the extrinsic pathway of coagulation. Recent observations on the role of factor XI indicate that the intrinsic pathway is also essential.[10] **Thrombophilia**, defined as a predisposition (susceptibility) to thrombosis, causes impaired neutralization of thrombin or failure to control thrombin generation, and thus predisposes to VTE (Tables 75.1 and 75.2).[11,12] The most common **inherited thrombophilias** are factor V Leiden (autosomal dominant single point mutation that brings resistance to activated protein C and actually predisposes to DVT, rather than PE per se)[2] and a mutation in the prothrombin gene. Factor V Leiden increases the frequency of VTE at any age, but mainly in those ≥70 years old.[12] A family history of thromboembolism in ≥2 siblings is a major risk factor for VTE.[13] The Women's Health Initiative study documented a 2-fold increase of VTE among women on combined oestrogen and progesterone preparations,[14] and a history of PE or DVT is an absolute contraindication to **oral contraceptives**. Combined oral contraceptives with levonorgestrel or norgestimate confer half the risk of venous thrombosis than oral contraceptives containing desogestrel, gestodene, or drospirenone. Progestogen-only pills do not confer an increased risk of venous thrombosis, and are safer in patients with cardiovascular disease.[15] Women who use combined contraceptive transdermal patches containing norelgestromin (the active metabolite of norgestimate) and ethinylestradiol, or vaginal rings with etonogestrel (third-generation progestogen) and ethinylestradiol, are at an increased risk of venous thrombosis, both absolute and in comparison to combined oral contraceptives.[16] The risk of venous thrombosis is not significantly increased with the use of subcutaneous implants containing etonogestrel only and the levonorgestrel intrauterine system.[16] Conjugated equine oestrogens are associated with a higher risk of venous thrombosis and possibly myocardial infarction than oestradiol.[17] **Pregnancy** is also a risk factor for VTE. **Obesity, smoking, and long-haul air travel** are also recognized causes of PE. Thrombosis of the popliteal vein or more proximally, and especially iliofemoral DVT, carries a higher risk for PE than isolated calf vein thrombosis.[18] **Orthopedic surgery, cancer, and pregnancy** are established predisposing factors. Peripherally inserted **central catheters** are associated with an increased risk of VTE, compared to central venous catheters, particularly in the critically ill or patients with a malignancy.[19] **Heart diseases** increase the near-term risk for PE not associated with diagnosed peripheral vein thrombosis.[20] VTE risk in heart failure is 1.5–2.9 higher than in patients without heart failure,[21] and a high NT-proBNP plasma concentration is a useful index of high short-term risk of VTE.[22] **Acute infection** that requires hospitalization, blood transfusion,

Table 75.1 Inherited thrombophilia*

Factor V Leiden (activated protein C resistance)
Prothrombin gene (factor II) mutation G20210A
Protein C deficiency
Protein S deficiency
Antithrombin deficiency

* For other rare mutations, see Cohoon KP, Heit JA. Inherited and secondary thrombophilia. *Circulation*. 2014;**129**:254–7.

Table 75.2 Acquired thrombophilia

Antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibody, anti-beta-2 glycoprotein-1 antibody)
Active cancer (including myeloproliferative and myelodysplastic disorders) and chemotherapy
Hormone replacement therapy and oral contraceptive pills (including progesterone-only, and especially third-generation, pills)
Tamoxifen and raloxifene (selective oestrogen receptor modulator)
Hip fracture
Surgery (orthopaedic or surgery for cancer)
Spinal cord injury
Heparin-induced thrombocytopenia
Infection (HIV, sepsis, urinary tract infection)
Intravascular coagulation and fibrinolysis/disseminated intravascular coagulation
Autoimmune disorders
Microalbuminuria, nephrotic syndrome, and paroxysmal nocturnal haemoglobinuria
Hyperhomocysteinaemia due to folate deficiency
Pregnancy/post-partum state
Long-haul air travel (flight distances >5000 km)
Congestive heart failure
Pacemaker or implantable cardiac defibrillator leads and indwelling venous catheters
Dehydration
Dyslipidaemia
Obesity
Smoking
Age

and the use of **erythropoiesis-stimulating agents** are also possible triggers for acute VTE in non-cancer patients.[23] Antiphospholipid antibody syndrome (**APLAS**) is a disorder of thrombotic events or obstetric complications such as repeated miscarriages in the presence of sustained high titres of antiphospholipid antibodies. The presence of **lupus anticoagulant** confers an odds ratio of 11 for thrombosis compared with control subjects, vs 1.6 in the presence of anticardiolipin antibodies alone. Patients who are positive for a lupus anticoagulant, anticardiolipin antibody, and anti-beta-2 glycoprotein-1 antibodies (so-called triple-positive patients) are at particularly high risk for rethrombosis.[24] **Cancer** is an established risk factor for VTE. However, among patients with a first unprovoked venous thromboembolism the prevalence of occult cancer is low. Routine screening with CT of the abdomen and pelvis do not provide any benefit.[25] In 30% of cases, PE occurs in the absence of any predisposing factors.[3]

Diagnostic thrombophilia testing

Thrombophilia is detected in approximately 30% of patients with symptomatic VTE.[12] Most persons with a thrombophilia do not develop thrombosis, and there are no absolute indications for thrombophilia testing.[11] In patients with PE, it is probably cost-effective in men <70 years of age and women <50 years of age.[12] In cases of young patients with VTE, in the absence of other predisposing factors, the laboratory evaluation should be selective and individualized and may include: **blood cell count with peripheral smear**, **liver and renal function**, and **serum protein electrophoresis**.

Genetic testing for **factor V leiden** and **prothrombin** mutations, especially if an inherited thrombophilia is suspected, and testing for **antiphospholipid antibodies** (e.g. lupus anticoagulant, anticardiolipin antibodies, anti-beta-2 glycoprotein-1 antibodies). Testing for antiphospholipid antibodies requires confirmation 12 weeks after an initial positive result. Testing for inherited deficiency of **antithrombin**, **protein C**, and **protein S**, at least 6 weeks after the event, should be considered if the initial evaluation is negative. Patients who develop arterial thrombosis, in particular, should be considered for testing for **antiphospholipid antibodies**, **heparin-induced thrombocytopenia**, **myeloproliferative disorders**, and **vasculitis**. Acute thrombosis can transiently reduce the levels of antithrombin and occasionally proteins C and S that are acute phase reactants. Testing therefore is recommended at least 6 weeks after the acute phase of thrombosis or childbirth. Heparin therapy can lower antithrombin activity and antigen levels and can impair the interpretation of clot-based assays for a lupus anticoagulant. A delay of at least 5 days after heparin is stopped before testing is usually needed. Warfarin therapy reduces the activity and antigen levels of the vitamin K-dependent factors, including proteins C and S (up to 6 weeks). Novel oral anticoagulants may cause false positive

lupus anticoagulant (dilute Russell viper venom time) testing and falsely low antithrombin activity. Testing should be delayed until the effects of warfarin or novel oral anticoagulant therapy have resolved. Direct leucocyte genomic DNA testing for factor V Leiden and prothrombin G20210A mutations is unaffected by anticoagulation therapy; such testing can be performed at any time.[11]

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Chapter 76

Pulmonary embolism

Pathophysiology of PE

Pulmonary emboli most often arise from the deep veins of the lower extremities and pelvis and, very rarely, from subclavian or arm veins. Their consequences become apparent when >30–50% of the pulmonary arterial bed is occluded. In addition to obstruction, acute PE leads to the release of pulmonary artery vasoconstrictors and hypoxaemia, with a subsequent increase in pulmonary vascular resistance and RV afterload, RV dilatation, and tricuspid regurgitation.[1] RV pressure overload can also lead to interventricular septal flattening and deviation toward the left ventricle in diastole, thereby impairing LV filling. The subsequent reduction in coronary artery perfusion pressure, in the context of the increased wall stress, leads to RV ischaemia and subsequent failure. Ventilation to perfusion mismatch increases the total dead space, and impairs transfer of carbon monoxide due to loss of gas exchange surface.

Pulmonary compliance caused by lung oedema results in arterial hypoxaemia and an increased alveolar-arterial oxygen gradient. Hyperventilation may contribute to hypocapnia and respiratory alkalosis. The presence of hypercapnia suggests massive PE, leading to increased anatomical and physiological dead space and impaired minute ventilation.[1,2]

Presentation

The presentation of PE ranges from mild dyspnoea to cardiogenic shock, thus making the disease difficult to diagnose. Dyspnoea is the most common symptom and tachypnoea the most common physical sign. Patients may be anxious, but otherwise completely asymptomatic, or present with hypotension and cyanosis. Pleuritic pain, cough, or haemoptysis indicate pulmonary infarction by a peripherally located PE. Patients may also be asymptomatic.

Diagnosis

Pulmonary embolism should be suspected in all patients who present with new or worsening dyspnoea, chest pain, or sustained hypotension without an alternative obvious cause, but the diagnosis is confirmed by objective testing in only about 20% of patients.[3] Clinical prediction scores[4,5] and diagnostic criteria are presented in Table 76.1. The simplified Wells and Revised Geneva rules are easier to use and appear to have the same accuracy as the original ones.

Chest X-ray is usually normal. Findings, such as focal oligaemia (Westermark sign), a peripheral wedge-shaped opacity, usually in the lower half of the lung field (Hampton's hump), or an enlarged right descending pulmonary artery (Pallas's sign) are rare.[2]

ECG may reveal signs of RV strain, including incomplete or complete RBBB, T wave inversion in the anterior precordium, and S wave in lead I and Q wave and T wave inversion in lead III (the $S_1Q_3T_3$ patterns), or may mimic an old inferior MI. It may also be normal, especially in the young.

Echocardiography is insensitive for diagnosis, but the detection of RV dysfunction is an ominous prognostic factor. Regional RV dysfunction with free wall hypokinesia sparing the apex (McConnel sign) is specific for PE but seen with massive emboli.[2]

D-dimer ELISA can be used to exclude PE in patients with a low suspicion of PE. D-dimer is a degradation product of fibrin that is also produced in a wide variety of conditions, such as cancer, inflammation and dissection of the aorta, and pregnancy. The test is therefore of limited value in high probability of PE because co-morbid conditions may have already raised the D-dimer levels. The specificity of the test is also reduced in hospitalized or elderly patients. The usually accepted threshold level is 500 ng/mL, but an age-adjusted D-dimer cut-off, defined as age × 10 in patients 50 years or older, appears to be more appropriate.[6] The sensitivity of the assay used should always be taken into account when interpreting D-dimer results.

Chest CT with a multidetector scanner (MCT) and the use of intravenous contrast is the principal diagnostic

Table 76.1 Clinical prediction scores for PE

Wells rule		
	Original	**Simplified**
Clinical signs and symptoms DVT	3	1
Tachycardia (>100/min)	1.5	1
Immobilization or surgery in the previous 4 weeks	1.5	1
Previous PE or DVT	1.5	1
Haemoptysis	1	1
Malignancy	1	1
An alternative diagnosis is less likely than PE	3	1
Clinical probability		
Low	0–1	NA
Intermediate	2–6	NA
High	≥7	N/A
PE unlikely	≤4	≤1
Geneva score		
Age >65 y	1	1
Previous DVT or PE	3	1
Surgery (under general anaesthesia) or fracture (of lower limbs) within 1 mo	2	1
Active malignant condition (solid or haematologic, currently active or considered cured <1 y)	2	1
Unilateral lower-limb pain	3	1
Haemoptysis	2	1
Heart rate, beats/min:		
75–94	3	1
≥95	2	1
Pain on lower-limb deep venous palpation and unilateral oedema	4	1
Clinical probability		
Low	0–3	0–1
Intermediate	4–10	2–4
High	≥11	≥5
PE unlikely	≤5	≤2

Gibson NS, *et al*. Further validation and simplification of the Wells clinical decision rule in pulmonary embolism. *Thromb Haemost*. 2008;**99**:229–34 with permission from Schattauer.
Klok FA, *et al*. Simplification of the revised Geneva score for assessing clinical probability of pulmonary embolism. *Arch Intern Med*. 2008;**168**:2131–6 with permission from American Medical Association.

imaging modality, with a negative predictive value of 95–99%.[2,3] In patients with a high clinical probability of PE and negative findings on MCT, the value of additional testing is controversial. Venous ultrasonography shows a DVT in <1% of such patients.[3] MCT is considered at least as accurate as invasive pulmonary angiography.[2] Isolated subsegmental PE can be detected in up to 9% of patients subjected to MCT, whereas incidental discovery of clinically unsuspected PE occurs in 1–2% of all thoracic CT examinations. The proper management of these cases is not established.[7] Magnetic resonance imaging is less sensitive.[1]

Ventilation perfusion (V/Q) scans are reserved for patients with renal failure, allergy to contrast dye, or when a multidetector CT scanner is not available. A normal scan rules out a PE but is diagnostic in 20–50% of patients with suspected PE.[3] MCT delivers a higher dose of radiation to the mother, but a lower dose to the fetus than V/Q lung scanning. Single photon emission tomography ventilation perfusion (SPECT V/Q) is a promising new modality with better sensitivity than planar V/Q.[8]

Venous ultrasonography (compression ultrasonography), which has now replaced venography, should precede imaging tests in pregnant women and in patients with contraindication to CT scanning. Confirmed DVT in patients with suspected PE is an indication for anticoagulation therapy.[3]

A diagnostic work-up is shown in Figures 76.1 and 76.2, and Tables 76.2 and 76.3. Thrombophilia testing is discussed in Chapter 75.

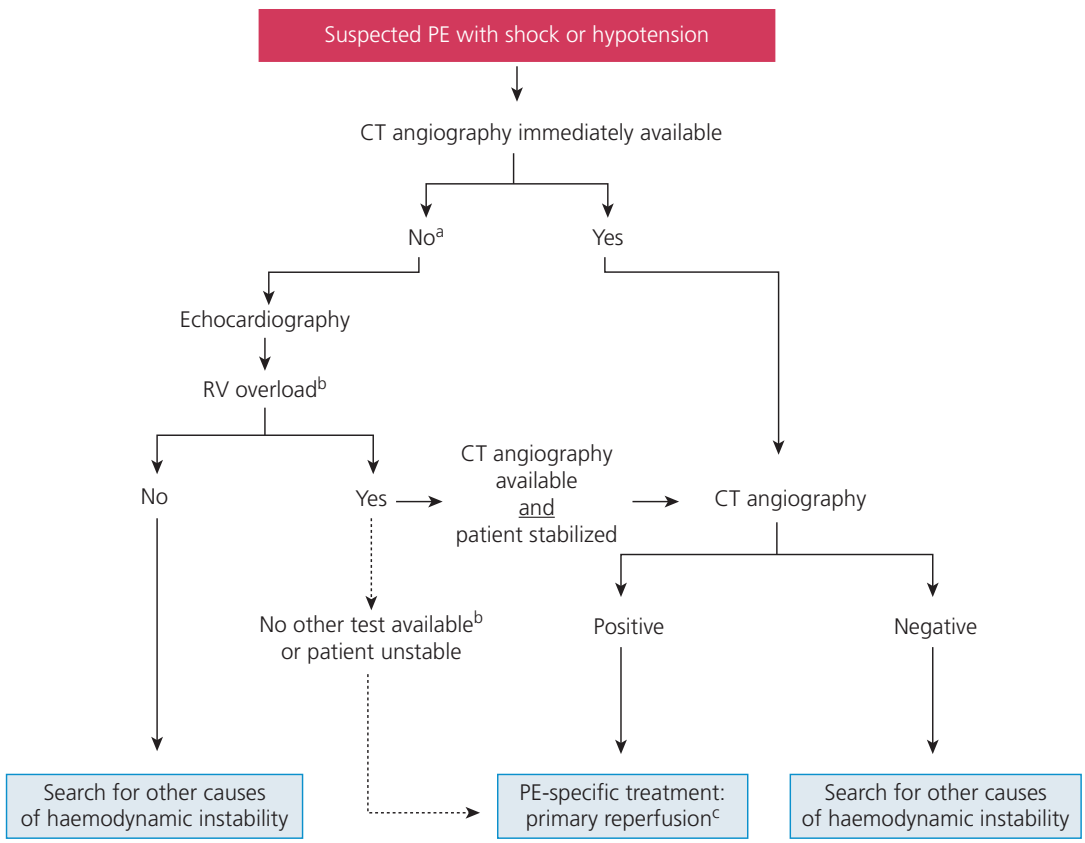


Figure 76.1 ESC 2014 GL on PE. Proposed diagnostic algorithm for patients with suspected high-risk PE, i.e. presenting with shock or hypotension.

CT, computed tomography; PE, pulmonary embolism; RV, right ventricle.
a: Includes the cases in which the patient's condition is so critical that it only allows bedside diagnostic tests.
b: Apart from the diagnosis of RV dysfunction, bedside transthoracic echocardiography may, in some cases, directly confirm PE by visualizing mobile thrombi in the right heart chambers. Ancillary bedside imaging tests include transoesophageal echocardiography, which may detect emboli in the pulmonary artery and its main branches, and bilateral compression venous ultrasonography, which may confirm DVT.
c: Thrombolysis; alternatively, surgical embolectomy or catheter-directed treatment.
ESC 2014 Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014;**35**:3033–69 with permission from Oxford University Press.

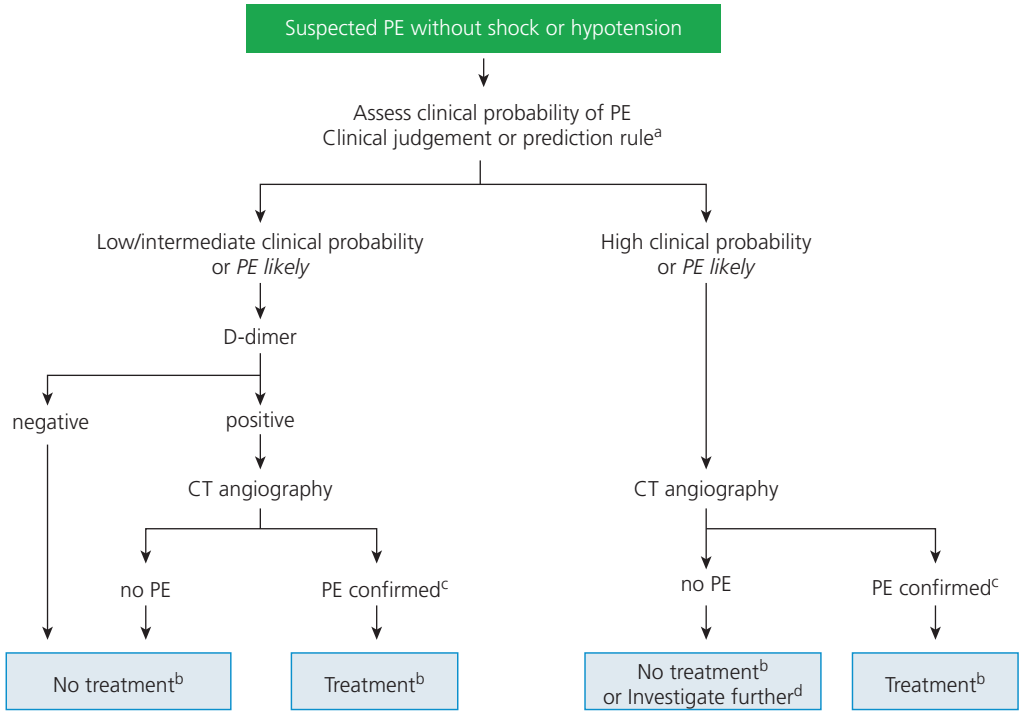


Figure 76.2 ESC 2014 GL on PE. Proposed diagnostic algorithm for patients with suspected not high-risk PE.

CT, computed tomography; PE, pulmonary embolism.
a: See Table 76.1. D-dimer measurements should be restricted to patients with low clinical probability of PE while high sensitivity assays may also be used with intermediate probability. D-dimer measurement is of limited use in hospitalized patients.
b: Anticoagulation for PE.
c: In case of a negative CT angiogram in patients with high clinical probability, further investigation may be considered before withholding PE-specific treatment.
ESC 2014 Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014;**35**:3033–69 with permission from Oxford University Press.

Table 76.2 ESC 2014 GL on PE. Diagnosis of PE

Suspected PE with shock or hypotension	
In suspected high-risk PE (shock or hypotension), emergency CT angiography or bedside transthoracic echocardiography.	I-C
In suspected high-risk PE and signs of RV dysfunction in patients too unstable to undergo CT angiography, bedside search for venous and/or pulmonary artery thrombi with CUS and/or TOE.	IIb-C
Pulmonary angiography in unstable patients referred directly to the catheterization laboratory, in case coronary angiography has excluded an acute coronary syndrome and PE is probable.	IIb-C
Suspected PE without shock or hypotension	
Use of validated criteria for diagnosing PE	I-B
Clinical evaluation	
It is recommended that the diagnostic strategy should be based on clinical probability assessed either by clinical judgement or a validated prediction rule.	I-A
D-dimer	
Plasma D-dimer measurement in outpatients/ emergency department patients with low or intermediate clinical probability, or PE-unlikely	I-A
In low clinical probability or PE-unlikely, normal D-dimer level using either a highly or moderately sensitive assay excludes PE.	I-A
Further testing in intermediate probability patients with a negative moderately sensitive assay.	IIb-C
D-dimer measurement not recommended in high clinical probability, as a normal result does not safely exclude PE, even when using a highly sensitive assay.	III-B

(*Continued*)

Table 76.2 Continued

Multi-detector CT angiography	
Normal CT angiography excludes PE low or intermediate clinical probability	I-A
Normal CT angiography may exclude PE in high clinical probability	IIa-B
CT angiography showing a segmental or more proximal	I-B
Further testing to confirm PE in case of isolated sub-segmental clots.	IIb-C
V/Q scintigraphy	
Normal perfusion lung scintigram excludes PE.	I-A
High probability V/Q scan confirms PE.	IIa-B
A non-diagnostic V/Q scan excludes PE when combined with a negative proximal CUS in low clinical probability or PE-unlikely.	IIa-B
Lower-limb CUS	
Lower-limb CUS in search of DVT in suspected PE, to obviate the need for further imaging tests if the result is positive.	IIb-B
CUS showing a proximal DVT in clinical suspicion of PE confirms PE.	I-B
If CUS shows only a distal DVT, further testing should be considered to confirm PE.	IIa-B
Pulmonary angiography	
Pulmonary angiography in cases of discrepancy between clinical evaluation and results of non-invasive imaging tests.	IIb-C
MRA	
MRA should not be used to rule out PE	III-A

CT: computed tomography (pulmonary angiography); CUS: compression venous ultrasonography; V/Q: ventilation–perfusion.
ESC 2014 Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J.* 2014;**35**:3033–69 with permission from Oxford University Press.

Table 76.3 ESC 2014 GL on PE. Validated diagnostic criteria (based on non-invasive tests) for diagnosing PE in patients without shock or hypotension according to clinical probability

Diagnostic criterion	Clinical probability of PE				
	Low	Intermediate	High	PE unlikely	PE likely
Exclusion of PE					
D-dimer					
Negative result, highly sensitive assay	+	+	–	+	–
Negative result, moderately sensitive assay	+	±	–	+	–
Chest CT angiography					
Normal multidetector CT alone	+	+	±	+	±
V/Q scan					
Normal perfusion lung scan	+	+	+	+	+
Non-diagnostic lung scan[a] and negative proximal CUS	+	±	–	+	–
Confirmation of PE					
Chest CT angiogram showing at least segmental PE	+	+	+	+	+
High probability V/Q scan	+	+	+	+	+
CUS showing proximal DVT	+	+	+	+	+

+/green = valid diagnostic criterion (no further testing required); –/red = invalid criterion (further testing mandatory); ±/yellow = controversial criterion (further testing to be considered).
[a] Low or intermediate probability lung scan according to the PIOPED classification.
CT= computed tomography; CUS = proximal lower limb venous ultrasonography; DVT = deep vein thrombosis; PE = pulmonary embolism; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; V/Q scan = ventilation – perfusion scintigram.
ESC 2014 Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J.* 2014;**35**:3033–69 with permission from Oxford University Press.

Risk stratification

The 30-day mortality risk for PE patients is 31%.[9]

Shock and sustained hypotension indicate an in-hospital mortality of 58% (ICOPE Registry).[10] In stable patients, the simplified version of the Pulmonary Embolism Severity Index (sPESI) is a practical way for risk stratification of patients with diagnosed PE (Tables 76.4 and 76.5, and Figure 76.3).[11]

RV dysfunction, detected on echocardiography or MCT (RV diameter/LV diameter >0.9), is an independent predictor of mortality.[12] RV failure with haemodynamic compromise is encountered in <5% of all patients with acute PE and is associated with an at least 15% risk of in-hospital death within the first hours after admission.[13]

BNP and **pro-BNP** elevated levels, as well as **troponins**, also indicate an adverse outcome, especially in the context of echocardiographic RV dysfunction.[14,15] High-sensitivity troponin (hsTnT cut-off level of 14 pg/mL) exhibits a high prognostic sensitivity for excluding early PE-related death, and combination of hsTnT with sPESI improves the prediction of both acute and long-term outcome.[16]

The AHA classifications are given in the following section.[17]

Classification

Massive PE

Acute PE with sustained hypotension (systolic blood pressure <90 mmHg for at least 15 minutes or requiring inotropic

Table 76.4 ESC 2014 GL on PE. Prognostic assessment

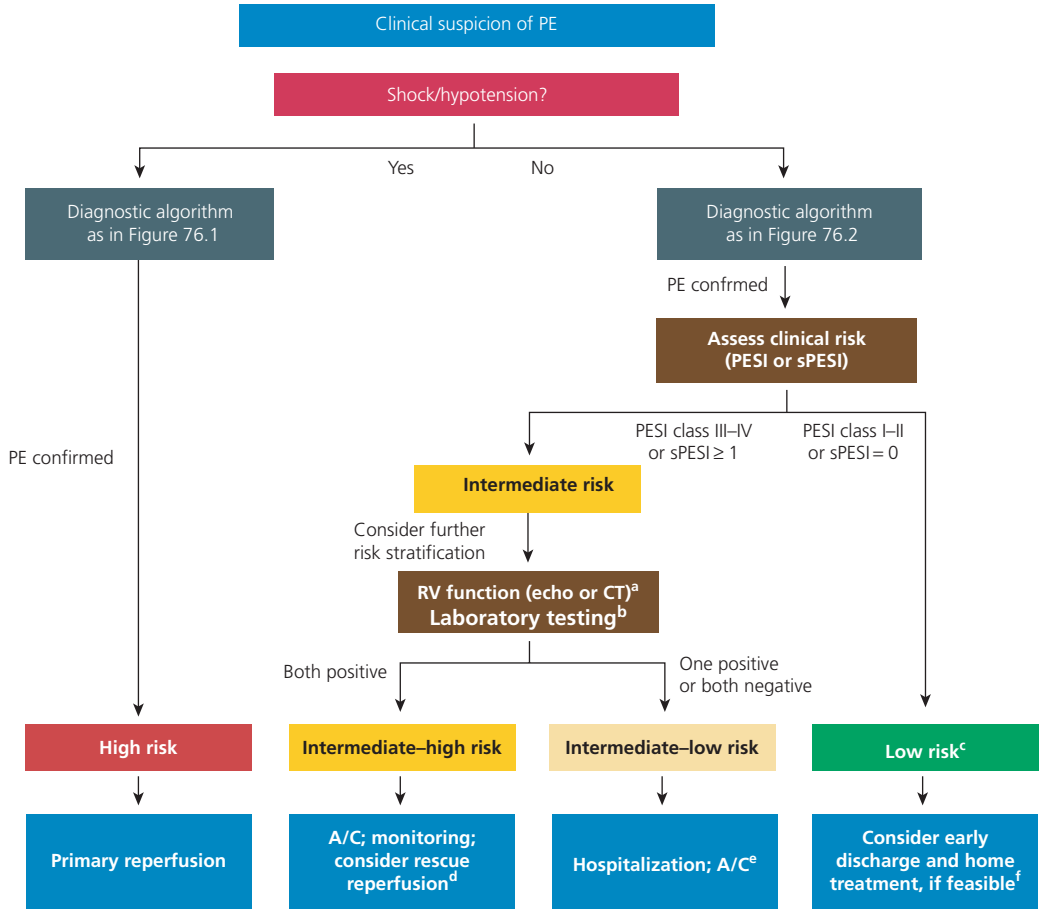
Initial risk stratification of suspected or confirmed PE—based on the presence of shock or persistent hypotension— to identify patients at high risk of early mortality.	I-B
In patients not at high risk, use of a validated clinical risk prediction score, preferably the PESI or sPESI, to distinguish between low- and intermediate-risk PE.	IIa-B
In patients at intermediate risk, assessment of the right ventricle with echocardiography or CT, and of myocardial injury using a laboratory biomarker, for further risk stratification.	IIa-B

CT: computed tomography (pulmonary angiography); PESI: pulmonary embolism severity index; sPESI: simplified pulmonary embolism severity index.
ESC 2014 Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014;**35**:3033–69 with permission from Oxford University Press.

Table 76.5 Risk stratification. Simplified Pulmonary Embolism Severity Index (sPESI)

Variable	Original PESI	Simplified PESI
Age	Age in years	1 (if age >80 years)
Male sex	+10	
History of cancer	+30 points	1
History of heart failure	+10 points	1
Chronic pulmonary disease	+10 points	
Pulse ≥110 b.p.m.	+20 points	1
Systolic blood pressure <100 mm Hg	+30 points	1
Respiratory rate >30 breaths/min	+20 points	
Temperature <36 °C	+20 points	
Altered mental status	+60 points	
Arterial oxyhaemoglobin saturation <90%	+20 points	1
Risk classes (30-day mortality risk %)		
Class I:	≤65 points (0–1.6%)	0 points
Class II:	66–85 points (1.7–3.5%)	≥1 points
Class III:	86–105 points (3.2–7.1%)	
Class IV:	106–125 points (4.0–11.4%)	
Class V:	>125 points (10.0–24.5%)	

Jimenez D, *et al*. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. *Arch Intern Med*. 2010;**170**:1383–89 with permission from American Medical Association.



A/C = anticoagulation; CT = computed tomographic pulmonary angiography; PE = pulmonary embolism; PESI = pulmonary embolism severity Index; RV = right ventricular; sPESI = simplified pulmonary embolism severity index.

[a]If echocardiography has already been performed during diagnostic work-up for PE and detected RV dysfunction, or if the CT already performed for diagnostic work-up has shown RV enlargement (RV/LV (left ventricular) ratio ≥ 0.9), a cardiac troponin test should be performed except for cases in which primary reperfusion is not a therapeutic option (e.g., due to severe comorbidity or limited life expectancy of the patient).

[b]Markers of myocardial injury (e.g., elevated cardiac troponin I or T concentrations in plasma), or of heart failure as a result of (right) ventricular dysfunction (elevated natriuretic peptide concentrations in plasma). If a laboratory test for a cardiac biomarker has already been performed during initial diagnostic work-up (e.g. in the chest pain unit) and was positive, then an echocardiogram should be considered to assess RV function, or RV size should be (re)assessed on CT

[c]Patients in the PESI Class I–II, or with sPESI of 0, and elevated cardiac biomarkers or signs of RV dysfunction on imaging tests, are also to be classified into the intermediate–low risk category. This might apply to situations in which imaging or biomarker results become available before calculation of the clinical severity index. These patients are probably not candidates for home treatment.

[d]Thrombolysis, if (and as soon as) clinical signs of haemodynamic decompensation appear; surgical pulmonary embolectomy or percutaneous catheter-directed treatment may be considered as alternative options to systemic thrombolysis, particularly if the bleeding risk is high.

[e]Monitoring should be considered for patients with confirmed PE and a positive troponin test, even if there is no evidence of RV dysfunction on echocardiography or CT.

[f]The simplified version of the PESI has not been validated in prospective home treatment trials; inclusion criteria other than the PESI were used in two single-armed (non-randomized) management studies.

Figure 76.3 ESC 2014 GL on PE. Risk-adjusted management strategies in acute PE (without shock or hypotension).

In patients with a high clinical probability and an elevated D-dimer level but with negative findings on multidetector CT, venous ultrasonography should be considered. Among critically ill patients with right ventricular dysfunction, thrombolysis is an option; multidetector CT should be performed when the patient's condition has been stabilized if doubts remain about clinical management. In patients who are candidates for percutaneous embolectomy, conventional pulmonary angiography can be performed to confirm the diagnosis of pulmonary embolism immediately before the procedure, after the finding of right ventricular dysfunction. ESC 2014 Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J.* 2014;**35**:3033–69 with permission from Oxford University Press.

support, not due to a cause other than PE, such as arrhythmia, hypovolaemia, sepsis, or left ventricular dysfunction), pulselessness, or persistent profound bradycardia (heart rate <40 bpm with signs or symptoms of shock).[17,18]

Submassive PE

Acute PE without systemic hypotension (systolic blood pressure >90 mmHg) but with either RV dysfunction or myocardial necrosis.

RV dysfunction is defined by the presence of at least one of the following:

- RV dilation (apical 4-chamber RV diameter divided by LV diameter >0.9) or RV systolic dysfunction on echocardiography
- RV dilation (4-chamber RV diameter divided by LV diameter >0.9) on CT
- Elevation of BNP (>90 pg/mL) or of N-terminal pro-BNP (>500 pg/mL)
- Electrocardiographic changes (new complete or incomplete RBBB, anteroseptal ST elevation or depression, or anteroseptal T wave inversion)

Myocardial necrosis is defined as elevation of troponin I (>0.4 ng/mL) or of troponin T (>0.1 ng/mL)

Low-risk PE

Acute PE in the absence of the clinical markers of adverse prognosis that define massive or submassive PE.

Acute therapy

Haemodynamically stable patients

Anticoagulation Acute pulmonary embolism requires initial short-term therapy with **heparin (UFH or LMWH) or fondaparinux** for at least 5 days, followed by therapy with a vitamin K antagonist for at least 3 months, depending on the risk of recurrence (Tables 76.6 to 76.8). In patients with a high clinical probability of pulmonary embolism, anticoagulant treatment should be initiated while diagnostic confirmation is awaited. LMWH are at least as efficacious and safe as UFH.[19] Dose adjustment is needed in renal failure (see Chapter 28 on UA/NSTEMI). Fondaparinux is also efficacious and safe, compared to UFH,[20] and may be used in heparin-induced thrombocytopenia (although not approved for this purpose) but is contraindicated in creatinine clearance <20 mL/min.

The risk of major bleeding with these agents is 3–6%. For heparin-induced thrombocytopenia, see also Chapter 28 on UA/NSTEMI.

- UFH: IV bolus 80 IU/kg (or 5000 IU), followed by continuous infusion 18 IU/kg/h (or 1000 IU/h), aiming at aPTT 1.5–2.5 control (measured 4–6 h after bolus and 3 h after each dose adjustment)
- Enoxaparin: 1 mg/kg/12 h SC (or 1.5 mg/kg/24 h)
- Fondaparinux: 5g SC (body weight <50 mg)
  - 7.5 mg SC (body weight 50–100 kg)
  - 10 mg SC (body weight >100 kg).

Other LMWH such as dalteparin (100 IU/kg /12 h or 200 IU/Kg/24 h) may also be used. Stable, low-risk patients might be managed on an outpatient basis after discharge ≤ 24 h after diagnosis, with instructions on self-performed SC injections,[21] but more data are certainly needed.

Vitamin K antagonists are started at the first day of IV/SC anticoagulation, with a target of INR 2–3. In patients with pulmonary embolism secondary to a temporary (reversible) risk factor, therapy with vitamin K antagonists should be given for 3 months (ACCP 2012, 1B). The risk of recurrent pulmonary embolism is less than 1% per year on anticoagulation and 2 to 10% per year after the discontinuation of such therapy.[3] Thus, the duration of long-term anticoagulation should be based on the risk of recurrence after cessation of treatment with vitamin K antagonists and the risk of bleeding during treatment.[22] Male sex, proximal DVT, elevated D-dimer levels after discontinuing anticoagulation,[23] as well as cancer, inherited thrombophilia (factors V and II), obesity, and unprovoked PE indicate candidates for indefinite anticoagulation with periodic reassessment of the risk–benefit ratio. An INR of 2.0–3.0 is recommended during the first 3–6 months after the acute event. After an initial course, low-intensity therapy (INR 1.5–1.9) may be an option.[24] The **new oral anticoagulants** are antithrombin (factor IIa) or factor Xa inhibitors (see also Chapter 53), and offer a safe alternative to warfarin without the need for monitoring. They are used either with initial treatment with heparin (dabigatran, edoxaban) or as a single-drug but with intensified dose for the initial 1 or 3 weeks (apixaban and rivaroxaban, respectively).[25,26] They are all now approved by the FDA for PE and DVT. The oral antithrombin **dabigatran** at a dose of 150 mg bd has been shown not to be inferior to warfarin in patients with PE or deep vein thrombosis, with reduced risk of bleeding in patients already having received heparin for 5–11 days (RE-COVER and RE-COVER II trials).[27,28] The short-acting oral Xa inhibitor **rivaroxaban** (15 mg twice daily for 3 weeks, followed by 20 mg once daily without initial heparin) was recently found to treat equally well PE compared to enoxaparin followed by a vitamin K antagonist, albeit with less bleeding risk (EINSTEIN-PE and EINSTEIN-DVT trials).[29] **Apixaban** (10 mg bd for 7 days, followed by 5 mg bd for 6 months without initial heparin) was found equally effective to conventional therapy (subcutaneous enoxaparin, followed by warfarin), but with significantly less bleeding in patients with PE or DVT (AMPLIFY trial).[30] In a recent meta-analysis, the UFH–vitamin K antagonist combination was the least effective strategy, while rivaroxaban and apixaban alone were associated with the lowest risk for bleeding.[31] **Edoxaban** (60 mg od, or 30 mg od in patients with creatinine clearance 30–50 mL/min or a body weight <60 kg) after initial treatment with heparin was also non-inferior to warfarin and caused significantly less bleeding (HOKUSAI-VTE trial).[32]

Statin therapy decreases the risk of recurrent PE, irrespective of VKA.[33]

Inferior vena cava filters are recommended only in patients in whom anticoagulation cannot be used (Table 76.9). In patients presenting with a significant bleeding risk, inferior vena cava filter insertion compared with anticoagulant therapy was associated with a lower risk of PE-related death and a higher risk of recurrent VTE.[34] **Retrievable vena cava filters** are preferable, since permanent vena cava filters increase the risk of DVT.[35]

Fibrinolysis confers no benefit over conventional anticoagulation in stable, low-risk patients with PE. However, in haemodynamically stable patients with right ventricular dysfunction, thrombolytic therapy is associated with lower rates of all-cause mortality and increased risks of major bleeding and intracranial haemorrhage (especially in patients >65 years of age).[36,37] In intermediate-risk, normotensive patients, fibrinolysis with tenecteplase and heparin has also conferred a reduction in death or haemodynamic collapse at 7 days, but at a significant excess in haemorrhagic stroke, especially in those ≥75 years old (PEITHO trial).[38] Thus, intermediate-risk patients should receive fibrinolysis only if they decompensate. An alternative strategy in normotensive patients might consist of reducing by 50% (or even more) the dosage of the thrombolytic agent used.[7] Fibrinolysis is recommended in hypotensive patients (SBP <90 mmHg) by the ACCP 2012 GL (2C). **Streptokinase** (250 000 IU over 30 min, followed by 100 000 IU/h over 12–24 h, or preferably 1.5 million IU over 2 h), **urokinase** (4400 IU/kg over 10 min, then 4400 IU/kg/h over 12–24 h, or 3 million IU over 2 h), and **alteplase** (tPA, 100 mg over 2 h or 0.6 mg/kg over 15 min up to 50 mg) are the approved agents, but **reteplase** and **tenecteplase** may also be used. UFH heparin is discontinued before thrombolysis and restarted when the aPTT is <80 s, but it can be continued with the direct plasminogen activators alteplase, reteplase or tenecteplase.[18] All thrombolytics should be given intravenously, since direct administration into the pulmonary artery has not been found superior. The greatest benefit is observed when treatment is initiated within 48 h of symptom onset, but thrombolysis can still be useful in patients who have symptoms for 6–14 days. A rate of 9.9% major bleeding and 1.7% death or intracranial haemorrhage has been reported in recent trials.[37] Contraindications to thrombolysis such as intracranial disease, uncontrolled hypertension, ischaemic stroke in previous 6 months, major surgery or trauma within the last 3 weeks, and gastrointestinal bleeding within the last month are discussed in the MI chapter.

Pharmacological therapy, i.e. low-dose, local fibrinolysis, combined with thrombus fragmentation or aspiration, may also be used in massive, centrally located thrombi. **Ultrasound accelerated thrombolysis** via the EkoSonic catheter is a new option for patients with at least 1 main or lower lobe pulmonary artery and echocardiographic RV/LV ratio ≥0.9–1.0. In the first randomized trial to test catheter intervention (ULTIMA) a fixed-dose, catheter-directed, ultrasound-assisted thrombolysis regimen (10 mg recombinant tissue plasminogen activator per treated lung over 15 h) was superior to anticoagulation alone in the reversal of RV dilatation in intermediate-risk patients.[39] Ultrasound causes reversible disaggregation of uncrosslinked fibrin fibres which may increase the thrombus permeability for thrombolytic drugs. Major bleedings, in particular intracranial haemorrhages, seem to be less frequent with this treatment regimen than with systemic thrombolysis.[40]

Haemodynamically unstable patients

They should be treated with primary reperfusion.[18] Pharmacological or mechanical fibrinolysis may be used. Fibrinolysis should be considered, even in the presence of an increased risk of bleeding, such as after recent surgery or trauma (except for those affecting the central nervous system), especially, if surgical embolectomy or catheter-directed treatment is not immediately available.[7]

Modest fluid challenge (500 mL dextran) may increase cardiac index. Aggressive volume expansion may worsen RV function. Nasal oxygen should be given for hypoxia. If mechanical ventilation is necessary, positive end-expiratory pressure should be applied with caution since it may worsen RV failure.

Dobutamine and **epinephrine** in case of hypotension are the agents of choice if inotropic support is needed.[3] Cardiac index should not be raised above physiological values without proper reperfusion therapy since this may aggravate the ventilation perfusion mismatch.

Fibrinolysis offers a 59% reduction in mortality and is clearly indicated in patients with haemodynamic instability.[37] Percutaneous mechanical thrombectomy (thrombus fragmentation and aspiration) and surgical embolectomy are offered to high-risk patients with contraindication to thrombolytic treatment and those in whom thrombolytic treatment has not improved haemodynamic status.

Percutaneous mechanical thrombectomy confers a clinical success in 86.5% of cases at a rate of major procedural complications of 2.4% (Tables 76.6 and 76.7).[39–42] Four main categories exist:

1. Catheter-directed, ultrasound-assisted thrombolysis.
2. Aspiration thrombectomy through a dedicated suction catheter.
3. Thrombus fragmentation through a balloon, manually rotating pigtail, or a dedicated device.
4. Rheolytic thrombectomy through high-velocity jet suction catheters.

Surgical embolectomy may be now performed off bypass and without aortic cross-clamping, with a <10% intraoperative mortality in experienced centres. It is indicated in patients with massive PE and contraindications to fibrinolysis who have surgically accessible, centrally located PE.[17,18]

Extended therapy

Apart from the known risk factors for VTE, additional risk factors for recurrences are proximal or multiple PEs, residual vein thrombosis after anticoagulation, and abnormal D-dimer after cessation of anticoagulation.[43] However, indications of extended anticoagulation beyond the initial 3 months of therapy are not well defined (Table 76.8).[26] Warfarin or a new oral anticoagulant may be used.[25] Following warfarin therapy for 3–6 months, **aspirin** administration reduces the overall risk of recurrence by more than

a third in patients with a first unprovoked VTE, without significantly increasing the risk of bleeding.[44–46] In patients who had already completed a 3-month course of anticoagulation with either warfarin or dabigatran, continuation of **dabigatran** 150 mg bd up to 36 months was as effective and carried a lower risk of bleeding than warfarin, although there was increased incidence of acute coronary syndromes (RE-MEDY, RE-SONATE trials).[47] Extended anticoagulation with **rivaroxaban** 20 mg od (EINSTEIN),[48] or **apixaban** 5 mg bd (AMPLIFY-Extension),[49] for up to 12 months in patients who had already completed a 6-month course of anticoagulation reduced the incidence of recurrent VTE, but at a higher bleeding risk than placebo. However, apixaban 2.5 mg bd was as efficacious as the higher dose, but without any significant increase in bleeding, compared to placebo.[49]

In elderly patients on anticoagulation, a high level of physical activity is associated with a decreased risk of major bleeding.[50] IVC filters are not indicated in patients who can receive anticoagulation following an acute PE associated with lower extremity venous thrombus.[51]

Prevention of VTE

In addition to high-risk patients who may need long-term anticoagulation after an episode of PE, VTE prevention in the absence of a previous episode may also be necessary in several clinical settings. Heparin, LMWH or UF, is used for thromboprophylaxis of VTE in surgical and medical hospitalized patients. When used for thromboprophylaxis in acutely ill medical patients, rivaroxaban (10 mg daily for 35 days) reduced the risk of venous thromboembolism but with an increased risk of bleeding compared to enoxaparin 50 mg SC od.[52] Apixaban, 2.5 mg po bd for 30 days, was not superior to enoxaparin 40 mg SC od for 6–14 days, and was associated with significantly more major bleeding events.[53] The American College of Physicians (ACP) recommends pharmacologic prophylaxis with LMW or UF heparin or a related drug in medical (including stroke) patients, and against the use of mechanical prophylaxis with graduated compression stockings for prevention of venous thromboembolism.[35] Recently, FXI-ASO, an antisense oligonucleotide that specifically reduces factor XI levels was equivalent to enoxaparin in preventing DVT after knee arthroplasty.[54]

The most detailed guidelines on prevention of thrombosis in both medical and surgical patients and in various clinical settings have been published by the American College of Chest Physicians (ACCP).[55] ACCP recommends graduated compression stockings only in medical patients who are bleeding or are at high risk for major bleeding.

Table 76.6 AHA 2011 Scientific statement on PE. Therapy

Recommendations for initial anticoagulation for acute PE	
Subcutaneous LMWH, intravenous or subcutaneous UFH with monitoring, unmonitored weight-based subcutaneous UFH, or subcutaneous fondaparinux in patients with objectively confirmed PE.	I-A
Therapeutic anticoagulation during the diagnostic workup to patients with intermediate or high clinical probability of PE and no contraindications to anticoagulation.	I-C
SC LMWH (one daily double dose) or fondaparinux are preferred to UFH by the ACCP 2012 GL (2C)	
Recommendations for fibrinolysis for acute PE	
Patients with massive acute PE and acceptable risk of bleeding complications	IIa-B
Patients with submassive acute PE and adverse prognosis (new haemodynamic instability, worsening respiratory insufficiency, severe RV dysfunction, or major myocardial necrosis) and low risk of bleeding complications.	IIb-C
Patients with low-risk PE, submassive acute PE with minor RV dysfunction, minor myocardial necrosis, and no clinical worsening	III-B
Undifferentiated cardiac arrest	III-B
Recommendations for catheter embolectomy and fragmentation	
Depending on local expertise, either catheter embolectomy and fragmentation or surgical embolectomy is reasonable for patients with massive PE and contraindications to fibrinolysis.	IIa-C
Catheter embolectomy and fragmentation or surgical embolectomy for patients with massive PE who remain unstable after receiving fibrinolysis.	IIa-C
Transfer patients with massive PE who cannot receive fibrinolysis or who remain unstable after fibrinolysis to an institution experienced in either catheter embolectomy or surgical embolectomy if these procedures are not available locally and safe transfer can be achieved	IIa-C
Catheter embolectomy or surgical embolectomy for patients with submassive acute PE judged to have clinical evidence of adverse prognosis (new haemodynamic instability, worsening respiratory failure, severe RV dysfunction, or major myocardial necrosis).	IIb-C
Catheter embolectomy or surgical thrombectomy for patients with low-risk PE or submassive acute PE with minor RV dysfunction, minor myocardial necrosis, and no clinical worsening.	III-C

Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: A scientific statement from the American Heart Association. *Circulation*. 2011;**123**:1788–1830 with permission from Wolters Kluwer.

Table 76.7 ESC 2014 GL on PE. Therapy. Acute phase treatment

PE with shock or hypotension (high-risk)	
IV anticoagulation with UFH without delay in high-risk PE.	I-C
Thrombolytic therapy	I-B
Surgical pulmonary embolectomy, if available, for patients in whom thrombolysis is contraindicated or has failed.	I-C
Percutaneous catheter-directed treatment as an alternative to surgical pulmonary embolectomy when full-dose systemic thrombolysis is contraindicated or has failed.	IIa-C
PE without shock or hypotension (intermediate- or low-risk)	
Combination of parenteral treatment with VKA	
Initiation of parenteral anticoagulation without delay in patients with high or intermediate clinical probability of PE while diagnostic work-up is in progress.	I-C
LMWH or fondaparinux	I-A
In parallel with parenteral anticoagulation, targeting an INR of 2.5 (2.0–3.0).	I-B
New oral anticoagulants	
Rivaroxaban (15 mg bd for 3 weeks, followed by 20 mg od)	I-B
Apixaban (10 mg bd for 7 days, followed by 5 mg bd)	I-B
Dabigatran (150 mg bd, or 110 mg bd for patients >80 years of age or those under concomitant verapamil treatment) following acute phase parenteral anticoagulation.	I-B
Edoxaban* following acute-phase parenteral anticoagulation.	I-B
Rivaroxaban, apixaban, dabigatran, edoxaban are not recommended in patients with severe renal impairment.**	IIa-A
Reperfusion	
Routine use of primary systemic thrombolysis is not recommended in patients without shock or hypotension.	III-B
Close monitoring of patients with intermediate-high risk PE for early detection of haemodynamic decompensation and timely initiation of 'rescue'reperfusion therapy.	I-B
Thrombolytic therapy for patients with intermediate-high-risk PE and clinical signs of haemodynamic decompensation.	IIa-B
Surgical pulmonary embolectomy, if available, in intermediate high-risk patients if the anticipated risk of bleeding under thrombolytic treatment is high.	IIb-C
Percutaneous catheter-directed treatment, if available, in intermediate-high-risk patients if the anticipated risk of bleeding under thrombolytic treatment is high.	IIb-B
Early discharge and home treatment	
Patients with acute low-risk PE should be considered for early discharge and continuation of treatment at home if proper outpatient care and anticoagulant treatment can be provided.	IIa-B

* CAUTION: Edoxaban is currently subject to regulatory review for the treatment of venous thromboembolism in the European Union.
**: Creatinine clearance <30 mL/min for rivaroxaban, dabigatran and edoxaban; and <25 mL/min for apixaban.
od: once daily, bd: twice daily.
ESC 2014 Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J.* 2014;**35**:3033–69 with permission from Oxford University Press.

Table 76.8 ESC 2014 GL on PE. Duration of anticoagulation after pulmonary embolism

For patients with PE secondary to a transient (reversible) risk factor, oral anticoagulation for 3 months.	I-B
For patients with unprovoked PE, oral anticoagulation for at least 3 months.	I-A
Extended oral anticoagulation for patients with a first episode of unprovoked PE and low bleeding risk	IIa-B
Anticoagulation treatment of indefinite duration for patients with a second episode of unprovoked PE.	I-B
Rivaroxaban (20 mg od), dabigatran (150 mg bd, or 110 mg bd for patients >80 years of age or those under concomitant verapamil treatment) or apixaban (2.5 mg bd) as an alternative to VKA (except for patients with severe renal impairment) if extended anticoagulation is necessary.*	IIa-B
In patients on extended anticoagulation, the risk–benefit ratio of continuing such treatment should be reassessed at regular intervals.	I-C
Aspirin for extended secondary VTE prophylaxis in refusal for or intolerance of any oral anticoagulant.	IIb-B
For patients with PE and cancer, weight adjusted subcutaneous LMWH for the first 3– 6 months.	IIa-B
For patients with PE and cancer, extended anticoagulation (beyond the first 3–6 months) for an indefinite period or until the cancer is cured.	IIa-C

*: Long-term data on patients taking new oral anticoagulants for secondary PE prophylaxis are not yet available.
ESC 2014 Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J.* 2014;**35**:3033–69 with permission from Oxford University Press.

Table 76.9 Venous filters

AHA 2011 scientific statement. Recommendations on IVC filters in the setting of acute PE	
IVC filter to patients with any confirmed acute PE (or proximal DVT) and contraindications to anticoagulation or with active bleeding complication.	I-C
Resume anticoagulation in patients with an IVC filter once contraindications to anticoagulation or active bleeding complications have been resolved.	I-C
Patients with retrievable IVC filters should be evaluated periodically for filter retrieval within the specific filter's retrieval window.	I-C
IVC filter to patients with recurrent acute PE despite therapeutic anticoagulation.	IIa-C
Permanent IVC filter device for DVT or PE patients who will require permanent IVC filtration (eg, those with a long-term contraindication to anticoagulation),	IIa-C
Retrievable IVC filter device or DVT or PE patients with a time-limited indication for an IVC filter (eg, those with a short-term contraindication to anticoagulation therapy).	IIa-C
IVC filter for patients with acute PE and very poor cardiopulmonary reserve, including those with massive PE.	IIb-C
Routine use of IVC filter as an adjuvant to anticoagulation.	III-C
ESC 2014 GL on PE. Recommendations for venous filters	
IVC filters in patients with acute PE and absolute contraindications to anticoagulation.	IIa-C
IVC filters in case of recurrence of PE, despite therapeutic levels of anticoagulation.	IIa-C
Routine use in patients with PE not recommended	III-A

Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: A scientific statement from the American Heart Association. *Circulation*. 2011;**123**:1788–1830 with permission from Wolters Kluwer.
ESC 2014 guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014;**35**:3033–69 with permission from Oxford University Press.

Special conditions

Thromboembolism in cancer

In patients with VTE, the risk of recurrence is 3-fold in patients with cancer compared to those without cancer.[35,56] Cancer should be suspected in patients who have recurrent idiopathic VTE,[56] but routine screening with CT of the abdomen and pelvis is not indicated.[57] Female sex, lung cancer, TNM stage >1, solid tumours subjected to chemotherapy, and previous VTE indicate a higher risk of VTE in cancer patients.[58] Thus, extended-duration anticoagulation may be recommended, but care is needed because there is also an increased risk of bleeding. The use of prophylactic anticoagulation therapy is controversial. It is advisable in patients undergoing surgery and, probably, in ambulatory cancer patients receiving chemotherapy, especially for multiple myeloma, and particularly in the presence of a history of previous VTE.[33]

Thromboembolism in pregnancy

Pregnant women have a 4- to 5-fold increased risk of thromboembolism compared with non-pregnant women and PE is a leading cause of mortality in pregnancy in developed countries (Tables 76.10 and 76.11). The risk is higher in the post-partum period, particularly after a Caesarian section.[18] Women are hypercoagulable for the first 6 weeks post-partum, but the risk levels off after 12 weeks.[59] Thus, following delivery, thrombotic prophylaxis

Table 76.10 ESC 2011 GL on pregnancy

Check list for risk factors for venous thromboembolism modified according to the Royal College of Obstetricians and Gynaecologists
Pre-existing risk factors
Previous recurrent VTE[a]
Previous VTE unprovoked or oestrogen related[b]
Previous VTE provoked
Family history of VTE
Known thrombophilia
Medical co-morbidities, e.g.heart or lung diseases, SLE, cancer, inflammatory conditions, nephritic syndrome, sickle cell disease, i.v. drug use
Age >35 years
Obesity, BMI >30 kg/m^2 [b]
Parity ≥3
Smoker
Gross varicose veins
Obstetric risk factors
Pre-eclampsia
Dehydration/hyperemesis/ovarian hyperstimulation syndrome
Multiple pregnancy or assisted reproductive therapy
Emergency Caesarean section
Elective Caesarean section
Mid-cavity or rotational forceps
Prolonged labour (>24 hours)

(*Continued*)

Table 76.10 Continued

Peripartum haemorrhage (>1 L or transfusion)
Transient risk factors
Current systemic infection
Immobility
Surgical procedure in pregnancy or <6 weeks post-partum
Patients with previous recurrent VTEs, or those with a previous unprovoked or oestrogen-related VTE belong to the high risk group.
Example: in a pregnant woman with a family history of VTE, age >35 years, and obesity (BMI >30 kg/m^2, the total number of risk factors is 3. This patient belongs to the intermediate risk group and requires VTE prophylaxis accordingly.

[a] Patients with previous recurrent VTEs (>1), or those with a previous unprovoked or oestrogen-related VTE belong to the high-risk group.
[b] Obesity based on booking weight.
ESC 2011 Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**:3147–97 with permission from Oxford University Press.

should be considered for 12 weeks in patients with risk factors, and oestrogen-containing contraception in patients without risk factors should be withheld for 12 weeks. Approximately 80% of thromboembolic events in pregnancy are venous with a prevalence of 0.5–3/1000 pregnant women. Compression ultrasonography of the proximal veins should be considered when new-onset DVT is suspected. When using anticoagulants, heparin compounds are preferred. In suspected PE the usefulness of D-dimers is controversial since they physiologically increase during pregnancy. Radiation conferred by other tests is presented in Table 76.12. The danger threshold for fetal damage is 50 mSv (50 000 mGy), thus a V/Q scan is preferable to CT. The ESC recommendations are provided in Tables 76.13 and 76.14.[60]

PE in heart failure

The relative risk of PE doubles in patients with heart failure.[61] Diagnosis may be difficult and is based on the

Table 76.11 ESC 2011 GL on pregnancy

Risk groups according to risk factors, definition and preventive measures modified according to the Royal College of Obstetricians and Gynaecologists

Risk groups	Definition according to risk factors	Preventive measures according to risk group
High risk	Patients with: (i) Previous recurrent VTE (>1) or (ii) VTE unprovoked / oestrogen related or (iii) Single previous VTE + thrombophilia or family history	High-risk patients should receive antenatal prophylaxis with LMWH as well as post-partum for the duration of 6 weeks. Graduated compression stockings are also recommended during pregnancy and post-partum.
Intermediate risk	Patients with: (i) 3 or more risk factors other than listed above as high risk (ii) 2 or more risk factors other than listed as high risk if patient is admitted to hospital	In intermediate risk patients antenatal prophylaxis with LMWH should be considered. Prophylaxis is recommended postpartum for at least 7 days or longer, if >3 risk factors persist Graduated compression stockings should be considered during pregnancy and postpartum.
Low risk	Patients with: <3 risk factors.	In low-risk patients early mobilization and avoidance of dehydration is recommended.

Several risk scores for identification of patients at different risk levels have been developed, yet all risk scores, including the above, still need validation in prospective studies.
ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**:3147–97 with permission from Oxford University Press..

Table 76.12 ESC 2014 GL on PE. Estimated radiation absorbed in procedures used for diagnosing PE

Test	Estimated fetal radiation exposure (mSv)	Estimated maternal radiation exposure to breast tissue (mSv)
Chest X-ray	<0.01	0.01
Perfusion lung scan with technetium-99m labelled albumin		
Low dose: 40 MBq	0.11–0.20	0.28–0.50
High dose: 200 MBq	0.20–0.60	1.20
Ventilation lung scan	0.10–0.30	<0.01
Computed tomographic angiography	0.24–0.66	10–70

mSv: millisievert
ESC 2014 Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014;**35**:3033–69 with permission from Oxford University Press.

Table 76.13 ESC 2011 on pregnancy

Recommendations for the prevention and management of venous thrombo-embolism in pregnancy and puerperium	
Assessment of risk factors for VTE in all women who are pregnant or consider pregnancy.	I-C
Mothers should be informed about the signs and symptoms of VTE in pregnancy and the necessity to contact the physicians if they occur.	I-C
Antenatal prophylaxis with LMWH as well as post-partum for 6 weeks in high risk patients.	I-C
Post-partum prophylaxis with LMWH for at least 7 days or longer, if >3 risk factors persist in intermediate risk patients.	I-C
Early mobilization and avoidance of dehydration in low risk patients.	I-C
Graduated compression stockings antepartum and post-partum in all women at high risk.	I-C
D-Dimer measurement and compression ultrasonography in patients with suspected VTE during pregnancy.	I-C
For acute VTE during pregnancy, UFH in high-risk and LMWH in non-high risk patients.	I-C
Graduated compression stockings in women with intermediate risk during pregnancy and post-partum.	IIa-C
Antenatal prophylaxis with LMWH in intermediate risk patients.	IIa-C
Routine screening for thrombophilia should not be performed.	III-C

ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**:3147–97 with permission from Oxford University Press.

Table 76.14 ESC 2014 GL on PE. Pulmonary embolism in pregnancy

Suspicion of PE in pregnancy warrants formal diagnostic assessment with validated methods.	I-C
D-dimer measurement in order to avoid unnecessary irradiation, as a negative result has a similar clinical significance as in non-pregnant patients.	IIb-C
Venous compression ultrasonography in order to avoid unnecessary irradiation, as a diagnosis of proximal DVT confirms PE.	IIb-C
Perfusion scintigraphy to rule out suspected PE in pregnant women with normal chest X-ray.	IIb-C
CT angiography if the chest X-ray is abnormal or if lung scintigraphy is not readily available.	IIa-C
A weight-adjusted dose of LMWH is the recommended therapy during pregnancy in patients without shock or hypotension.	I-B

ESC 2014 Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014;**35**:3033–69 with permission from Oxford University Press.

presence of dyspnoea and hypoxaemia out of proportion to findings of vascular congestion, new or worsened right greater than left heart failure (especially high JVP in the absence of pulmonary rales), and demonstration of new or worsened RV dilatation and dysfunction on echocardiography or chest CT. Elevated biomarkers and D-dimers are of no help. Oral anticoagulation is more difficult to manage due to stasis and concomitant medications (amiodarone and clopidogrel potentiate the effect of warfarin whereas spironolactone accelerates its metabolism). VTE prophylaxis with stockings, pneumatic compression devices, or LMWH or warfarin are indicated in all hospitalized patients with heart failure.[61]

Right heart thrombi

Thrombolysis is also indicated in the presence of right heart thrombi (in <4% of patients with PE), although surgical embolectomy may be required in the presence of massive thrombi, especially those straddling the interatrial septum through the foramen ovale. Conventional anticoagulation is not effective.

Non-thrombotic PE

Air embolism may occur during catheterization procedures. Haemodynamic consequences depend on the amount injected. Nasal oxygen is the treatment of choice. **Fat** embolism occurs after fracture of long bones and, rarely, with liposuction, lipid and propofol infusions, and hepatic necrosis. **Septic, tumour, and talc** (drug abusers) emboli may also occur. **Amniotic fluid embolism** is rare but potentially catastrophic (1/8000–1/80 000 pregnancies). Treatment is supportive.

PFO in the presence of PE

Recommendations of AHA are presented in Table 76.15.

Anticoagulation following bleeding

Recent data suggest that anticoagulation should be restarted following discharge after an episode of GI bleeding, especially in patients with malignancy.[62] However, this study was small, and although a trend towards more bleeding in the anticoagulated group was not statistically significant, this could represent a type II error due to a small sample size.

Table 76.15 AHA 2011 scientific statement

Recommendations on PFO in the face of a PE	
Screening for PFO with an echocardiogram with agitated saline bubble study or transcranial Doppler study in patients with massive or submassive PE.	IIb-C
Surgical embolectomy for patients with any type of PE found to have impending paradoxical embolism (thrombus entrapped within a PFO).	IIb-C

Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: A scientific statement from the American Heart Association. *Circulation*. 2011;**123**:1788–1830 with permission from Wolters Kluwer.

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Chapter 77

Deep vein thrombosis

Diagnosis and therapy

Deep vein thrombosis (DVT) carries a 3% 30-day mortality risk compared to 0.4% for a comparison cohort, and unlike mortality with PE, it remains constant the last three decades.[1]

Diagnosis is established by D-dimer test (moderately or highly sensitive) and venous duplex ultrasound with compression manoeuvres and colour and spectral Doppler evaluation. Loss of compressibility of a venous segment, often with associated Doppler abnormalities, identifies DVT with a high degree of accuracy, and no additional testing is needed to initiate treatment.[2] Negative whole-leg venous duplex ultrasound has a very high negative predictive value for suspected lower-extremity DVT. A cut-off D-dimer value of 750 μg/L for patients aged 60 years and older has also been proposed for the exclusion of DVT.[3] A non-invasive diagnostic algorithm combining the Constans clinical score, D-dimer testing, and ultrasonography has also recently been found effective in excluding upper extremity deep venous and superficial venous thrombosis.[4] Up to 10% of patients with superficial venous thrombosis have extension of the thrombus to the deep veins and are at increased risk for PE, myocardial infarction, and stroke.[5] Varicose veins are associated with a 7-fold increased risk of DVT.[6]

Table 77.1 AHA 2011 scientific statement. Iliofemoral deep vein thrombosis

Recommendations for initial anticoagulation for patients with iliofemoral deep vein thrombosis (IFDVT)	
In the absence of suspected or proven heparin-induced thrombocytopenia, patients with IFDVT should receive therapeutic anticoagulation with either	
IV UFH	I-A
or UFH by subcutaneous injection	I-B
or LMWH	I-A
or fondaparinux	I-A
Patients with suspected or proven heparin-induced thrombocytopenia should receive a direct thrombin inhibitor	I-B
Recommendations for long-term anticoagulation therapy for patients with IFDVT	
Warfarin overlap with initial anticoagulation therapy for a minimum of 5 days and until the INR is >2.0 for, at least, 24 hours, and then targeted to an INR of 2.0–3.0.	I-A
Patients with first-episode IFDVT related to a major reversible risk factor should have anticoagulation stopped after 3 months.	I-A
Patients with recurrent or unprovoked IFDVT should have at least 6 months of anticoagulation and be considered for indefinite anticoagulation, with periodic reassessment of the risks and benefits of continued anticoagulation.	I-A
Cancer patients with IFDVT should receive LMWH monotherapy for, at least, 3 to 6 months or as long as the cancer or its treatment (e.g. chemotherapy) is ongoing.	I-A
LMWH monotherapy in children with DVT.	IIb-C
Recommendations for use of compression therapy for patients with IFDVT	
30 to 40 mmHg knee-high graduated elastic compression stockings (ECS) on a daily basis for, at least, 2 years.	I-B
Daily use of 30 to 40 mmHg knee-high graduated ECS in patients with prior IFDVT and symptomatic post-thrombotic syndrome (PTS).	IIa-C
Intermittent sequential pneumatic compression, followed by daily use of 30 to 40 mmHg knee-high graduated ECS in patients with prior IFDVT and severe oedema.	IIb-B
Recommendations for filters for patients with IFDVT (as described in Chapter 76 on PE)	
Recommendations for endovascular thrombolysis and surgical venous thrombectomy for patients with IFDVT	
Catheter-directed thrombolysis (CDT) or pharmacomechanical CDT (PCDT) to patients with IFDVT associated with limb-threatening circulatory compromise (i.e. phlegmasia cerulea dolens).	I-C
Transfer to a centre with expertise in endovascular thrombolysis if indications for endovascular thrombolysis are present.	I-C
CDT or PCDT for patients with IFDVT associated with rapid thrombus extension despite anticoagulation, and/or	IIa-C
Symptomatic deterioration from the IFDVT despite anticoagulation	IIa-B

(*Continued*)

Table 77.1 Continued

CDT or PCDT as first-line treatment of patients with acute IFDVT to prevent PTS in selected patients at low risk of bleeding complications.	IIa-B
Surgical venous thrombectomy by experienced surgeons in patients with IFDVT.	IIb-B
Systemic fibrinolysis routinely to patients with IFDVT.	III-A
CDT or PCDT to most patients with chronic DVT symptoms (>21 days) or patients who are at high risk for bleeding complications.	III-B
Recommendations for percutaneous transluminal venous angioplasty and stenting for patients with IFDVT	
Stent placement in the iliac vein to treat obstructive lesions after CDT, PCDT, or surgical venous thrombectomy.	IIa-C
Percutaneous transluminal angioplasty without stenting for isolated obstructive lesions in the common femoral vein.	IIa-C
Iliac vein stents to reduce PTS symptoms and heal venous ulcers in patients with advanced PTS and iliac vein obstruction.	IIa-C
After venous stent placement, the use of therapeutic anticoagulation after venous stent placement; similar dosing, monitoring, and duration as without stents.	IIa-C
Use of antiplatelet therapy with concomitant anticoagulation in patients perceived to be at high risk of rethrombosis.	IIb-C

Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: A scientific statement from the American Heart Association. *Circulation*. 2011;**123**:1788–1830 with permission from Wolters Kluwer.

Catheter-directed thrombolysis is the treatment of choice for iliofemoral DVT. It refers to the infusion of a thrombolytic drug directly into the thrombus through a multisidehole catheter placed under fluoroscopic guidance. The usual protocol entails 20 mg alteplase over 15 hours (without bolus), with a continuous infusion of alteplase at a rate of 2 mg/h for the first 5 hours, then reduced to 1 mg/h for the remaining 10 hours, with normal saline coolant at a rate of 35 mL/h, with concomitant administration of UFH or LMWH. Catheter-directed thrombolysis followed by angioplasty and stenting is useful in cases such as extensive iliofemoral/IVC, and SVC thrombosis,[7] although its actual benefit is debatable.[8] Addition of intravascular ultrasound did not facilitate thrombus resolution.[9] The management of superficial vein thrombosis, not proximal to the saphenofemoral junction, is not established, but without anticoagulation 10% of patients progress to more extensive thrombosis, and fondaparinux, 2.5 mg od for 45 days, has been found effective in patients with acute, symptomatic superficial-vein thrombosis of the legs (CALISTO trial).[10] Thus, a 3-month course of anticoagulation with warfarin or a new oral anticoagulant is probably reasonable in this setting. Dosing of anticoagulants for DVT is the same as for pulmonary embolism. Elastic compression stockings following DVT are not useful for preventing post-thrombotic syndrome.[11] The **post-thrombotic syndrome** is the main long-term complication of DVT, and only restoration of iliofemoral patency reduces the risk. The AHA 2011 recommendations for the management of iliofemoral deep vein thrombosis are presented in Table 77.1.[12] Recommendations are dealing with iliofemoral deep vein thrombosis.

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Part XVI

Pulmonary hypertension

Relevant guidelines

ACCF/AHA 2009 Statement on pulmonary hypertension

ACCF/AHA 2009 Expert consensus document on pulmonary hypertension. *Circulation*. 2009;**119**:2250–94.

ESC 2015 Guidelines on pulmonary hypertension

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2016;**37**:67–119.

AHA 2011 Scientific statement on management of submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension

Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation*. 2011;**123**:1788–830.

Chapter 78

Definitions and classification of pulmonary hypertension

Definition and classification

Pulmonary hypertension (PH) is defined as a mean PA pressure ≥25 mmHg at rest, as assessed by right heart catheterization.[1,2] Clinical classification and haemodynamic definition of pulmonary hypertension are presented in Tables 78.1 and 78.2. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis represent a distinct category, but not completely separated, from pulmonary arterial hypertension and have been designated as clinical group 1. The key haemodynamic feature that differentiates group 2 PH is wedge pressure elevation >15 mmHg (post-capillary pulmonary hypertension). There is no sufficient data to support the definition of 'PH on exercise'.[1]

Table 78.1 ESC 2015 GL on PH. Comprehensive clinical classification of pulmonary hypertension

I. Pulmonary arterial hypertension
1.1 Idiopathic
1.2 Heritable
1.2.1 BMPR2 mutation
1.2.2 Other mutations
1.3 Drugs and toxins Induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 Human immunodeficiency virus (HIV) infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease (Table 6)
1.4.5 Schistosomiasis
1′. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
1′.1 Idiopathic
1′.2 Heritable
1′.2.1 EIF2AK4 mutation
1′.2.2 Other mutations
1′.3 Drugs, toxins and radiation induced
1′.4 Associated with:
1′.4.1 Connective tissue disease
1′.4.2 HIV Infection
1″. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital / acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathles
2.5 Congenital / acquired pulmonary veins stenosis
3. Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases (Web Table III)
4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
4.1 Chronic thromboembolic pulmonary hypertension
4.2 Other pulmonary artery obstructions
4.2.1 Angiosarcoma
4.2.2 Other intravascular tumors
4.2.3 Arteritis
4.2.4 Congenital pulmonary arteries stenoses
4.2.5 Parasites (hydatidosis)
5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease. Gaucher disease, thyroid disorders
5.4 Others: pulmonary tumoral thrombothic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

BMPR2, bone morphogenetic protein receptor, type 2; EIF2AK4, eukaryotic translation initiation factor 2 alpha kinase 4; HIV, human immunodeficiency virus. ESC/ERS 2015 Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J.* 2016;**37**:67–119 with permission from Oxford University Press.

Presentation and differential diagnosis

The symptoms of pulmonary hypertension are non-specific, such as shortness of breath on exertion, fatigue, and weakness (Tables 78.3 and 78.4). They are progressively related to progressive RV dysfunction. Diagnostic work-up is presented in Tables 78.5 to 78.10 and Figure 78.1.

Table 78.2 ESC 2015 GL on PH. Haemodynamic definitions of pulmonary hypertensiona

Definition	Characteristics	Clinical group(s)
PH	PAPm ≥ 25 mmHg	All
Pre-capillary PH	PAPm ≥ 25 mmHg	1. Pulmonary arterial hypertension
	PAWP ≥ 15 mmHg	3. PH due to lung diseases
		4. Chronic thromboembolic PH
		5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	PAPm ≥ 25 mmHg	2. PH due to left heart disease
	PAWP > 15 mmHg	5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG < 7 mmHg and/or PVR ≤3 WU[c]	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥ 7 mmHg and/or	
	PVR > 3 WU	

CO, cardiac output; DPG, diastolic pressure gradient (diastolic PAP – mean PAWP); mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WU, Wood units.
All values measured at rest.
ESC/ERS 2015 Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J.* 2016;**37**:67–119 with permission from Oxford University Press.

Table 78.3 ACCF/AHA Consensus document 2009 on PH. Physical examination in pulmonary hypertension

Sign	Implication
Physical signs that reflect severity of PH	
Accentuated pulmonary component of S_2 (audible at apex in over 90%)	High pulmonary pressure increases force of pulmonic valve closure
Early systolic click	Sudden interruption of opening of pulmonary valve into high-pressure artery
Midsystolic ejection murmur	Turbulent transvalvular pulmonary outflow
Left parasternal lift	High right ventricular pressure and hypertrophy present
Right ventricular S_4 (in 38%)	High right ventricular pressure and hypertrophy present
Increased jugular "a" wave	Poor right ventricular compliance
Physical signs that suggest moderate to severe PH	
Moderate to severe PH	
Holosystolic murmur that increases with inspiration	Tricuspid regurgitation
Increased jugular v waves	
Pulsatile liver	
Diastolic murmur	Pulmonary regurgitation
Hepatojugular reflux	High central venous pressure
Advanced PH with right ventricular failure	
Right ventricular S_3 (in 23%)	Right ventricular dysfunction
Distention of jugular veins	Right ventricular dysfunction or tricuspid regurgitation or both
Hepatomegaly	Right ventricular dysfunction or tricuspid regurgitation or both
Peripheral edema (in 32%)	
Ascites	
Low blood pressure, diminished pulse pressure, cool extremities	Reduced cardiac output, peripheral vasoconstriction

Table 78.3 (Continued)

Physical signs that suggest possible underlying cause or associations of PH	
Central cyanosis	Abnormal V/Q, intra-pulmonary shunt, hypoxemia, pulmonary-to-systemic shunt
Clubbing	Congenital heart disease, pulmonary venopathy
Cardiac auscultatory findings, including systolic murmurs, diastolic murmurs, opening snap, and gallop	Congenital or acquired heart or valvular disease
Rales, dullness, or decreased breath sounds	Pulmonary congestion or effusion or both
Fine rales, accessory muscle use, wheezing, protracted expiration, productive cough	Pulmonary parenchymal disease
Obesity, kyphoscoliosis, enlarged tonsils	Possible substrate for disordered ventilation
Sclerodactyly, arthritis, telangiectasia, Raynaud phenomenon, rash	Connective tissue disorder
Peripheral venous insufficiency or obstruction	Possible venous thrombosis
Venous stasis ulcers	Possible sickle cell disease
Pulmonary vascular bruits	Chronic thromboembolic PH
Splenomegaly, spider angiomata, palmary erythema, icterus, caput medusa, ascites	Portal hypertension

ACCF/AHA 2009 Expert consensus document on pulmonary hypertension. *Circulation.* 2009;**119:**2250–94 with permission from Wolters Kluwer.

Table 78.4 NYHA/WHO Classification of functional status of patients with pulmonary hypertension

I	Patients with pulmonary hypertension in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnoea, fatigue, chest pain or pre-syncope.
II	Patients with pulmonary hypertension who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnoea, fatigue, chest pain or pre-syncope.
III	Patients with pulmonary hypertension who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnoea, fatigue, chest pain or pre-syncope.
IV	Patients with pulmonary hypertension who are unable to perform any physical activity and who may have signs of right ventricular failure at rest. Dyspnoea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity. (ESC)

NYHA/WHO Classification of functional status of patients with pulmonary hypertension.

Table 78.5 ESC 2015 GL on pulmonary hypertension

Echocardiographic probability of pulmonary hypertension in symptomatic patients with a suspicion of pulmonary hypertension

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'[a]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	Intermediate
2.9–3.4	Yes	High
>3.4	Not required	High

Echocardiographic signs suggesting pulmonary hypertension used to assess the probability of pulmonary hypertension in addition to tricuspid regurgitation velocity measurement (as above)

A: The ventricles[a]	B: Pulmonary artery[a]	C: Inferior vena cava and right atrium[a]
Right ventricle/left ventricle basal diameter ratio >1.0	Right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/sec	Right atrial area (end-systole) >18 cm^2
	PA diameter >25 mm	

[a]Echocardiographic signs from at least two different categories (A/B/C) from the list should be present to alter the level of echocardiographic probability of pulmonary hypertension.

ESC/ERS 2015 Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J.* 2016;**37**:67–119 with permission from Oxford University Press.

Table 78.6 ESC 2015 GL on pulmonary hypertension. Diagnostic management suggested according to echocardiographic probability of pulmonary hypertension in patients with symptoms compatible with pulmonary hypertension, with or without risk factors for pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension

Echocardiographic probability of PH	Without risk factors or associated condition for PAH or CTEPH[a]		Without risk factors or associated condition for PAH or CTEPH[a]	
Low	Alternative diagnosis	IIa-C	Echo follow-up	IIa-c
Intermediate	Alternative diagnosis, echo follow-up	IIa-C	Further assessment of PH including RHC[b]	IIa-B
Intermediate	Further investigation of PH	IIb-C		
High	Further investigation of PH (including RHC[b])	I-C	Further assessment of PH including RHC[b]	I-C

CTEPH, chronic thromboembolic pulmonary hypertension; Echo, echocardiographic; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RHC, right heart catheterization.
[a] These recommendations do not apply to patients with diffuse parenchymal lung disease or left heart disease.
[b] Depending on the presence of risk factors for PH group 2, 3 or 5.
Further investigation strategy may differ depending on whether risk factors/associated conditions suggest higher probability of PAH or CTEPH – see Figure 79.2.
ESC/ERS 2015 Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2015; 2016;**37**:67–119 with permission from Oxford University Press.

Table 78.7 ESC 2015 GL on pulmonary hypertension. Recommendations for right heart catheterization

To confirm the diagnosis of pulmonary arterial hypertension (group 1) and to support treatment decisions	I-C
Perform RHC in expert centres as it is technically demanding and may be associated with serious complications	I-B
In PAH (group 1) to assess the treatment effect of drugs	IIa-C
In congenital cardiac shunts to support decisions on correction	I-C
In PH due to left heart disease (group 2) or lung disease (group 3) if organ transplantation is considered	I-C
When measurement of PAWP is unreliable, left heart catheterization to measure LVEDP	IIa-C
In suspected PH and left heart disease or lung disease to assist in the differential diagnosis and support treatment decisions	IIb-C
In CTEPH (group 4) to confirm the diagnosis and support treatment decisions	I-C

CTEPH, chronic thromboembolic pulmonary hypertension; LVEDP, left ventricular end-diastolic pressure; PAWP, pulmonary artery wedge pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RHC, right heart catheterization.
ESC/ERS 2015 Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2016;**37**:67–119 with permission from Oxford University Press.

Table 78.8 ESC 2015 GL on pulmonary hypertension. Recommendations for vasoreactivity testing

Vasoreactivity testing only in expert centres	I-C
In IPAH, HPAH and PAH associated with drugs use to detect patients who can be treated with high doses of a CCB	I-C
A positive response is defined as a reduction of mean PAP ≥10 mmHg to reach an absolute value of mean PAP ≤40 mmHg with an increased or unchanged cardiac output	I-C
Nitric oxide for performing vasoreactivity testing	I-C
IV epoprostenol as an alternative	I-C
Adenosine as an alternative	IIa-C
Inhaled iloprost as an alternative	IIb-C
The use of oral or intravenous CCBs in acute vasoreactivity testing is not recommended	III-C
Vasoreactivity testing to detect patients who can be safely treated with high doses of a CCB is not recommended in patients with PAH other than IPAH, HPAH and PAH associated with drugs use and is not recommended in PH groups 2, 3, 4 and 5	III-C

CCB, calcium channel blocker; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; PAP, pulmonary arterial pressure; PAH, pulmonary arterial hypertension.
ESC/ERS 2015 Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2016;**37**:67–119 with permission from Oxford University Press.

Table 78.9 Vasodilator therapy. ACCF/AHA consensus document 2009 on PH. Agents for acute vasodilator testing

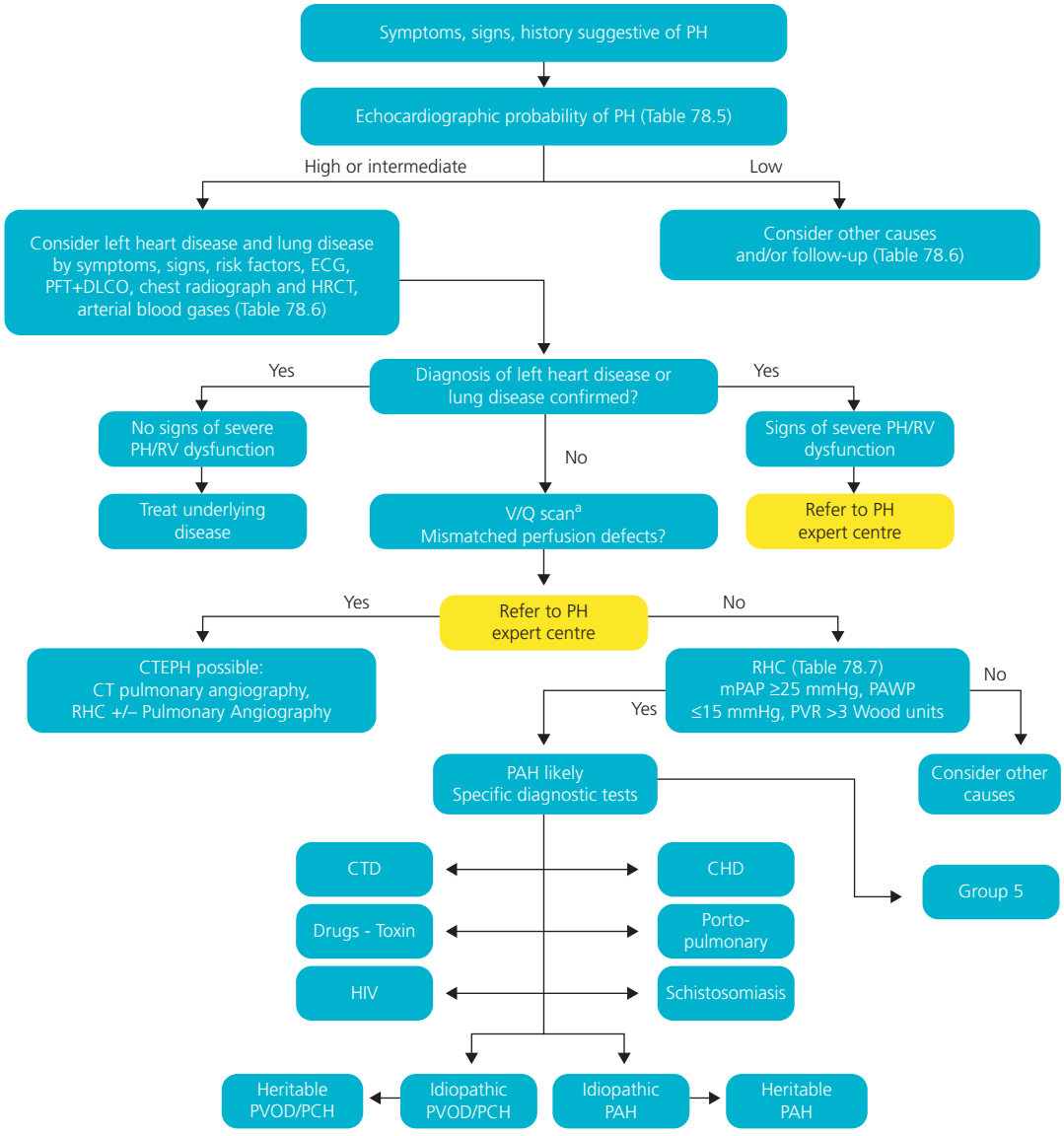
	Epoprostenol	Adenosine	Nitric oxide
Route of Administration	Intravenous infusion	Intravenous infusion	Inhaled
Dose Titration	2 ng/kg/min every 10 to 15 min	50 mcg/kg/min every 2 min	None
Dose Range	2 to 10 ng/kg/min	50 to 250 mcg/kg/min	10 to 80 ppm
Side Effects	Headache, nausea, lightheadedness	Dyspnea, chest pain, AV block	Increased left heart filling pressure in susceptible patients

ACCF/AHA 2009 Expert consensus document on pulmonary hypertension. *Circulation*. 2009;**119**:2250–94 with permission from Wolters Kluwer.

Table 78.10 ESC 2015 GL on pulmonary hypertension. Recommendations for diagnostic strategy

Echocardiography as a first-line non-invasive diagnostic investigation in case of suspicion of PH	I-C
Ventilation/perfusion or perfusion lung scan in patients with unexplained PH to exclude CTEPH	I-C
Contrast CT angiography of the PA in the workup of patients with CTEPH	I-C
Routine biochemistry, haematology, immunology, HIV testing and thyroid function tests in all patients with PAH to identify the specific associated condition	I-C
Abdominal ultrasound is recommended for the screening of portal hypertension	I-C
Lung function test with DLCO in the initial evaluation of patients with PH	I-C
High-resolution CT in all patients with PH	IIa-C
Pulmonary angiography in the workup of patients with CTEPH	IIa-C
Open or thoracoscopic lung biopsy is not recommended in patients with PAH	III-C

CT, computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; DLCO, diffusing capacity of the lung for carbon monoxide; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.
ESC/ERS 2015 Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2016;**37**:67–119 with permission from Oxford University Press.



CHD = congenital heart diseases; CT = computed tomography; CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; DLCO = carbon monoxide diffusing capacity; ECG = electrocardiogram; HIV = Human immunodeficiency virus; HR-CT = high resoultion CT; mPAP = mean pulmonary arterial pressure; PA = pulmonary angiography; PAH = pulmonary arterial hypertension; PAWP = pulmonary artery wedge pressure; PFT = pulmonary function tests; PH - pulmonary hypertension; PVOD/PCH = pulmonary veno-occlusive disease or pulmonary capilary hemangiomatosis; PVR = pulmonary vascular resistance; RHC = right heart catheterisation; RV = right ventricular; V/Q = ventilation/perfusion.
[a]CT pulmonary angiography alone may miss diagnosis of chronic thromboembolic pulmonary hypertension.

Figure 78.1 ESC 2015 GL on pulmonary hypertension. Diagnostic algorithm.

ESC/ERS 2015 Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2016;**37**:67–119 with permission from Oxford University Press.

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1. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2016;**37**:67–119
2. McLaughlin VV, *et al*. ACCF/AHA 2009 Expert consensus document on pulmonary hypertension. *Circulation*. 2009; **119**:2250–94

Chapter 79

Pulmonary arterial hypertension and hypertension associated with pulmonary venous abnormalities

Pulmonary arterial hypertension

Definition

Pulmonary arterial hypertension (PAH) is a clinical condition characterized by the presence of pre-capillary PH, and pulmonary vascular resistance >3 Wood units, in the absence of other causes of pre-capillary PH, such as PH due to lung diseases, chronic thromboembolic PH, or other rare diseases. PAH is caused by restricted flow through the pulmonary arterial circulation resulting in increased pulmonary vascular resistance and ultimately in right heart failure.

Epidemiology

The prevalence of PAH is estimated to 15 per million.[1]

Aetiology

Causes are presented in Table 78.1 of Chapter 78 on the classification of pulmonary hypertension. **Idiopathic pulmonary arterial hypertension**, the most common type of PAH (6 per million), is more prevalent in women. **Heritable forms** of PAH (<10%) include clinically sporadic idiopathic PAH, with germline mutations mainly of bone morphogenetic protein receptor 2 (BMPR2) gene, as well as the activin receptor-like kinase type 1 gene (ALK1) or the endoglin gene, and clinical familial cases with or without identified mutations.[2,3] PAH due to BMPR2 mutations is inherited as an autosomal dominant disease with incomplete penetrance and genetic anticipation. Recently, an association of a novel gene, *KCNK3*, with familial and idiopathic pulmonary arterial hypertension was identified. Mutations in this gene produced reduced potassium-channel current, which was successfully remedied by pharmacologic manipulation.[4] **Drugs** that may cause PAH are presented in Table 79.1. Several conditions are also associated with PAH as shown in Table 78.1 of Chapter 78. Pulmonary hypertension, in the context of **congenital heart disorders**, may lead to Eisenmenger's syndrome, as discussed in Chapter 1 on ACHD (Tables 79.2 and 79.3). The mechanism of PAH in patients with **schistosomiasis** is probably multifactorial and includes portal hypertension and local vascular inflammation. **Chronic haemolytic anaemia**, such as sickle cell disease, thalassaemia, hereditary spherocytosis, stomatocytosis, and microangiopathic haemolytic anaemia, may result in PAH. The prevalence of PAH in β-thalassaemia is 2.1%, and the β-thalassaemia intermedia phenotype, splenectomy, and advanced age are risk factors.[5] The mechanism of PAH in chronic haemolysis is related to a high rate of nitric oxide (NO) consumption, leading to a state of resistance to NO bioactivity.[6] The rise in PA pressure in **chronic hypoxia** is generally modest, but there is a wide variation of response in humans.[7] **POEMS syndrome** (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) is a rare cause of precapillary pulmonary hypertension and acute heart failure.[8]

Table 79.1 ESC 2015 GL on pulmonary hypertension. Risk level of drugs and toxins known to induce pulmonary arterial hypertension

Definite
Aminorex
Fenfluramine
Dexfenfluramine
Toxic rapeseed oil
Benfluorex
Selective serotonin reuptake inhibitors[a]
Likely
Amphetamines
Dasatinib
L-tryptophan
Meta-amphetamines
Possible
Cocaine
Phenylpropanolamine
St John's Wort
Amphetamine-like drugs
Interferon α and β
Some chemotherapeutic agents such as alkylating agents (mytomycine C, cyclophosphamide)[b]

[a] Increased risk of persistent pulmonary hypertension in the newborns of mothers with intake of selective serotonin reuptake inhibitors.
[b] Alkylating agents are possible causes of pulmonary veno-occlusive disease.
ESC/ERS 2015 Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J.* 2016;**37**:67–119 with permission from Oxford University Press.

Table 79.2 ESC 2015 GL on pulmonary hypertension. Clinical classification of pulmonary arterial hypertension associated with congenital heart disease

1. Eisenmenger's syndrome
Includes all large Intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of PVR and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis, and multiple organ involvement are usually present.
2. PAH associated with prevalent systemic-to-pulmonary shunts
• Correctable[a] • Non-correctable
Includes moderate to large defects; PVR is mildly to moderately increased, systemic-to-pulmonary shunting is still prevalent, whereas cyanosis at rest is not a feature.
3. PAH with small/coincidental defects[b]
Marked elevation in PVR in the presence of small cardiac defects (usually ventricular septal defects <l cm and atrial septal defects <2 cm of effective diameter assessed by echo), which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. Closing the defects is contra-indicated.
4. PAH after defect correction
Congenital heart disease is repaired, but PAH either persists immediately after correction or recurs/develops months or years after correction in the absence of significant postoperative haemodynamic lesions.

PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance.
[a] With surgery or intravascular percutaneous procedure.
[b] The size applies to adult patients. However, also in adults the simple diameter may be not sufficient for defining the haemodynamic relevance of the defect and also the pressure gradient, the shunt size and direction, and the pulmonary to systemic flows ratio should be considered.
ESC/ERS 2015 Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J.* 2016;**37**:67–119 with permission from Oxford University Press.

Table 79.3 Differences between Eisenmenger syndrome and idiopathic pulmonary arterial hypertension

	Idiopathic PAH	Eisenmenger syndrome
RV response		
RV dimensions	Dilation	Typically significantly hypertrophied in post-tricuspid defects
RV function	Rapid deterioration	Often preserved (in ventricular or atrioventricular septal defect cases), quite stable over time
Cardiac output	Reduced	Supported by right–left shunting
Vasoreactivity	May have significant vasoreactivity	Minimal/no acute vasoreactivity
Prognosis without ATs	Poor, survival limited to few years after diagnosis	Not as poor, patients often survive decades after diagnosis
Cyanosis		
Prevalence	When low cardiac output or patent foramen ovale/atrial septal defect present	The rule in Eisenmenger syndrome
Severity	Rarely severe at rest	Mild—severe at rest even in stable patients, severe on effort
Haematologic effect	Rare haematologic manifestations. Iron deficiency frequent	Secondary erythrocytosis common in Eisenmenger syndrome. Frequently iron deficient. Commonly thrombocytopenic. Predisposed to bleeding and thrombosis. Little evidence on the use of anticoagulation
Systemic complications	Not common (late)	Common (renal dysfunction, gout, gallstones, etc.)
Associated genetic/chromosomal disorders	BMPR2 mutation in <25% of iPAH, low penetrance	Common (Down's syndrome)
Perception of limitation	Normal perception of limitation	Typically underestimate the degree of limitation, as present from infancy
Coexisting left heart disease/valve disease	Rare until tricuspid regurgitation develops	Common (e.g. atrioventricular septal defect, univentricular circulation)
Transplantation	Rapid progression, likely to benefit from transplantation	Slow progression, common systemic complications, complex cardiac disease: not ideal candidates for transplantation

Dimopoulos K, *et al*. Pulmonary hypertension related to congenital heart disease: A call for action. *Eur Heart J*. 2014;**35**:691–700 with permission from Oxford University Press.

Pathophysiology

PAH is a panvasculopathy, predominantly affecting small pulmonary arteries (<500 microns) that regulate regional blood flow in the lung (resistance arteries), whereas pulmonary veins are unaffected. Intimal hyperplasia, medial hypertrophy, adventitial proliferation, thrombosis *in situ*, varying degrees of inflammation, and plexiform arteriopathy are histological characteristics.[6] Multiple pathogenic pathways have been implicated in the development of PAH, including those at molecular and genetic levels in the smooth muscle and endothelial cells. Excessive cell proliferation and reduced rates of apoptosis, as well as excessive vasoconstriction in 20% of patients, induce vascular remodelling with loss of vascular luminal cross section. Excessive vasoconstriction has been related to abnormal function or expression of potassium channels in the smooth muscle cells and to endothelial dysfunction that leads to chronically impaired production of vasodilator and antiproliferative agents, such as NO and prostacyclin, along with overexpression of vasoconstrictor and proliferative substances, such as thromboxane A2 and endothelin-1. Eventually, pathological increases in PVR cause right heart failure characterized by reduced RV ejection fraction and increased RV diastolic stiffness.[9] Left ventricular atrophy with resultant reduced LV contractility also occurs.[10]

Presentation

Patients initially present with dyspnoea and fatigue. Peripheral oedema and other signs of RV failure follow. Syncope in PAH is associated with worsening right heart function and is an independent predictor of a poor prognosis.[11]

Physical examination

Initial findings are $\mathbf{S_3}$ (right ventricular), accentuated $\mathbf{P_2}$, **early systolic click** from PV, pansystolic murmur of **TR**, diastolic murmur of **PR**, and **left parasternal lift**.

Jugular vein distension, hepatomegaly, peripheral oedema, ascites, and cool extremities characterize patients in a more advanced state.[6]

Lung sounds are usually normal. Signs of associated disorders may be also seen.

Investigation

Chest X-ray is abnormal in 90% of patients and typically displays decreased peripheral lung vascular markings (pruning) and hilar pulmonary artery prominence due to central pulmonary arterial dilatation (Figure 79.1). Right atrium and RV enlargement may be seen in more advanced cases.

ECG may reveal right atrial enlargement, right ventricular hypertrophy and strain, and right axis deviation of the QRS complex. A normal ECG does not exclude PAH.

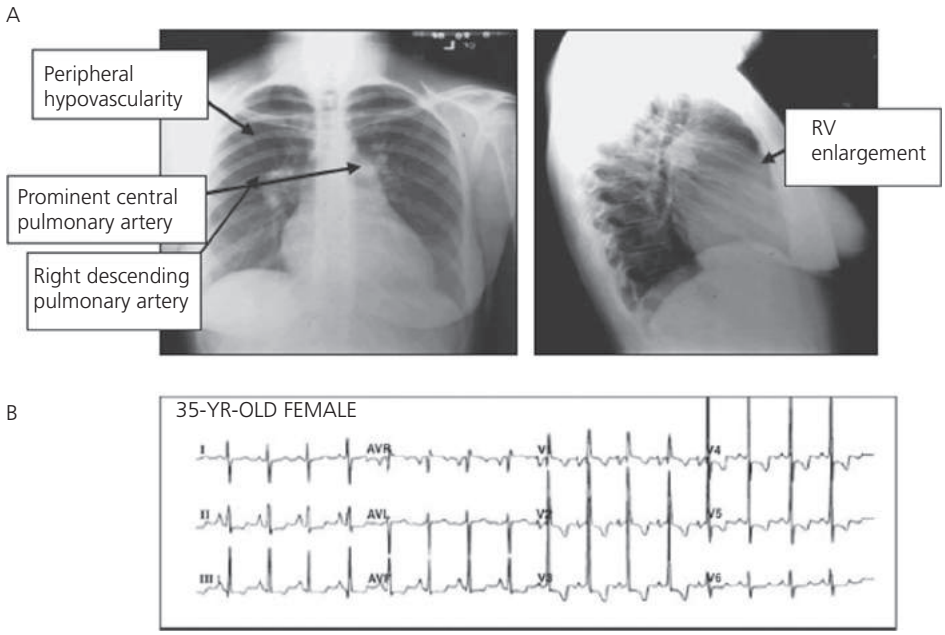

Figure 79.1 Chest X-ray (A) and ECG (B) from a patient with PAH.

ACCF/AHA 2009 Expert consensus document on pulmonary hypertension. *Circulation*. 2009;**119**:2250–94 with permission from Wolters Kluwer.

Echocardiography shows right atrial and right ventricular enlargement, abnormal contour, flattening, or reverse curvature of the interventricular septum, TR, and underfilled left heart chambers (see also Table 78.5). The Doppler echocardiographic index (Tei index or myocardial performance index), an index of combined RV systolic and diastolic function obtained by dividing the sum of both isovolumetric contraction and relaxation intervals by the ejection time, appears to be predictive of an adverse outcome.[1] In addition, stress Doppler echocardiography is useful for the assessment of RV contractile reserve (increase of systolic PA pressure >30 mm Hg).[12] Doppler measurements of the PA pressure, however, may be significantly inaccurate (by as much as 38 mmHg).[13]

Cardiac catheterization It is necessary to establish the diagnosis and allow vasodilator testing (Table 78.7). Typically, there is a mean pulmonary artery pressure (mPAP) >25 mmHg (and usually >42 mmHg); a pulmonary capillary wedge pressure (PCWP), left atrial pressure, or left ventricular end-diastolic pressure (LVEDP) ≤15 mmHg; and a pulmonary vascular resistance (PVR) greater than 3 Wood units. Associated mortality of the procedure is 0.05%.

Vasoreactivity testing is useful both for diagnostic and therapeutic purposes (Tables 78.8 and 78.9).

Lung function tests There is decreased lung diffusion capacity for carbon monoxide (typically in the range of 40–80% predicted) and mild to moderate reduction of lung volumes. Mild peripheral airway obstruction can also be detected. PO_2 is usually normal and PCO_2 low due to hyperventilation.

High-resolution CT is important to exclude interstitial lung disease and emphysema. The presence of interstitial markings similar to those seen with advanced left ventricular failure, such as diffuse central (as opposed to panlobular that is seen with PAH) ground glass opacification and thickening of interlobular septa, suggest **pulmonary veno-occlusive disease**. Diffuse bilateral thickening of the interlobular septae and the presence of small, centrilobular, poorly circumscribed nodular opacities suggest **pulmonary capillary haemangiomatosis**.

MRI is the imaging modality of choice for assessment of RV function. Poor RV function, including stroke volume ≤25 mL/m^2, RV end-diastolic volume ≥84 mL/m^2, and LV end-diastolic volume ≤40 mL/m^2, are independent predictors of mortality and treatment failure.[14]

Lung biopsy is not generally indicated.

Genetic counselling and recommendation for BMPR2 genotyping might be indicated in first-degree relatives of patients with this mutation or within pedigree of two or more patients with a diagnosis of PAH.[6]

Diagnosis of pulmonary arterial hypertension is by excluding other possibilities (Figure 79.2). Differential diagnosis of pulmonary hypertension in general is discussed in Chapter 78.

Risk stratification

The prognosis of PAH is poor, with an approximately 15% mortality within 1 year on modern therapy. Predictors of a poor prognosis include: advanced functional class, poor exercise capacity as measured by 6-minute walk test or cardiopulmonary exercise test, high right atrial pressure, tricuspid annular displacement (TAPSE), significant RV dysfunction or failure, low cardiac index, elevated BNP, and underlying diagnosis of scleroderma spectrum of diseases (Table 79.4).[15,16] Exercise-induced pulmonary artery systolic pressure (>30 mm Hg) indicates RV contractile reserve and a better prognosis.[12] Table 79.5 presents recommendations for assessment and follow-up of patients with pulmonary arterial hypertension.

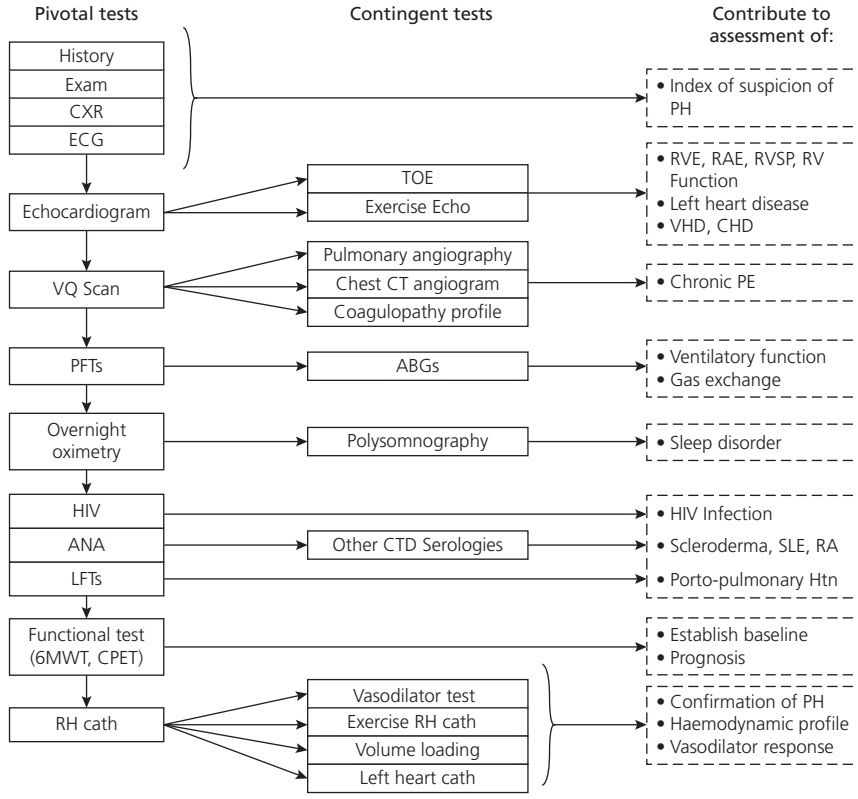

Figure 79.2 AHA 2009 recommendations: diagnostic approach to PAH.

The diagnosis of idiopathic pulmonary arterial hypertension is one of excluding all other reasonable possibilities.
Pivotal tests are those that are essential to establishing a diagnosis of any type of PAH either by identification of criteria of associated disease or exclusion of diagnoses other than IPAH. All pivotal tests are required for a definitive diagnosis and baseline characterization.
An abnormality of one assessment (such as obstructive pulmonary disease on PFTs), does not preclude that another abnormality (chronic thromboembolic disease on VQ scan and pulmonary angiogram) is contributing or predominant. Contingent tests are recommended to elucidate or confirm results of the pivotal tests, and need only to be performed in the appropriate clinical context. The combination of pivotal and appropriate contingent tests contribute to assessment of the differential diagnoses in the right-hand column. It should be recognized that definitive diagnosis may require additional specific evaluations not necessarily included in this general guideline.
6MWT indicates 6-minute walk test; ABGs, arterial blood gases; ANA, antinuclear antibody serology; CHD, congenital heart disease; CPET, cardiopulmonary exercise test; CT, computerized tomography; CTD, connective tissue disease; CXR, chest X-ray; ECG, electrocardiogram; HIV, human immunodeficiency virus screening; Htn, hypertension; LFT, liver function test; PE, pulmonary embolism; PFT, pulmonary function test; PH, pulmonary hypertension; RA, rheumatoid arthritis; RAE, right atrial enlargement; RH Cath, right heart catheterization; RVE, right ventricular enlargement; RVSP, right ventricular systolic pressure; SLE, systemic lupus erythematosus; TOE, transoesophageal echocardiography; VHD, valvular heart disease; and VQ Scan, ventilation-perfusion scintigram.
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Table 79.4. ESC 2015 GL on pulmonary hypertension. Risk assessment in pulmonary arterial hypertension

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk > 10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I,II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (<35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP < 50 ng/l NT-proBNP <300 ng/ml	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 >60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 >60%

6MWD: 6-minute walking distance; BNP: brain natriuretic peptide; CI: cardiac index; CMR: cardiac magnetic resonance; NT-proBNP: N-terminal pro-brain natriuretic peptide; pred.: predicted; RA: right atrium; RAP: right atrial pressure; SvO_2: mixed venous oxygen saturation; VE/VCO_2: ventilatory equivalents for carbon dioxide; VO_2: oxygen consumption; WHO: World Health Organization.
a: Most of the proposed variables and cut-off values are based on expert opinion. They may provide prognostic information and may be used to guide therapeutic decisions, but application to individual patients must be done carefully. One must also note that most of these variables have been validated mostly for IPAH and the cut-off levels used above may not necessarily apply to other forms of PAH. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk.
b: Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.
c: Repeated episodes of syncope, even with little or regular physical activity.

Table 79.5. ESC 2015 GL on pulmonary hypertension. Suggested assessment and timing for the follow-up of patients with pulmonary arterial hypertension

	At baseline	Every 3–6 months[a]	Every 6–12 months[a]	3–6 months after changes in therapy[a]	In case of clinical worsening
Medical assessment and determination of functional class	+	+	+	+	+
ECG	+	+	+	+	+
6MWT/Borg dyspnoea score	+	+	+	+	+
CPET	+		+		+[e]
Echo	+		+		+
Basic lab[b]	+	+	+	+	+
Extended lab[c]	+		+		+
Blood gas analysis[d]	+		+	+	+
Right heart catheterization	+		+[f]	+[e]	+[e]

ALAT: alanine aminotransferase; ASAT: aspartate aminotransferase; BGA: blood gas analysis; BNP: brain natriuretic peptide; CPET: cardiopulmonary exercise testing; Echo: echocardiography; ECG: electrocardiogram; ERAs: endothelin receptor antagonists; FC: functional class; INR: international normalized ratio; lab: laboratory assessment; NT-proBNP: N-terminal pro-brain natriuretic peptide; RHC: right heart catheterization; TSH: thyroid stimulating hormone; 6MWT: 6-minute walking test.
a: Intervals to be adjusted according to patient needs.
b: Basic lab includes blood count, INR (in patients receiving vitamin K antagonists), serum creatinine, sodium, potassium, ASAT/ALAT (in patients receiving ERAs), bilirubin and BNP/ NT-proBNP.
c: Extended lab includes TSH, troponin, uric acid, iron status (iron, ferritin, soluble transferrin receptor) and other variables according to individual patient needs.
d: From arterial or arterialized capillary blood; may be replaced by peripheral oxygen saturation in stable patients or if BGA is not available.
e: Should be considered.
f: Some centres perform RHCs at regular intervals during follow-up.

Therapy

Treatment of PAH is not easy (Table 79.6 and Figures 79.3 and 79.4).[17,18] Acute vasodilator testing to test the presence of pulmonary vasoreactivity has prognostic value and should be performed in all patients with idiopathic PAH who might be considered potential candidates for long-term calcium channel blocker therapy (Table 79.9). Those with overt right heart failure or haemodynamic instability should not undergo acute vasodilator testing. The definition of an acute responder is a reduction in mPAP of at least 10 mmHg to an absolute mPAP of less than 40 mmHg without a decrease in cardiac output.[6] It should be noted, however, that changes in haemodynamics at 12 weeks following therapy are not a surrogate marker for clinical events.[19]

General measures that should be addressed include diet, exercise, appropriate vaccinations, and avoidance of pregnancy (Table 79.7). In-flight O_2 administration (2 L/min) should be considered for patients in WHO-FC III and IV and those with arterial blood O_2 pressure consistently <8 kPa (60 mmHg). Patients should avoid going to altitudes above 1500–2000 m without supplemental O_2. If AF intervenes, rhythm control is recommended.[6]

Oxygen is recommended to maintain oxygen saturation greater than 90%.

Warfarin anticoagulation is recommended in all patients with idiopathic PAH, heritable PAH, PAH due to anorexigens, and those receiving therapy with long-term IV prostaglandins. However, recent data from the COMPERA European registry indicate that the use of anticoagulants is associated with a survival benefit in patients with idiopathic, but not other forms of PAH such as due to connective tissue disease (mainly), congenital heart disease, portopulmonary hypertension, HIV, drugs, haemolytic anaemia, and hereditary PAH.[20] No survival benefit with warfarin was also detected in patients with PAH due to systemic sclerosis (REVEAL trial).[21]

Diuretics are used for symptomatic management of RV volume overload.

Calcium channel blockers (diltiazem up to 720 mg daily, long-acting nifedipine up to 240 mg daily, and amlodipine up to 20 mg daily, in all starting with low doses, but not the more potent negative inotropic verapamil) are indicated only for patients who have a positive acute vasodilator response (Table 79.8). Patients treated with calcium channel blockers, as with other vasodilators, should be followed closely for both the safety and efficacy of this therapy.

Endothelin receptor antagonists are oral therapies that improve exercise capacity in PAH (Tables 79.9 to 79.11). ***Bosentan*** (62.5 mg twice daily and uptitrated to 125 mg twice daily after 4 weeks),[22] and more selective antagonists such as ***ambrisentan*** (5–10 mg daily)[23] have been successfully tried in various forms of PAH. Another antagonist, sitaxentan, was withdrawn in 2010 due to reported cases of hepatic toxicity. Aminotransferase rise (3–10%) is less with ambrisentan, but liver function tests must be monitored indefinitely on a monthly basis.

Macitentan a new dual endothelin-receptor antagonist, significantly reduced morbidity and mortality (3–10 mg daily) without aminotransferase rise, but with increased incidence of headache, nasopharyngitis, and anaemia (SERAPHIN trial).[24] The FDA approved the 10 mg dose in 2013.

Prostanoids Continuous intravenous **epoprostenol** improves exercise capacity and haemodynamics (and survival in idiopathic PAH),[25] and is the preferred treatment option for the most critically ill patients. Epoprostenol is a therapy for PAH that has been shown to prolong survival, but its use may be prohibited by its high cost. Treatment is initiated at a dose of 2–4 ng/kg/min, with doses increasing at a rate limited by side effects (flushing, headache, diarrhoea, leg pain). The optimal dose varies between individual patients, ranging in the majority between 20 and 40 ng/kg/min. Serious adverse events related to the delivery system include pump malfunction, local site infection, catheter obstruction, and sepsis. Abrupt interruption of the epoprostenol infusion should be avoided as, in some patients, this may lead to death.[6]

Treprostinil, a prostanoid, may be delivered via either continuous intravenous or subcutaneous infusion. Initial dose is 1–2 ng/kg/min, with doses increasing at a rate limited by side effects (local site pain, flushing, headache), up to 20 and 80 ng/kg/min. Oral and inhaled formulations that avoid Gram-negative infections induced by IV administration are promising. Recently, ***oral treprostinil diolamine*** was shown to improve exercise capacity in PAH patients not receiving other treatment (FREEDOM-M trial).[26] Therapy was generally well tolerated; the most common adverse events were headache (69%), nausea (39%), diarrhoea (37%), and pain in jaw (25%). The FDA approved oral trepostinil for PAH in December 2013.

Iloprost is a prostanoid delivered by an adaptive aerosolized device six times daily (2.5–5 mg/inhalation). Inhaled iloprost is well tolerated, with flushing and jaw pain being the most frequent side effects.[27]

Selexipag, an oral selective prostacyclin receptor antagonist, has been shown to reduce a composite of death and PAH-related complications compared to placebo.[28] FDA approved its use in December 2015.

Phosphodiesterase (PDE)-5 inhibitors (sildenafil and tadalafil) also improve exercise capacity and haemodynamics in PAH.[29,30] Side effects are mild to moderate and mainly related to vasodilation (headache, flushing, epistaxis). A combination of ambrisentan with tadalafil has also been found useful (AMBITION trial).[31]

Riociguat is a soluble guanylate cyclase activator, acting in synergy with endogenous nitric oxide and also directly stimulating guanylate cyclase independently of nitric oxide availability. It increases the level of cGMP,

with resultant vasorelaxation and antiproliferative and antifibrotic effects. In the recent PATENT-1 trial, per os riociguat significantly improved exercise capacity and secondary efficacy end points such as PVR, NTpro-BNP and functional class in patients with pulmonary arterial hypertension.[32] The drug received FDA approval in 2013. Treatment response is assessed by improvement in exercise capacity (6-minute walk test, cardiopulmonary exercise test, treadmill test) and haemodynamics.

Imatinib is a specific inhibitor of the Bcr-Abl protein tyrosine kinase that has activity against platelet-derived growth factor (PDGF)-driven pathways. Among patients with advanced PAH who remained symptomatic on at least two PAH-specific drugs, treatment with imatinib compared with placebo was associated with significant improvements in echocardiographic measures of RV function, in addition to LV size and LV early diastolic relaxation (IMPRES trial).[33]

Nebivolol, has also been found to attenuate experimental pulmonary hypertension by correcting endothelial dysfunction.[34]

In patients with pre-capillary pulmonary hypertension (mainly PAH and chronic thromboembolic PH) and sleep-disturbed breathing on optimized pharmacological therapy, nocturnal **oxygen** (3 L/min) and **acetazolamide** (250 mg bd) may improve exercise capacity and functional class.[35]

Heart-lung or **lung transplantation** are options for selected patients who progress despite optimal medical management (Table 79.12). Percutaneous interventional therapies such as atrial septostomy and transcatheter Pott's shunt are specialized procedures under assessment.[36]

Mechanical support of a failing right ventricle is an option as a bridge to transplantation or recovery.[37]

Treatment of specific groups is presented in Tables 79.13 to 79.16.

Non-cardiac surgery Patients with severe PAH, who are undergoing elective surgery, should be managed in a centre with appropriate resources and by the multidisciplinary pulmonary hypertension team.[38]

Table 79.6 ESC 2015 GL on pulmonary hypertension. Evaluation of the severity of pulmonary arterial hypertension and clinical response to therapy.

Evaluate the severity of PAH patients with a panel of data derived from clinical assessment, exercise tests, biochemical markers and echocardiographic and haemodynamic evaluations (Tables 79.4 and 79.5)	I-C
Perform regular follow-up assessments every 3–6 months in stable patients (Table 79.5)	I-C
Achievement/maintenance of a low-risk profile (Table 79.4) as an adequate treatment	I-C
Achievement/maintenance of an intermediate-risk profile (Table 79.4) as an inadequate treatment	IIa-C

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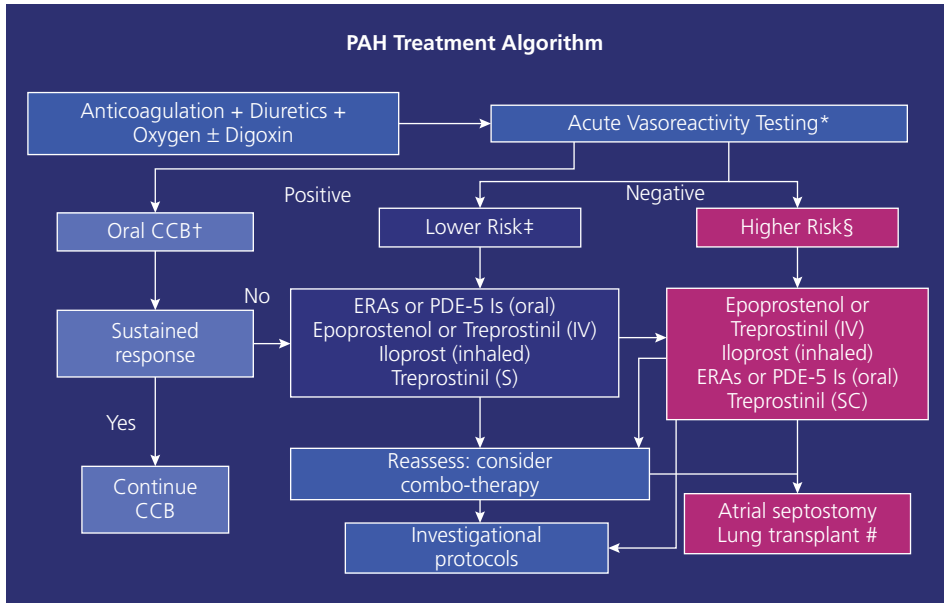
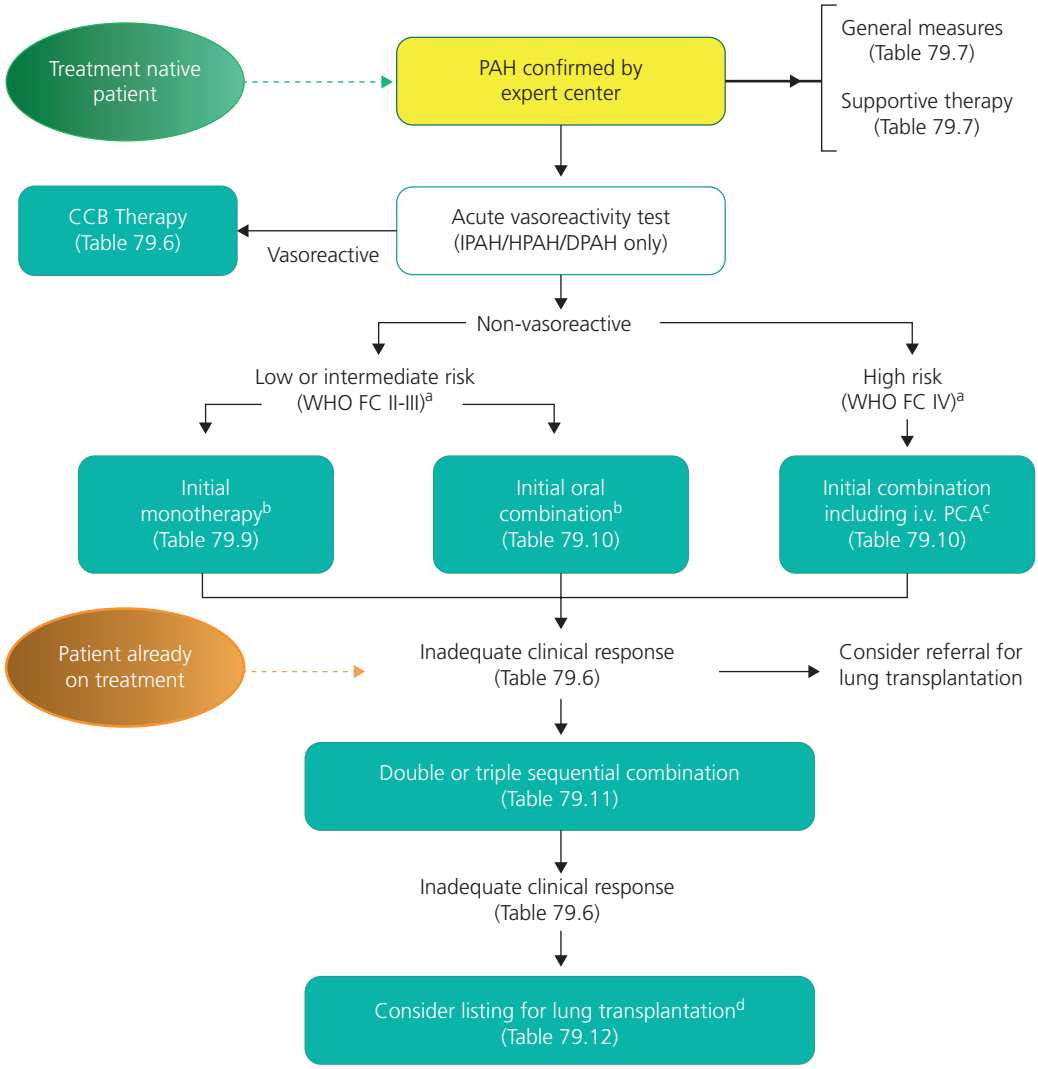


Figure 79.3 AHA 2009 recommendations: treatment algorithm for PAH. Background therapies include warfarin anticoagulation, which is recommended in all patients with IPAH without contraindication. Diuretics are used for management of right heart failure. Oxygen is recommended to maintain oxygen saturation greater than 90%.

* Acute vasodilator testing should be performed in all IPAH patients who may be potential candidates for long-term therapy with calcium channel blockers (CCBs). Patients with PAH due to conditions other than IPAH have a very low rate of long-term responsiveness to oral CCBs, and the value of acute vasodilator testing in such patients needs to be individualized. IPAH patients in whom CCB therapy would not be considered, such as those with right heart failure or haemodynamic instability, should not undergo acute vasodilator testing.
† CCBs are indicated only for patients who have a positive acute vasodilator response, and such patients need to be followed closely both for safety and efficacy.
‡ For patients who did not have a positive acute vasodilator testing and are considered lower risk based on clinical assessment, oral therapy with ERA or PDE-5I would be the first line therapy recommended. If an oral regimen is not appropriate, the other treatments would need to be considered, based on the patient's profile and side effects and risk of each therapy. § For patients who are considered high risk based on clinical assessment, continuous treatment with intravenous (IV) prostacyclin (epoprostenol or treprostinil) would be the first line of therapy recommended. If a patient is not a candidate for continuous IV treatment, the other therapies would have to be considered, based on the patient's profile and side effects and risk of each treatment. Combination therapy should be considered when patients are not responding adequately to initial monotherapy.
# Timing for lung transplantation and/or atrial septostomy is challenging and is reserved for patients who progress despite optimal medical treatment.
ACCF/AHA 2009 Expert consensus document on pulmonary hypertension. Circulation. 2009;119:2250–94 with permission from Wolters Kluwer.



CCB = calcium channel blockers; DPAH = drug-induced PAH; HPAH = heritable PAH; IPAH = idiopathic PAH; i.v. = intravenous; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogues; WHO-FC = World Health ORganization functional class.
[a]Some WHO-FC III patients may be considered high risk (see Table 79.4).
[b]Initial combination with ambrisentan plus tadalafil has proven to be superior to intial monotherapy with ambrisentan or tadalafil in delaying clinical failure.
[c]Intravenous epoprostenol should be prioritised as it has reduced the 3 months rate for moratility in high risk PAH patients also as monotherapy.
[d]Consider also ballon atrial septostomy.

Figure 79.4 ESC 2015 GL on pulmonary hypertension. Evidence based treatment algorithm for pulmonary arterial hypertension patients (group 1 patients only).

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Table 79.7 ESC 2015 GL on pulmonary hypertension.

Recommendations for general measures	
Avoid pregnancy	I-C
Immunization against influenza and pneumococcal infection	I-C
Psychosocial support is recommended in PAH patients	I-C
Supervised exercise training in physically deconditioned PAH patients under medical therapy	IIa-B
In-flight O2 administration for patients in WHO-FC III and IV and those with arterial blood O2 pressure consistently <8 kPa (60 mmHg)	IIa-C
In elective surgery, epidural rather than general anaesthesia whenever possible	IIa-C
Excessive physical activity that leads to distressing symptoms is not recommended	III-C
Supportive therapy	
Diuretic treatment with signs of RV failure and fluid retention	I-C
Continuous long-term O2 therapy when arterial blood O2 pressure is consistently <8 kPa (60 mmHg)[a]	I-C
Oral anticoagulant treatment with IPAH, HPAH and PAH due to anorexigens	IIb-C
Correction of anaemia and/or iron status	IIb-C
ACE inhibitors, ARBs, beta-blockers and ivabradine not recommended unless required by co-morbidities (i.e. high blood pressure, coronary artery disease or left heart failure)	III-C

HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; O2, oxygen; PAH, pulmonary arterial hypertension; RV, right ventricular.

[a] See also recommendations for PAH associated with congenital cardiac shunts.

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Table 79.8 ESC 2015 GL on pulmonary hypertension. Calcium channel blocker therapy in patients who respond to the acute vasoreactivity test

High doses of CCBs in IPAH, HPAH and DPAH responders to acute vasoreactivity testing	I-C
Close follow-up with complete reassessment after 3–4 months of therapy (including RHC) is in IPAH, HPAH and DPAH treated by high doses of CCBs	I-C
Continuation of high doses of CCBs in IPAH, HPAH and DPAH in WHO-FC I or II with marked haemodynamic improvement (near normalization)	I-C
Specific PAH therapy in patients in WHO-FC III or IV or those without marked haemodynamic improvement (near normalization) after high doses of CCBs	I-C
High doses of CCBs are not indicated in patients without a vasoreactivity study or non-responders unless standard doses are prescribed for other indications (e.g. Raynaud's phenomenon)	III-C

CCB, calcium channel blocker; DPAH, drug-induced PAH; HPAH, heritable PAH; IPAH, idiopathic PAH; PAH, pulmonary arterial hypertension; RHC, right heart catheterization; RV, right ventricular; WHO-FC, World Health Organization functional class.

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Table 79.9 ESC 2015 GL on pulmonary hypertension. Efficacy of drug monotherapy for pulmonary arterial hypertension (group 1) according to World Health Organization functional class. The sequence is by pharmacological group, by rating and by alphabetical order

	WHO-FC II	WHO-FC III	WHO-FC IV
Calcium channel blockers	I-C[a]	I-C[a]	-
Endothelin receptor antagonists			
Ambrisentan	I-A	I-A	IIb-C
Bosentan	I-A	I-A	IIb-C
Macitentan[b]	I-B	I-B	IIb-C
Phosphodiesterase type 5 inhibitors			
Sildenafil	I-A	I-A	IIb-C
Tadalafil	I-B	I-B	IIb-C
Vardenafil[d]	IIb-B	IIb-B	IIb-C
Guanylate cyclase stimulators			
Riociguat	I-B	I-B	IIb-C
Prostacyclin analogues			
Epoprostenol IV[b]	-	I-A	I-A
Iloprost inhaled	-	I-B	IIb-C
Iloprost IV[d]	-	IIa-C	IIb-C
Treprostinil SC	-	I-B	IIb-C
Treprostinil inhaled[d]	-	I-B	IIb-C
Treprostinil IV[c]	-	IIa-C	IIb-C
Treprostinil oral[d]-		IIb-B	-
Beraprost[d]	-	IIb-B	-
IP receptor agonists			
Selexipag (oral)[d]	I-B	I-B	-

IV, intravenous; SC, subcutaneous.
[a] Only in responders to acute vasoreactivity tests (class I for idiopathic PAH, heritable PAH and PAH due to drugs; class II, for conditions associated with PAH).
[b] Time to clinical worsening as primary endpoint in RCTs or drugs with demonstrated reduction in all-cause mortality.
[c] In patients not tolerating the subcutaneous form.
[d] This drug is not approved by the European Medicines Agency (EMA) at the time of publication of these guidelines.
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Table 79.10 ESC 2015 GL on pulmonary hypertension. Efficacy of initial drug combination therapy for pulmonary arterial hypertension (group 1) according to World Health Organization functional class. Sequence is by rating

	WHO-FC II	WHO-FC III	WHO-FC IV
Ambrisentan+tadalafil[a]	I-B	I-B	IIb-C
Other ERA +PDE-5i	IIa-C	IIa-C	IIb-C
Bosentan +sildenafil +IV epoprostenol	-	IIa-C	IIa-C
Bosentan + IV epoprostenol	-	IIa-C	IIa-C
Other ERA or PDE-5i + SC. treprostinil		IIb-C	IIb-C
Other ERA or PDE-5i + other		IIb-C	IIb-C
i.v. prostacyclin analogues			

ERA, endothelin receptor antagonist; PDE-5i , phosphodiesterase type 5 inhibitor.
[a] Time to clinical failure as primary endpoint in RCTs or drugs with demonstrated reduction in all-cause mortality (prospectively defined).
ESC/ERS 2015 Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2016;**37**:67–119 with permission from Oxford University Press.

Table 79.11 ESC 2015 GL on pulmonary hypertension. Efficacy of sequential drug combination therapy for pulmonary arterial hypertension (group 1) according to World Health Organization functional class. Sequence is by rating and by alphabetical order

	WHO-FC II	WHO-FC III	WHO-FC IV
Macitentan added to sildenafil[a]	I-B	I-B	IIa-C
Riociguat added to bosentan	I-B	I-B	IIa-C
Selexipag[b] added to ERA and/or PDE-5i[a]	I-B	I-B	IIa-C
Sildenafil added to epoprostenol	-	I-B	IIa-B
Treprostinil inhaled added to sildenafil or bosentan	IIa-B	IIa-B	IIa-C
Iloprost inhaled added to bosentan	IIb-B	IIb-B	IIb-C
Tadalafil added to bosentan	IIa-C	IIa-C	IIa-C
Ambrisentan added to sildenafil	IIb-C	IIb-C	IIb-C
Bosentan added to epoprostenol	-	IIb-C	IIb-C
Bosentan added to sildenafil	IIb-C	IIb-C	IIb-C
Sildenafil added to bosentan	IIb-C	IIb-C	IIb-C
Other double combinations	IIb-C	IIb-C	IIb-C
Other triple combinations	IIb-C	IIb-C	IIb-C
Riociguat added to sildenafil or other PDE-5i	III-B	III-B	III-B

ERA, endothelin receptor antagonist; PDE-5i, phosphodiesterase type 5 inhibitor.
[a] Time to clinical worsening as primary endpoint in RCTs or drugs with demonstrated reduction in all-cause mortality (prospectively defined).
[b] This drug was not approved by the EMA at the time of publication of these guidelines.
ESC/ERS 2015 Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2016;**37**:67–119 with permission from Oxford University Press.

Table 79.12 ESC 2015 GL on pulmonary hypertension. Efficacy of intensive care unit management, balloon atrial septostomy and lung transplantation for pulmonary arterial hypertension (group 1) according to World Health Organization functional class

	WHO-FC II	WHO-FC III	WHO-FC IV
Hospitalization in ICU with heart rate >110 beats/min, systolic blood pressure <90 mmHg, low urine output and rising lactate levels due or not due to co-morbidities	-	-	I-C
Inotropic support in hypotensive patients		I-C	I-C
Lung transplantation soon after inadequate clinical response on maximal medical therapy	-	I-C	I-C
Balloon atrial septostomy where available after failure of maximal medical therapy	-	IIb-C	IIb-C

BAS, Balloon atrial septostomy; ICU, intensive care unit; PH, pulmonary hypertension; WHO-FC World Health Organization functional class.
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Table 79.13 ESC 2015 GL on pulmonary hypertension

Correction of congenital heart disease with prevalent systemic-to-pulmonary shunts			
PVRi	**PVR**	**Correctable[a]**	
(WU /m²)	**(WU)**		
<4	<2.3	Yes	IIa-C
>8	>4.6	No	IIa-C
4–8	2.3–4.6	Individual patient evaluation in tertiary centres	IIa-C
Pulmonary arterial hypertension associated with congenital heart disease			
Bosentan in WHO-FC III in Eisenmenger syndrome			I-B
Other ERAs, PDE-5is and prostanoids in Eisenmenger syndrome			IIa-C
In the absence of significant haemoptysis, oral anticoagulant treatment in patients with PA thrombosis or signs of heart failure			IIb-C
O_2 therapy when it produces a consistent increase in arterial O_2 saturation and reduces symptoms			IIa-C
With symptoms of hyperviscosity, phlebotomy with isovolumic replacement should be considered, usually when the haematocrit is >65%			IIa-C
Iron treatment with low ferritin plasma levels			IIb-C
Combination drug therapy in Eisenmenger syndrome			IIb-C
CCBs are not recommended in Eisenmenger syndrome			III-C

CCBs, calcium channel blockers; ERAs, endothelin receptor antagonists; PDE-5is, phosphodiesterase type 5 inhibitors; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; WU, Wood units.
[a] With surgery or intravascular percutaneous procedure.
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Table 79.14 ESC 2015 GL on pulmonary hypertension. Pulmonary arterial hypertension associated with connective tissue disease

Same treatment algorithm as for patients with IPAH	I-C
Resting echocardiography as a screening test in asymptomatic patients with systemic sclerosis, followed by annual screening with echocardiography, DLCO and biomarkers	I-C
RHC in all cases of suspected PAH associated with connective tissue disease	I-C
Oral anticoagulation on an individual basis and in the presence of thrombophilic predisposition	IIb-C

DLCO, diffusing capacity of the lung for carbon monoxide; IPAH, idiopathic pulmonary arterial hypertension; RHC, right heart catheterization.
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Table 79.15 ESC 2015 GL on pulmonary hypertension. Pulmonary arterial hypertension associated with portal hypertension

Echocardiographic assessment for signs of PH in symptomatic patients with liver disease or portal hypertension and in all candidates for liver transplantation	I-B
Refer patients with PAH and portal hypertension to centres with expertise in managing both conditions	I-C
The treatment algorithm for other forms of PAH should be applied taking into account the severity of liver disease	I-C
Anticoagulation is not recommended in PH associated with portal hypertension	III-C
Liver transplantation in selected patients responding well to PAH therapy	IIb-C
Liver transplantation is contraindicated in patients with severe and uncontrolled PAH	III-C

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Table 79.16 ESC 2015 GL on pulmonary hypertension. Pulmonary arterial hypertension associated with human immunodeficiency virus infection

Echocardiographic screening in asymptomatic HIV patients to detect PH is not recommended	III-C
The same treatment algorithm used for patients with PAH should be considered, taking into consideration co-morbidities and drug–drug interactions	IIa-C
Anticoagulation is not recommended because of a lack of data on the efficacy:risk ratio	III-C

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Pulmonary hypertension associated with pulmonary venous capillary abnormalities

In rare instances, the typical histological findings of PAH are associated with an occlusive venopathy (**pulmonary veno-occlusive disease**, PVOD) or a microvasculopathy (**pulmonary capillary haemangiomatosis**). In addition to the histology of PAH, these entities also exhibit the findings of pulmonary venous hypertension, including pulmonary haemosiderosis, interstitial oedema, and lymphatic dilation. Although the clinical presentation is usually indistinguishable from PAH, rapid development of pulmonary oedema after administration of vasodilators, such as epoprostenol, has been reported in both entities and is often a clue to the appropriate diagnosis.

In pulmonary veno-occlusive disease, intimal fibrosis and thrombosis originate in the small pulmonary veins and venules.[39] The pathogenesis is unknown, but mutations in the bone morphogenetic protein receptor II (BMPR2) gene have been identified as also happens with idiopathic pulmonary hypertension.[40] Patients with PVOD are more severely hypoxaemic and have a much lower diffusion capacity of carbon monoxide than in other forms of PAH. High-resolution CT scanning is the investigation of choice. Typical findings suggestive of PVOD are the presence of **subpleural thickened septal lines**, **centrilobular ground glass opacities** (contrasting with a panlobular distribution found in idiopathic PAH), and **mediastinal lymphadenopathy**. Changes consistent with pulmonary oedema may also be seen on CT imaging in patients with PVOD. **Wedge pressure** is normal in veno-occlusive disease. Pulmonary capillary haemangiomatosis is difficult to differentiate from PVOD, and the diagnostic and therapeutic aspects are very similar. Medical therapy is unsatisfactory, and lung transplantation is the only curative option. Therapy is undertaken in specializing centres (Table 79.17).

Table 79.17 ESC 2015 GL on pulmonary hypertension. Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary haemangiomatosis (PCH)

A combination of clinical findings, physical examination, bronchoscopy and radiological findings to diagnose PVOD/PCH	I-C
Identification of a bi-allelic EIF2AK4 mutation to confirm a diagnosis of heritable PVOD/PCH without histological confirmation	I-B
Referral of eligible patients with PVOD/PCH to a transplant centre for evaluation as soon as the diagnosis is established	I-C
Patients with PVOD/PCH should be managed only in centres with extensive experience in PH due to the risk of lung oedema after the initiation of PAH therapy	IIa-C

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Chapter 80

Pulmonary hypertension associated with left heart disease and lung disease, high-altitude disease, and chronic thromboembolic pulmonary hypertension

Pulmonary hypertension associated with left heart disease

Definition

Patients have elevated pulmonary venous pressure (as reflected by a pulmonary capillary wedge pressure ≥15 mmHg), usually as a consequence of either mitral valve disease or LV diastolic dysfunction.[1] It is, therefore, a **post-capillary pulmonary hypertension**, as opposed to the other pre-capillary forms. Pulmonary hypertension related to left heart disease (LHD) by far represents the most common form of PH, accounting for 65–80% of cases.[2]

Pathophysiology

Chronic elevation of the LA or diastolic LV filling pressure causes a backward transmission of the pressure to the pulmonary venous system that triggers vasoconstriction in the arterial pulmonary bed. For reasons that remain unclear, some patients do not progress to reactive pulmonary vasoconstriction despite the presence of chronic advanced heart failure.[1]

Diagnosis

Exertional dyspnoea is the most common symptom. Diagnostic tests may reveal the causative condition and differentiate pulmonary venous hypertension from pulmonary arterial hypertension (PAH).

ECG LV, rather than RV, hypertrophy may be present.

Chest X-ray Pulmonary vascular congestion, pleural effusions, and, on occasion, pulmonary oedema.

Echocardiography Valve disease and reduced LV function can be detected. Left atrial enlargement, concentric remodelling of the LV (relative wall thickness >0.45), LV hypertrophy, and the presence of echocardiographic indicators of elevated LV filling pressure suggest PH due to left heart disease rather than PAH (Table 80.1). However, in the absence of detectable significant valve disease, Doppler echocardiography alone may not exclude PAH since pulmonary hypertension itself produces diastolic filling abnormalities in the LV.[3]

Chest CT Ground glass opacities and a mosaic perfusion pattern, consistent with chronic pulmonary oedema, that are not seen in PAH.

Cardiac catheterization An elevated wedge pressure at end-expiration establishes the diagnosis but may not always be accurately measured and may be normal due to the use of diuretics. Exercise or inotropic challenges may increase cardiac output and reveal increased wedge pressure. Short-acting pulmonary vasodilators may also be used in cases with low wedge pressure and normal cardiac output.

Table 80.1 ESC 2015 GL on pulmonary hypertension. Examples of key factors suggestive of group 2 pulmonary hypertension

Clinical presentation	Echocardiography	Other features
Age >65 years	Structural left heart abnormality	ECG
		• LVH and/or LAH
	• Disease of left heart valves	• AF/Afib
	• LA enlargement (>4.2 cm)	• LBBB
	• Bowing of the IAS to the right	• Presence of Q waves
	• LV dysfunction	
	• Concentric LV hypertrophy and/or increased LV mass	

(*continued*)

Table 80.1 (Continued)

Clinical presentation	Echocardiography	Other features
Symptoms of left heart failure	Doppler indices of increased filling pressures	Other imaging
		• Kerley B lines
	• Increased E/e'	• Pleural effusion
	• >Type 2–3 mitral flow abnormality	• Pulmonary oedema
		• LA enlargement
Features of metabolic syndrome	Absence of	
	• RV dysfunction	
	• Mid systolic notching of the PA flow	
	• Pericardial effusion	
History of heart disease (past or current)		
Persistent atrial fibrillation		

AF, atrial flutter; Afib, atrial fibrillation; ECG, electrocardiogram; IAS, inter-atrial septum; LA, left atrium; LAH, left atrial hypertrophy/dilatation; LBBB, left bundle branch block; LV, left ventricle; LVH, left ventricular hypertrophy; PA, pulmonary artery; RV, right ventricle.
ESC/ERS 2015 Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2016;**37**:67–119 with permission from Oxford University Press.

Prognosis

Prognosis of these patients is poor, with >50% mortality in 2 years.[3] An elevated transpulmonary gradient (mean PAP minus mean PWP) >12 mmHg is suggestive of progressive intrinsic changes in the pulmonary circulation overriding the passive increase in PWP.[1] This progressed form is also called **reactive PH** and resembles pre-capillary forms.

Therapy

It is targeting the underlying condition (Tables 80.2). No heart failure drugs are contraindicated because of PH. Although preliminary results with phosphodiesterase type-5 inhibitors have been promising,[4,5] pulmonary vasodilators may be harmful. The potential role of vasodilators, in cases where the pulmonary hypertension is clearly disproportionate to the extent of underlying left heart disease, is also under investigation.[6,7]

Table 80.2 ESC 2015 GL on pulmonary hypertension. Pulmonary hypertension in left heart disease

Optimization of the treatment of the underlying condition before considering assessment of PH-LHD (i.e. treating structural heart disease)	I-B
Identify other causes of PH (i.e. COPD, sleep apnoea syndrome, PE, CTEPH) and treat them when appropriate before considering assessment of PH-LHD	I-C
Perform invasive assessment of PH in patients on optimized volume status	I-C
Refer patients with PH-LHD and a severe pre-capillary component as indicated by a high DPG and/or high PVR, to an expert PH centre	IIa-C
The importance and role of vasoreactivity testing is not established in PH-LHD, except in patients who are candidates for heart transplantation and/ or LV assist device implantation	III-C
The use of PAH-approved therapies is not recommended in PH-LHD	III-C

COPD, chronic obstructive pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; DPG, diastolic pressure gradient; LHD, left heart disease; PE, pulmonary embolism; PH, pulmonary hypertension; PVR, pulmonary vascular resistance.
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Pulmonary hypertension associated with lung disease

Chronic obstructive pulmonary disease and interstitial lung disease are the most common causes.

Pathophysiology

Hypoxia induces muscularization of distal vessels and medial hypertrophy of more proximal arteries as well as a loss of vessels, which is compounded by a loss of lung parenchyma in the setting of lung disease.[2] In patients with mild pulmonary hypertension in association with smoking, severe fibroproliferative neointimal formation can also be seen but not the development of plexiform lesions. A marked reduction in diffusing capacity for carbon monoxide is a consistent feature of the patients with connective tissue diseases who have pulmonary hypertension.

Clinical forms

Chronic obstructive pulmonary disease

Patients present with **dyspnoea and RV failure** in the setting of marked **hypoxaemia**. The typical ECG pattern of **cor pulmonale** is tall, pointed P waves in leads II, III, and aVF, and right axis deviation with RV hypertrophy pattern or simply rS complexes across the precordium. Pulmonary hypertension is usually mild but still predictive of the prognosis (Table 80.3). Severe pulmonary hypertension may be seen in genetically predisposed patients (<5%). COPD, as a cause of hypoxic PH, is diagnosed on the evidence of irreversible airflow obstruction, together with increased residual volumes and reduced diffusion capacity for carbon monoxide and normal or increased carbon dioxide tension. The only effective treatment is supplemental oxygen. Pulmonary vasodilators may worsen the ventilation perfusion mismatch (Tables 80.4).

Interstitial lung disease

This can be due to either a connective tissue disorder or to idiopathic pulmonary fibrosis. Pulmonary hypertension is relatively mild (**mean <40 mmHg**). Results with pulmonary vasodilators have not been consistent,[8] and the only treatment of severely symptomatic patients is lung transplantation. A decrease in **lung volume**, together with a decrease in **diffusion capacity for carbon monoxide**, may indicate a diagnosis of interstitial lung disease.

High-altitude disease

The rise in PA pressure in chronic hypoxia is generally modest, but there is a wide variation of response in humans. Extreme responders are at risk of **high-altitude pulmonary oedema** within 2–4 days of arrival at altitudes above 2500 m.[9] The emphasis in management is on prevention. Travellers should manage their rate of ascent to 300–500 m per day along with a day of rest every 3–4 days when travelling above 3000 m. Pharmacologic measures include slow-release nifedipine (30 mg bd), the phosphodiesterase type 5 inhibitor tadalafil (10 mg bd), and dexamethasone (8 mg bd).[9] The defining feature of **chronic mountain sickness** is excessive erythrocytosis (haemoglobin ≥21 g/dL in men and ≥19 g/dL in women) accompanied by neurologic symptoms, such as headache, dizziness, and fatigue. Descent to low altitudes is the best treatment. Acetazolamide (250 mg daily) is an alternative to phlebotomy.

Table 80.3 ESC 2015 GL on pulmonary hypertension. Haemodynamic classification of pulmonary hypertension due to lung disease

Terminology	Haemodynamics (right heart catheterization)
COPD/IPF/CPFE without PH	PAPm <25 mmHg
COPD/IPF/CPFE with PH	PAPm ≥25 mmHg
COPD/IPF/CPFE with severe PH	PAPm >35 mmHg, or PAPm ≥25 mmHg in the presence of a low cardiac output (CI <2.5 L/min, not explained by other causes)

CI, cardiac index; COPD, chronic obstructive pulmonary disease; CPFE, combined pulmonary fibrosis and emphysema; IPF, idiopathic pulmonary fibrosis; PAP, pulmonary artery pressure; PAPm, mean pulmonary arterial pressure; PH, pulmonary hypertension.
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Table 80.4 ESC 2015 GL on pulmonary hypertension. Pulmonary hypertension due to lung diseases

Echocardiography for the non-invasive diagnostic assessment of suspected PH in patients with lung disease	I-C
Refer patients with echocardiographic signs of severe PH and/or severe right ventricular dysfunction and considered candidates for transplant to an expert centre.	I-C
Optimal treatment of the underlying lung disease, including long-term O_2 therapy in patients with chronic hypoxaemia	I-C
Referral to PH expert center patients with signs of severe PH/severe RV failure for individual-based treatment	IIa-C
RHC is not recommended for suspected PH in patients with lung disease, unless therapeutic consequences are to be expected (e.g. lung transplantation, alternative diagnoses such as PAH or CTEPH, potential enrolment in a clinical trial)	III-C
The use of drugs approved for PAH is not recommended in patients with PH due to lung diseases	III-C

CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RHC, right heart catheterization. ESC/ERS 2015 Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J.* 2016;**37**:67–119 with permission from Oxford University Press.

Chronic thromboembolic pulmonary hypertension

Definition

Chronic thromboembolic pulmonary hypertension is defined as precapillary PH by invasive right heart catheterization (mean pulmonary artery pressure ≥25 mmHg, mean pulmonary arterial wedge pressure ≤15 mmHg) in the presence of chronic/organized flow-limiting thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental, subsegmental) after at least 3 months of effective anticoagulation.[10,11] It is differentiated by recurrent pulmonary embolism by a gradual progression of symptoms and signs of pulmonary hypertension, as opposed to profound episodic exacerbations, and a lack of response to fibrinolytic therapy or at least 6 months of antithrombotic therapy.[10,12]

Epidemiology

It occurs in 1–3% of acute pulmonary embolism cases,[13,14] but its true incidence is unknown.

Aetiology

Predisposing factors are presented in Table 80.5.[15,16] Patients usually, but not invariably, present in their 40s, and the disease is twice as common in women. Microemboli of tumour cells may also cause pulmonary hypertension and right heart failure in patients with breast cancer or other types of carcinoma (pulmonary tumour thrombotic microangiopathy). Mediastinal fibrosis secondary to tuberculosis, sarcoidosis, histoplasmosis, and radiation therapy may resemble chronic thromboembolic disease, although the typical thromboembolic lesions on high-resolution CT are missing.

Pathophysiology

Within months or years after PE, the original embolic material is replaced by fibrous tissue that is incorporated in the intima and media of the PAs. Abnormal degradation of fibrinogen, autoimmunity, and chronic staphylococcal infections are proposed mechanisms of ineffective fibrinolysis. Neurohumoral factors, such as endothelin-1, induce additional vasoconstriction, with resultant small-vessel arteriopathy, intimal proliferation, microvascular thrombosis, and plexiform lesion formation.

At least 60–70% of pulmonary vasculature is occluded before pulmonary hypertension develops. Four types of disease have been described.[16]

Table 80.5 Risk factors of CTPE

Unprovoked and recurrent venous thromboembolism
PA pressure > 50 mm Hg at PE or 6 months after therapy
Ventriculo-atrial shunts and infected pacemakers
Splenectomy
Sickle-cell disease
Blood groups other than 0
Lupus anticoagulant/antiphospholipid antibodies
Thyroid disease and thyroid replacement therapy
History of malignancy
Dysfibrinogenemia
Chronic inflammatory disorders (osteomyelitis, inflammatory bowel disease)

Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: A scientific statement from the American Heart Association. *Circulation.* 2011;**123**:1788–1830 with permission from Wolters Kluwer.

Presentation and physical findings

Exercise intolerance and dyspnoea are the most common presenting symptoms. Peripheral oedema, syncope, and haemoptysis may be late findings. Careful history reveals previous PE in up to 75% of the cases.[17]

A loud **P_2**, with reduction of the respiratory variation of the **S_2 splitting**, and **palpable RV** are the initial findings, followed by typical RV failure signs (right S_3, TR, hepatomegaly and ascites, and peripheral oedema) and bruits over the peripheral lungs due to turbulent pulmonary flow.

A thrombophilic disorder can be found in 30% of patients and splenectomy in 3% of them.[15]

Diagnosis

Chest X-ray is usually unremarkable. Hilar fullness due to enlarged PAs is a late finding, and peripheral lung opacities due to scarring from previous PE are rare.

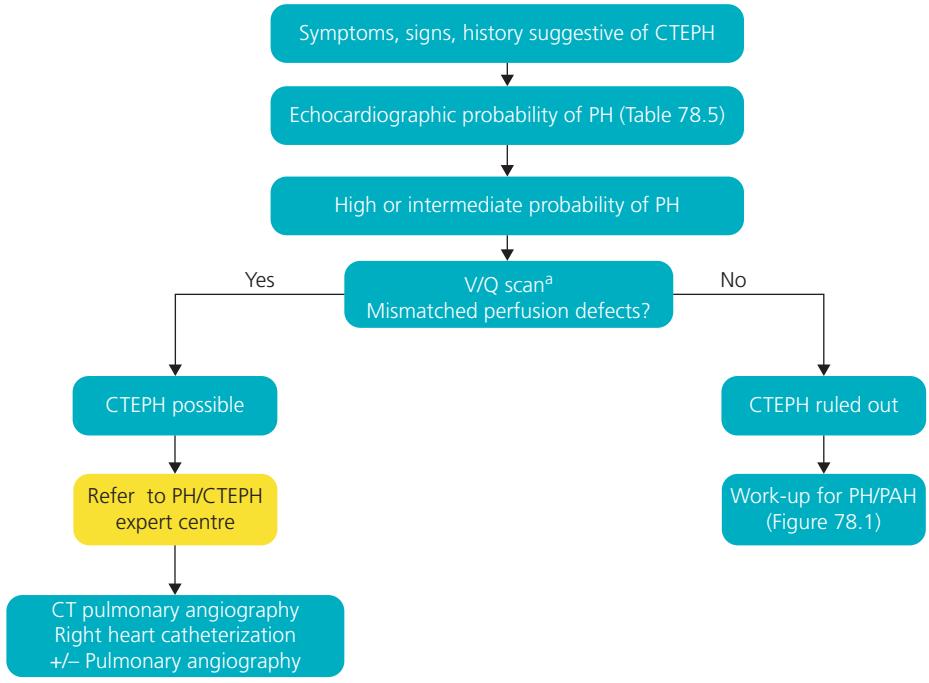
Echocardiography reveals pulmonary hypertension and RV dysfunction (Table 80.6 and Figure 80.1). Exercise-induced pulmonary artery systolic pressure (>30 mmHg assessed by stress Doppler echocardiography) indicates RV contractile reserve and a better prognosis.[18]

Arterial blood oxygen levels may show hypoxaemia or be normal.

Table 80.6 AHA 2011 Scientific statement on PE, IDVT and CTEPH. Recommendations for diagnostic evaluation of CTEPH

Patients presenting with unexplained dyspnea, exercise intolerance, or clinical evidence of right-sided heart failure, with or without prior history of symptomatic VTE, should be evaluated for CTEPH.	I-C
It is reasonable to evaluate patients with an echocardiogram 6 weeks after an acute PE to screen for persistent pulmonary hypertension that may predict the development of CTEPH.	IIa-C

Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: A scientific statement from the American Heart Association. *Circulation.* 2011;**123**:1788–1830 with permission from Wolters Kluwer.



CT - computed thomography; CTEPH - chronic thromboembolic pulmonary hypertension; PAH - pulmonary arterial hypertension; PH - pulmonary hypertension; V/Q - ventilation perfusion.
[a]CT pulmonary angiography alone may miss diagnosis of chronic thromboembolic pulmonary hypertension.

Figure 80.1 ESC 2015 GL on pulmonary hypertension. Diagnostic algorithm for chronic thromboembolic pulmonary hypertension.

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Lung function tests are necessary to exclude obstructive or fibrotic lung disease.

V/Q scanning typically shows multiple bilateral perfusion defects. A normal scan rules out the disease. It has a higher sensitivity than CT for diagnosis of CTEPH.[19]

Contrast-enhanced CT may show central pulmonary artery dilatation, abrupt narrowing or tapering of peripheral pulmonary vessels, right ventricular hypertrophy, right ventricular and atrial enlargement, dilated bronchial arteries, and a ground glass or mosaic pattern of attenuation due to variable lung perfusion. Microemboli of tumour cells are beyond the resolution of the CT pulmonary angiogram.

MRI may also be used but has less sensitivity in diagnosing PE.

Right heart catheterization with pulmonary angiography still remains the gold standard for establishing the diagnosis and assessing operability. Systolic and mean PA pressures are >40 mmHg and 25 mmHg, respectively, and PVR >3 Wood units. Capillary wedge pressure is <15 mmHg (excluding left-sided heart disease). In some patients, the wedge pressure may be higher because of severe RV dilation, interventricular dependence, and resultant LV diastolic dysfunction; in these cases, the PVR is usually high (>600 dyn.s.cm^{-5}).[17] Specific angiographic patterns include pulmonary artery webs or bands, intimal irregularities, abrupt stenoses of major pulmonary arteries, and obstruction of lobar or segmental arteries at their origins. Pulmonary angioscopy may also be performed.[17]

Therapy

Chronic anticoagulation is recommended in all patients (Tables 80.7 and 80.8, and Figure 80.2). The value of specific medical therapy is limited, and the most effective therapy is pulmonary thromboendarterectomy.[20] Preoperative predictors of a favourable outcome are PVR <1200 dyn.s.cm^{-5} and the absence of co-morbid conditions. A reduction in PA pressure after administration of inhaled nitric oxide is also indicative of a response to pulmonary thromboendarterectomy. In experienced centres, the intraoperative mortality is 5–10%.

In inoperable patients, the endothelin receptor antagonist bosentan, the phosphodiesterase inhibitor sildenafil, and prostacyclin analogues, such as treprostinil, may be used.[21–23] Recently, riociguat, a new oral stimulator of guanylate cyclase with vasodilating and antiproliferative activity, improved exercise capacity and quality of life.[24] In patients with sleep-disturbed breathing, nocturnal oxygen (3 L/min) and acetazolamide (250 mg bd) may be of help.[25]

The role of balloon angioplasty is not established. There is no specific treatment for (the usually fatal) pulmonary tumour thrombotic microangiopathy, apart from that directed at the underlying cancer.[26]

A summary of overall recommendations in patients with various forms of pulmonary hypertension is presented in Table 80.9.

Table 80.7 AHA 2011 Scientific statement on PE, IDVT and CTEPH. Recommendations for medical therapy and pulmonary endarterectomy in patients with CTEPH

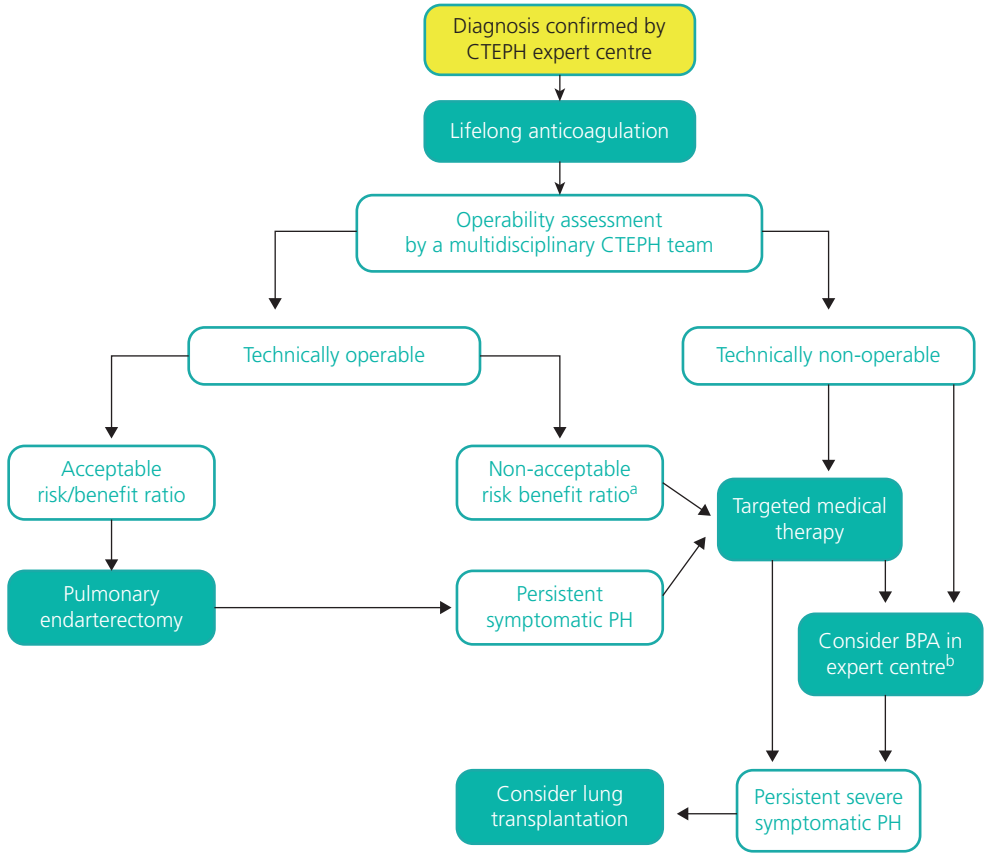
Patients with objectively proven CTEPH should be promptly evaluated for pulmonary endarterectomy, even if symptoms are mild.	I-B
Patients with objectively proven CTEPH should receive indefinite therapeutic anticoagulation in the absence of contraindications.	I-C
PAH (WHO Group I)-specific medical therapy for patients with CTEPH who are not surgical candidates (because of comorbidities or patient choice) or who have residual pulmonary hypertension after operation not amenable to repeat pulmonary endarterectomy at an experienced center	IIb-B
PAH (WHO Group I)-specific medical therapy should not be used in lieu of pulmonary endarterectomy or delay evaluation for pulmonary endarterectomy for patients with objectively proven CTEPH who are or may be surgical candidates at an experienced center.	III-B

Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: A scientific statement from the American Heart Association. *Circulation.* 2011;**123**:1788–1830 with permission from Wolters Kluwer.

Table 80.8 ESC 2015 GL on pulmonary hypertension. Chronic thromboembolic pulmonary hypertension

Consider CTEPH in PE survivors with exercise dyspnoea	IIa-C
Life-long anticoagulation in all patients with CTEPH	I-C
Assessment of operability and decisions regarding other treatment strategies by a multidisciplinary team of experts	I-C
Surgical pulmonary endarterectomy in deep hypothermia circulatory arrest for patients with CTEPH	I-C
Riociguat in symptomatic patients who have been classified as having persistent/recurrent CTEPH after surgical treatment or inoperable CTEPH by a CTEPH team including at least one experienced pulmonary endarterectomy surgeon	I-B
Off-label use of drugs approved for PAH in symptomatic patients who have been classified as having inoperable CTEPH by a CTEPH team including at least one experienced pulmonary endarterectomy surgeon	IIb-B
Interventional BPA in patients who are technically non-operable or carry an unfavourable risk:benefit ratio for pulmonary endarterectomy	IIb-C
Screening for CTEPH in asymptomatic survivors of PE is currently not recommended	III-C

BPA, balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; PE, pulmonary embolism.
ESC/ERS 2015 Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2016;**37**:67–119 with permission from Oxford University Press.



BPA, balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension; PH, pulmonary hypertension.
[a]Technically operable patients with non-acceptable risk/benefit ratio can be considered also for BPA.
[b]In some contexts medical therapy and BPA are initiated concurrently.

Figure 80.2 ESC 2015 GL on pulmonary hypertension. Treatment algorithm for chronic thromboembolic pulmonary hypertension.

ESC/ERS 2015 Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2016;**37**:67–119 with permission from Oxford University Press.

Table 80.9 ACCF/AHA Consensus Document 2009 on PH. Summary of recommendations in PH

1. Patients with PH require a thorough diagnostic evaluation to elucidate the roles of pulmonary venous hypertension, chronic lung disease with hypoxemia, and/or pulmonary thromboembolism to the pathogenesis of their disease. Accordingly, RHC, lung function and imaging studies, determination of arterial oxygen saturation (at rest, with activity, and overnight), and ventilation-perfusion scanning are all mandatory elements of the assessment of these patients.
2. Patients with PH related to pulmonary venous hypertension may be considered for PAH-specific therapy provided:
a. the cause of the pulmonary venous hypertension is first optimally treated; and
b. the PCWP is normal or only minimally elevated; and
c. the transpulmonary gradient (TPG) and PVR are significantly elevated; and
d. the patient's symptoms suggest that PAH-specific therapy may yield clinical benefit.
3. Patients with PH related to chronic lung disease and hypoxemia may be considered for PAH-specific therapy provided:
a. the chronic lung disease and hypoxemia are first optimally treated; and
b. the TPG and PVR are significantly elevated; and
c. the patient's symptoms suggest that PAH-specific therapy may yield clinical benefit.
4. Patients with chronic thromboembolic PH may be considered for PAH-specific therapy provided:
a. appropriate secondary preventative measures, including anticoagulation, has been instituted; and
b. PTE has been performed or is not indicated; and
c. the TPG and PVR are significantly elevated; and
d. the patient's symptoms suggest that PAH-specific therapy may yield clinical benefit.
5. Patients with PH following cardiac surgery may be considered for PAH-specific therapy provided:
a. the surgery and concomitant medical therapy provide optimal treatment of the underlying cardiac disease; and
b. the surgery and concomitant medical therapy result in a normal or only minimally elevated PCWP; and
c. the TPG and PVR remain significantly elevated; and
d. the patient's clinical condition suggests that PAH-specific therapy may yield clinical benefit.
Treatment of such patients with PAH-specific therapy should be undertaken with great care, as these treatments may result in an increase in fluid retention, left-sided cardiac filling pressures, and pulmonary edema, and result in clinical deterioration. Decisions about whether and how to treat such patients should be made on a case by case basis by experienced PH caregivers.

ACCF/AHA 2009 Expert consensus document on pulmonary hypertension. *Circulation*. 2009;**119**:2250–94 with permission from Wolters Kluwer.

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Part XVII

Infective endocarditis

Relevant guidelines

AHA 2015 Statement on endocarditis

Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: A scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;**132**:1435–86.

ESC 2015 guidelines on infective endocarditis

ESC 2015 Guidelines for the management of infective endocarditis. *Eur Heart J*. 2015;**36**:3075–128.

AHA/ACC 2014 Guidelines on valve disease

2014 AHA/ACC Guideline for the management of patients with valvular heart disease. *JACC* 2014;**63**:2438–88.

ESC 2012 guidelines on valve disease

Guidelines on the management of valvular heart disease. *Eur Heart J*. 2012;**33**:2451–96.

Chapter 81

Infective endocarditis

Definition

Infective endocarditis (IE) denotes infection of the endocardial surface of the heart. It most commonly involves heart valves (especially mitral and aortic) but may also occur at the site of a septal defect, on the chordae tendineae, or on the mural endocardium.[1–3] The characteristic lesion, a vegetation, is composed of a collection of platelets, fibrin, microorganisms, and inflammatory cells.[2] IE is either **acute** or **subacute-chronic**, and is usually classified in four categories: **native valve** endocarditis, **prosthetic valve** endocarditis (***early*** ie <1 year after valve surgery or ***late***), infective endocarditis in **intravenous drug users**, and **nosocomial** infective endocarditis.

Epidemiology

The incidence of IE ranges within 3–10 episodes/100 000 person-years, and has not changed over the past two decades.[1,2] In the western world, there is an increasing incidence of IE associated with a prosthetic valve and a possible decrease in patients with underlying rheumatic heart disease, which is more frequent in underdeveloped countries. New at-risk groups in developed countries include injection drug addicts, elderly with valvular sclerosis, people with prosthetic valves, patients on haemodialysis, and those with nosocomial exposure. IE is now more often an acute disease; most cases occur in patients over 60 years old, and men are more likely to be affected than women.[4,5] Prosthetic valve endocarditis is the most severe form of IE and occurs in 1–6% of patients with valve prostheses, with an incidence of 0.3–1.2% per patient-year.[5] Although endocarditis is an uncommon coexisting condition in bacterial meningitis (in 2% of patients and usually due to *Streptococcus pneumoniae* and *Staphylococcus aureus*), it is associated with a high rate of unfavourable outcome.[6]

Aetiology

According to the International Collaboration on Endocarditis Prospective Cohort Study, a multinational and multicentre study of 2781 adults with IE conducted at 58 sites in 25 countries, *Staphylococcus aureus* is currently the most common cause of IE in much of the world, followed by *viridans streptococci*, *enterococci*, and coagulase-negative *staphylococci*.[4] This finding was confirmed by the recent French AEPEI report.[7] Gram-positive organisms account for >80% of all cases (Figure 81.1). *Candida* is the most frequent cause of fungal endocarditis, and culture-negative IE comprise 5–12% of all cases.

Cardiac abnormalities that are associated with high risk of IE are prosthetic cardiac valves or prosthetic material used for cardiac valve repair, previous infective endocarditis, congenital conditions unrepaired or repaired with prosthetic material, and cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve (see Prophylaxis). However, 50% of cases of infective endocarditis develop in patients with no known history of valve disease.[1]

Pathophysiology

The primary event is bacterial adherence to damaged endocardium. Excoriation of the endothelium triggers coagulation, and is colonized by bacteria that attract monocytes to produce tissue factor and cytokines. Cytokines and procoagulant factors contribute to continuing enlargement of the infected coagulum that eventually creates the vegetation. Organisms, such as *Staphylococcus (S.) aureus*, streptococci, and enterococci, have surface adhesins that mediate attachment to the vegetation. *S. aureus* also carries fibronectin-binding proteins on its surface that are adhered to the endothelium through the affinity of integrins, proteins produced as a response of endothelial cells to local inflammation.[2] Microorganisms become enveloped within the vegetation and trigger further tissue factor production and platelet activation that both kill bacteria through microbicidal proteins and have procoagulant effects. Tissue invasion and abscess formation then follows. Infective endocarditis is more often due to Gram-positive than Gram-negative

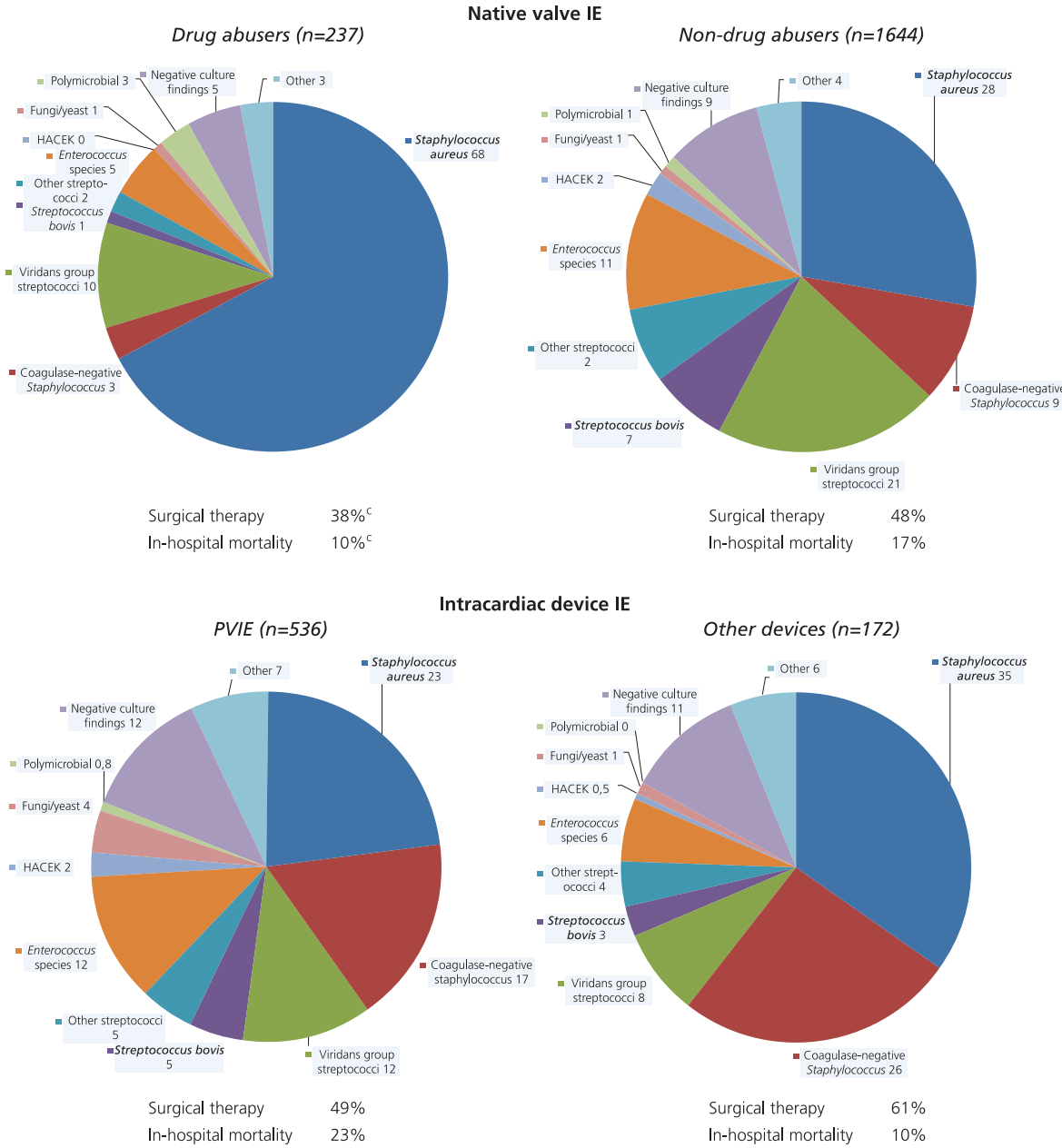


Figure 81.1 Microbiology of IE.

Numbers indicate percentages of patients. HACEK, bacteria consisting of *Haemophilus* species, *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens*, and *Kingella* species; IE, infective endocarditis; PVIE, prosthetic valve IE.
Data sourced from Murdoch DR, *et al.* Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. *Arch Intern Med*. 2009;**169**:463–732.

bacteria possibly because of differences in adherence to damaged valves or because of differences in their susceptibility to serum-induced killing.[2] Bacterial adherence is completed within minutes during transient bacteraemia that can be caused by various activities. There is now evidence that most cases of infective endocarditis are not attributable to an invasive procedure, and bacteraemia resulting from daily activities is much more likely to cause infective endocarditis than bacteraemia associated with a dental, or other, procedure. Thus, antibiotic prophylaxis in this setting is not mandatory.

Presentation

More than 90% of patients present with **fever**, often associated with systemic symptoms of malaise, anorexia, myalgias, and weight loss. Fever may be absent or minimal in patients with congestive heart failure, chronic renal or liver failure, previous use of antimicrobial drugs, or infective endocarditis caused by less virulent organisms, in the elderly, and in immunocompromised patients. **Embolic events** to the brain (>50% of emboli), spleen, or lung occur in 15–30% of patients with IE and may be the presenting feature.

Native valve endocarditis Degenerative lesions, such as mitral regurgitation and senile aortic stenosis, are present in up to 50% of patients with IE older than 60 years.[2] Mitral valve prolapse predisposes patients to IE, with an estimated incidence of 0.01% per patient-year of follow-up. The risk is significantly higher in the presence of flail leaflets and mitral regurgitation (1.5% per year).[8]

Prosthetic valve endocarditis is found in 5–25% of patients with IE.[3,4] It may be **early** (within 2 months post-operatively, usually due to *S. aureus*) or **late** (typically >12 months post-operatively), often due to streptococci and Gram-negative bacteria of the **HACEK** group. Although mechanical valves probably have a higher rate of infection during the first 3 months after surgery, similar rates with bioprostheses are seen later.[3] Prosthetic valve endocarditis may be manifested as an indolent illness with low-grade fever or it can be acute with new or changing murmurs and congestive heart failure. Unexplained fever in a patient with a prosthetic valve should prompt careful evaluation for prosthetic valve endocarditis.

In patients with **implanted devices**, clinical manifestations of pocket infection are present in the majority of patients with early lead-associated endocarditis (<6 months after device implantation). However, late lead-associated endocarditis should be considered in any patient who presents with fever, bloodstream infection, or signs of sepsis, even if the device pocket appears uninfected. Prompt recognition and management may improve outcomes.[9]

In **IV drug addicts**, IE usually occurs in the absence of pre-existing valve lesions. The tricuspid valve is affected in >50% of cases, but only one-third of patients have a murmur on admission. *S. aureus* is the most common pathogen (up to 70%), followed by streptococci, *Pseudomonas aeruginosa*, and **polymicrobial** causes (including **anaerobes**).[4,9,10] In HIV-positive IV drug abusers, the risk is inversely related to the CD4 count (4-fold higher if CD4 <200 cells/microlitre).[11]

Nosocomial endocarditis is defined as IE developing in patients hospitalized >48 h prior to the onset of symptoms or signs of IE.

Clinical features

Most, but not all, patients present with **fever**.[5]

Heart murmurs are found in up to 50% of patients while worsening of **old murmurs** is found in 20% of patients.[5]

Myoskeletal symptoms (arthralgia, myalgia, back pain) may appear early with the disease.

Peripheral stigmata of IE are increasingly uncommon (2–8%), as patients generally present at an early stage of the disease, are not pathognomonic, and are virtually absent in tricuspid valve endocarditis.

Splinter haemorrhages (linear petechiae in the mid-nailbed).

Osler's nodes (tender, raised nodules on the pads of fingers or toes).

Janeway's lesions (non-tender, slightly raised haemorrhages on palms and soles).

Conjunctival haemorrhage.

Roth's spots (haemorrhagic spots with a central white area in the retina).

Systemic embolism usually occurs to the **brain**, **spleen**, and **kidneys** or other organs in left-sided IE, and to **lungs** in right-sided IE (see Complications).

Neurological findings may be due to embolism or intracranial haemorrhage.

Heart failure may be seen with ensuing valve destruction or chordal rupture.

Diagnosis

Diagnostic schemes according to the **modified Duke criteria as considered** by AHA/ACC and ESC are presented in Table 81.1. The usefulness of Duke criteria has been validated in many studies worldwide.[12]

Transthoracic echocardiography has a sensitivity of 60–70% for detecting vegetations (Tables 81.2 and 81.3 and Figures 81.2 and 81.3).

Transoesophageal echocardiography is the first-line imaging modality. It increases sensitivity to 75–95% while maintaining specificity of 85–98%.[3] It is also more sensitive for detecting perivalvular extension of the infection, valve perforations, and myocardial abscess.

Cerebral angiography or **magnetic resonance angiography** is used for detection of intracranial mycotic aneurysms.

Table 81.1 Diagnosis of infective endocarditis (IE)

Diagnosis of IE according to the modified Duke Criteria (universally accepted)

Definite IE

Pathological criteria

- Microorganisms demonstrated by culture or on historlogical examination of a vegetation, a vegetation that has embolized, or an intracardiac absecess specimen; or
- Pathological lesions; vegetation or intracardiac abscess confimed by histological examination showing active endocaditis

Clinical criteria

- 2 major criteria; or
- 1 major criterion and 3 minor criteria; or
- 5 minor criteria

Possible IE

- 1 major criterion and 1 minor criterion; or
- 3 minor criteria

Rejected IE

- Firm alternate diagnosis; or
- Resolution of symptoms suggesting IE with antibiotic therapy for ≤4 days; or
- No pathological evidence of IE at surgery or autopsy, with antibiotic therapy for ≤ 4 days; or
- Does not meet criteria for possible IE, as above

AHA 2015 Statement on IE. Definition of terms used in the modified Duke Criteria for the diagnosis of IE	ESC 2015 GL on IE. Definitions of the terms used in the ESC 2015 modified criteria for the diagnosis of infective endocarditis
Major criteria	**Major criteria**
Blood culture positive for IE Typical microoganisms consistent with IE from 2 separate blood cultures: Viridans streptococci, Streptococcus bovis, HACEK group, ***Staphylococcus aureus***; or community-acquired enterococci in the absence of a primary focus, or microorganisms consistent with IE from persistently positive blood cultures defined as follows: at least 2 positive cultures of blood samples drawn >12 h apart or all 3 or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least 1 h apart). Single positive blood culture for *Coxiella burnetii* or anti–phase 1 IgG antibody titre ≥1:800 **Evidence of endocardial involvement** Echocardiogram positive for IE (**TEE recommended for patients with prosthetic valves, rated at least possible IE by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients**) defined as follows: oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; abscess; or new partial dehiscence of prosthetic valve or new valvular regurgitation (worsening or changing or pre-existing murmur not sufficient)	**1. Blood cultures positive for IE** a. Typical microorganisms consistent with IE from 2 separate blood cultures: • *Viridans streptococci, Streptococcus gallolyticus (Straptococcus bovis), HACEK group, Strephylococcus aureus; or* • Community-acquired enterococci, in the absence of a primary focus; or b. Microorganisms consistent with IE from persistently positive blood cultures: • ≥2 positive blood cultures of blood samples drawn >12 h apart; or • All of 3 or a mojority of ≥4 separate cultures of blood (with first and last samples drawn ≥1 h apart); or c. Single positive blood culture for Coxiella burnetii or phase I IgG antibody titre >1:800 **2. Imaging positive for IE** a. Echocardiogram positive for IE: • Vegetation; • Abscess, pseudoaneurysm, intracardiac fistula; • Valvular perforation or aneurysm; • New partial dehiscence of prosthetic valve. b. Abnormal activity around the site of prosthetic valve implantation detected by ^{18}F-FDG PET/CT (only if the prosthesis was implanted for >3 months) or radiolabelled leukocytes SPECT/CT. c. Definite paravalvular lesions by cardiac CT.

(*continued*)

Table 81.1 (Continued)

Minor criteria	Minor criteria
Predisposition, predisposing heart condition, or IDU	1. Predisposition such as predisposing heart condition, or injection drug use.
Fever, temperature >38°C	2. Fever defined as temperature >38°C.
Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival haemorrhages, and Janeway lesions	3. Vascular phenomena (including those detected by imaging only): major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway lesions.
Immunological phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor	4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor.
Microbiological evidence: positive blood culture but does not meet a major criterion as noted above (excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis) or serological evidence of active infection with organism consistent with IE	5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE.
Echocardiographic minor criteria eliminated	
HACEK indicates *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species; IDU, injection drug use; IE, infective endocarditis; IgG, immunoglobulin G; TEE transesophageal echocardiography; and TTE, transthoracic echocardiography.	

Infective endocarditis in adults: Diagnosis, antimicrobial therapy, and management of complications: A scientific statement for healthcare professionals from the American Heart Association. Circulation. 2015;**132**:1435–86.
CT: computed tomography; FDG: fluorodeoxyglucose; HACEK: Haemophilus parainfluenzae, H. aphrophilus, H. paraphrophilus, H. influenzae,Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae, and K. denitrificans;IE: infective endocarditis; Ig: immunoglobulin; PET: positron emission tomography; SPECT: single photon emission computerized tomography
2015 ESC Guidelines for the management of infective endocarditis. *Eur Heart J.* 2015;**36**:3075–128.

Table 81.2 AHA 2015 Statement on IE Diagnosis of IE

At least 3 sets of blood cultures obtained from different venipuncture sites should be obtained ,with the first and last samples drawn at least 1 hour apart	I-A
Echocardiography should be performed expeditiously in patients suspected of having IE	I-A
TTE should be performed in all cases of suspected IE	I-B
TEE should be done if initial TTE images are negative or inadequate in patients for whom there is an ongoing suspicion for IE or when there is concern for intracardiac complications in patients with an initial positive TTE	I-B
If there is a high suspicion of IE despite an initial negative TEE, then a repeat TEE in 3 to 5 days or sooner if clinical findings change	I-B
Repeat TEE should be done after an initially positive TEE if clinical features suggest a new development of intracardiac complications	I-B
TTE at the time of antimicrobial therapy completion to establish baseline features	IIa-C

Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals From the American Heart Association. Circulation. 2015;**132**:1435–86.

CT or **MRI** have limited value for diagnosing intracardiac infections, but can be useful for detection of cerebral bleeding and embolic events or splenic abscess. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET-CT is also a promising modality for detecting infection.[13,14]

ESR and **CRP** (elevated in >60% of patients), as well as **leucocytosis**, **anaemia**, and **microscopic haematuria**, may be present but are not specific.

Blood cultures In patients with possible infective endocarditis, three, or at least two, sets of cultures of blood (one aerobic and one anaerobic), collected by separate venepunctures, should be obtained within the first 1–2 hours of presentation. Patients with cardiovascular collapse should have three cultures of blood obtained at 5- to 10-minute intervals and thereafter receive empirical antibiotic therapy. For the main causative agents, the first two blood cultures may be positive in more than 90% of cases. Sampling from central venous catheters carries a high risk of contaminants (mainly staphylococci).

Culture-negative endocarditis occurs in 10–20% of IE patients. It is often associated with antibiotic use within the previous 2 weeks and fastidious (*Bartonella*, *Coxiella burnetii, HACEK* group, fungi) or intracellular pathogens (*Brucella, Rickettsiae, Chlamydia, Tropheryma whipplei*) that are not easily detected by standard culture conditions (Figures 81.4 and 81.5). Subacute right-sided IE, mural IE, and uraemia are other causes. Serologic testing, **polymerase-chain-reaction (PCR)** assay on valve samples or blood, and highly specialized

Table 81.3 ESC 2015 GL on endocarditis. Role of echocardiography in infective endocarditis

A. Diagnosis	
TTE as the first-line imaging modality in suspected IE.	I-B
TOE in clinical suspicion of IE and a negative or non-diagnostic TTE.	I-B
TOE in clinical suspicion of IE, when a prosthetic heart valve or an intracardiac device is present.	I-B
Repeat TTE and /or TOE within 5–7 days in case of initially negative examination when clinical suspicion of IE remains high.	I-C
Echocardiography in Staphylococcus aureus bacteraemia.	IIa-B
TOE in suspected IE, even in cases with positive TTE, except in isolated right-sided native valve IE with good quality TTE examination and unequivocal echocardiographic findings.	IIa-C
B. Follow-up under medical therapy	
Repeat TTE and/or TOE as soon as a new complication of IE is suspected (new murmur, embolism, persisting fever, HF, abscess, atrioventricular block).	I-B
Repeat TTE and/or TOE during follow-up of uncomplicated IE, in order to detect new silent complications and monitor vegetation size. The timing and mode (TTE or TOE) of repeat examination depend on the initial findings, type of microorganism, and initial response to therapy.	IIa-B
C. Intraoperative echocardiography	
Intraoperative echocardiography in all cases of IE requiring surgery.	I-B
D. Following completion of therapy	
TTE at completion of antibiotic therapy for evaluation of cardiac and valve morphology and function.	I-C

HF, heart failure; IE, infective endocarditis; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography.
ESC 2015 Guidelines for the management of infective endocarditis. *Eur Heart J*. 2015;**36**:3075–128 with permission from Oxford University Press.

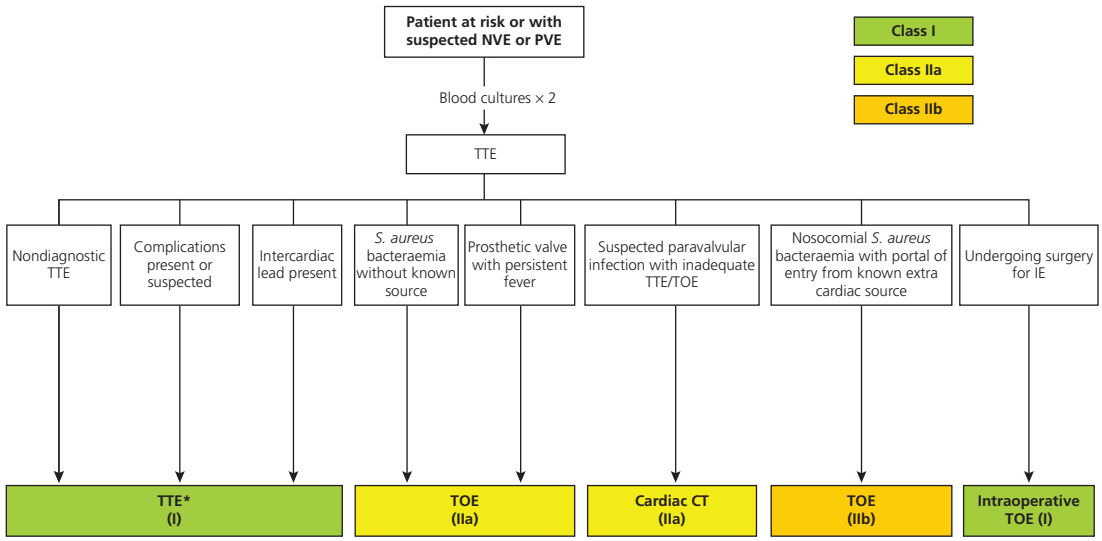
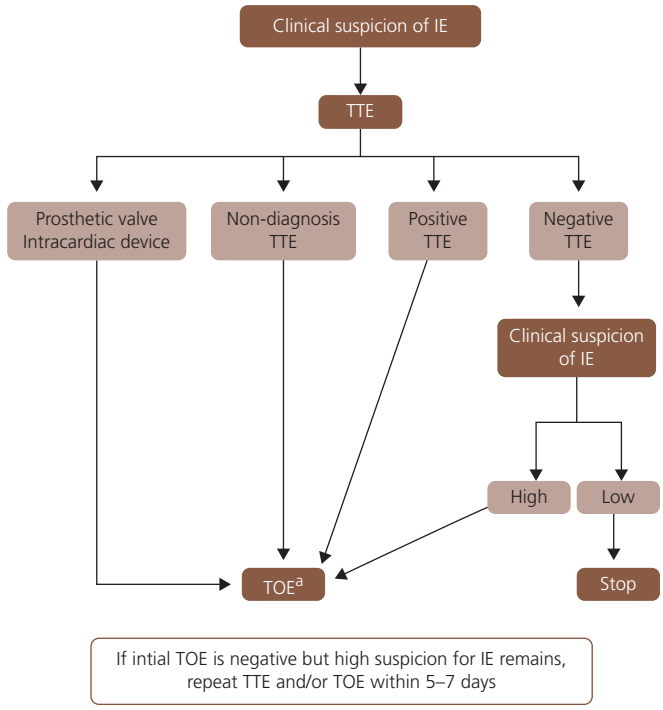


Figure 81.2 AHA/ACC 2014 GL on VHD. Recommendations for imaging studies in native and prosthetic valve endocarditis.

*Repeat TOE and/or TTE recommended for reevaluation of patients with IE and a change in clinical signs or symptoms and in patients at high risk of complications.
CT indicates computed tomography; IE, infective endocarditis; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis; *S. aureus*, *Staphylococcus aureus*; TEE, transoesophageal echocardiography; and TTE, transthoracic echocardiography.
AHA/ACC 2014 Guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:2438–88 with permission from Elsevier.

microbiologic techniques lead to the identification of the pathogen in up to 60% of cases.[1] PCR amplification of the 16S ribosomal RNA gene that is specific for bacteria in tissue samples, including valves and peripheral emboli, can remain positive even after long-term treatment with antibiotics.[15]

HACEK group are fastidious, Gram-negative bacilli that grow slowly in standard blood culture media, and recovery may require prolonged incubation. Thus, the microbiology laboratory should be asked to retain blood cultures for ≥2 weeks in all patients suspected of having IE but whose blood cultures are initially negative. Bacteraemia caused



IE = infective endocarditis; TOE = transesophageal echocardiography; TTE = transthoracic echocardiography.
[a]TOE is not mandatory in isolated right-sided native valve IE with good quality TTE examination and unequivocal echocardiographic findings.

Figure 81.3 ESC 2015 GL on IE. Indications for echocardiography in suspected infective endocarditis.
2015 ESC Guidelines for the management of infective endocarditis. *Eur Heart J*. 2015;**36**:3075–12

by HACEK microorganisms in the absence of an obvious focus of infection is highly suggestive of endocarditis, even in the absence of typical physical findings. HACEK IE is very uncommon in North America.[2]

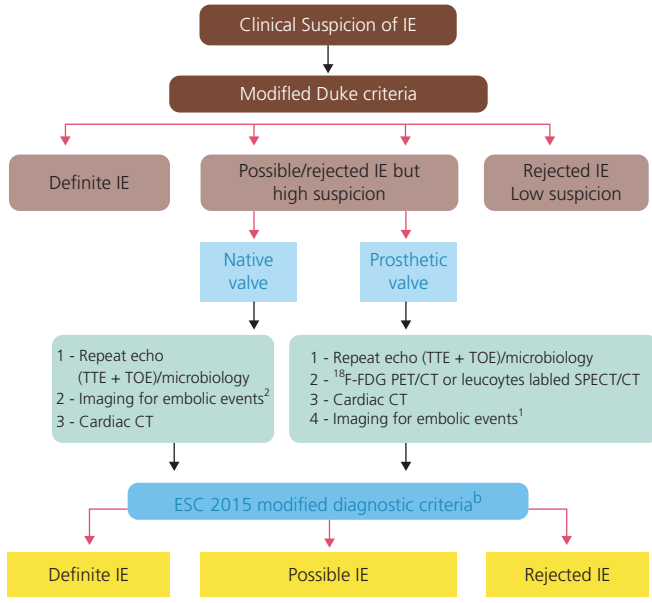
Q fever endocarditis (*Coxiella burnetii*) and *Bartonella* endocarditis are also more common in Europe than in North America.[4] Q fever IE (a zoonosis) is one of the most common causes of culture-negative IE. Serology (IgG phase 2 >1:800), tissue culture and immunohistology, and PCR of surgical material are needed for diagnosis of Q fever IE. *Bartonella* species (*B. quintana* and *B. henselae*) IE is a subacute form that may present with heart failure due to aortic regurgitation. Predisposing factors are alcoholism, homelessness, and exposure to body lice. Blood cultures, serology, culture and immunohistology, and PCR of surgical material are needed for identification of *Brucella* or *Bartonella* or *Legionella* species.

Serology, culture and immunohistology, and PCR of surgical material are needed for Mycoplasma species and histology and PCR of surgical material for identification of *Tropheryma whipplei*. Non-tuberculous mycobacteria is a rare cause of endocarditis following cardiac surgery.[16]

Blood cultures, serology, and PCR of surgical material are needed for diagnosis of *fungal* endocarditis.

Therapy

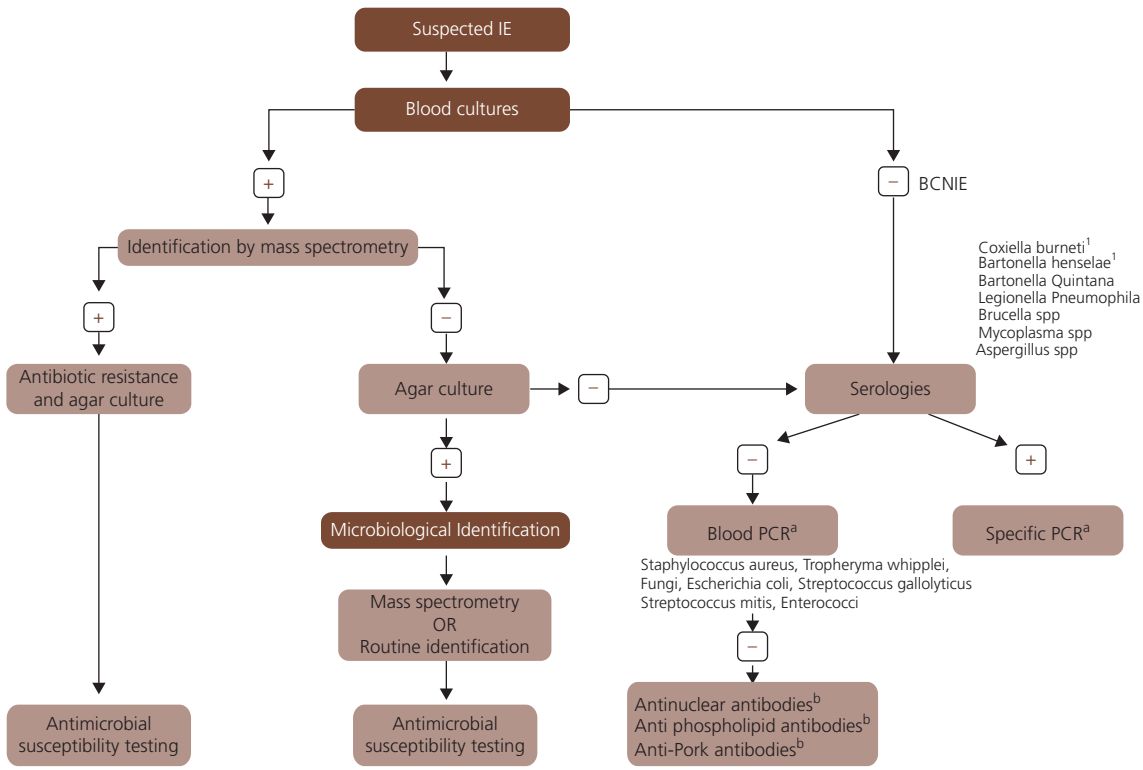
Management of endocarditis should be carried out ideally by a dedicated 'endocarditis team', consisting of cardiologists, cardiac surgeons, infectious diseases, and, if needed, ACHD specialists.[5] Appropriate antibiotic therapy should be initiated and continued after blood cultures are obtained with guidance from antibiotic sensitivity data and infectious disease consultants (AHA/ACC 2014 GL on VHD, I-B). Patients with known valve disease should not receive antibiotics before blood cultures are obtained for unexplained fever (AHA/ACC 2014 GL on VHD, III-C Harm). Epidemiological clues that may assist aetiologic diagnosis are provided in Table 81.4 and general recommendations on therapy in Table 81.5. Detailed antibiotic schemes have been published by the ACC/AHA and ESC



CT = computed tomography, FDG = fluorodeoxyglucose; IE = inefective endocarditis;
PET = position emission tomography; SPECT = single photon emission computerized tomography;
TOE = transesophageal echocardiography; TTE = transthoracic echocardiography.
'May include cerebral MRI, whole body CT, and/or PET/CT.
[b]See Table 82.1.

Figure 81.4 ESC 2015 GL on IE. Algorithm for diagnosis of infective endocarditis.

2015 ESC Guidelines for the management of infective endocarditis. *Eur Heart J*. 2015;**36**:3075–128, with permission of Oxford University Press.



BCNIE = blood culture-negative infective endocarditis; IE = infective endocarditis; PCR = polymerase chain reaction.
[a]Qualified microbiological laboratory
[b]Qualified microbiological laboratory

Figure 81.5 ESC 2015 GL on IE. Microbiological diagnostic algorithm in culture-positive and culture-negative IE.

ESC 2015 Guidelines for the management of infective endocarditis. *Eur Heart J*. 2015;**36**:3075–128 with permission from Oxford University Press.

Table 81.4 AHA 2015 Statement on IE. Epidemiological clues that may be helpful in defining the etiological diagnosis of culture-negative endocarditis

Epidemiological Feature	Common Microorganism
IDU	*S aureus*, including community-acquired oxacillin-resistant strains Coagulase-negative staphylococci β-Hemolytic streptococci Fungi Aerobic Gram-negative bacilli, including *Pseudomonas aeruginosa* Polymicrobial
Indwelling cardiovascular medical devices	*S aureus* Coagulase-negative staphylococci Fungi Aerobic Gram-negative bacilli *Corynebacterium* sp
Genitourinary disorders, infection, and manipulation, including pregnancy, delivery, and abortion	*Enterococcus* sp Group B streptococci (*S agalactiae*) *Listeria monocytogenes* Aerobic Gram-negative bacilli *Neisseria gonorrhoeae*
Chronic skin disorders, including recurrent infections	*S aureus* β-Hemolytic streptococci
Poor dental health, dental procedures	VGS Nutritionally variant streptococci *Abiotrophia defective* *Granulicatella* sp *Gemella* sp HACEK organisms
Alcoholism, cirrhosis	*Bartonella* sp *Aeromonas* sp *Listeria* sp *S pneumoniae* β-Hemolytic streptococci
Burn	*S aureus* Aerobic Gram-negative bacilli, including *P aeruginosa* Fungi
Diabetes mellitus	*S aureus* β-Hemolytic streptococci *S pneumoniae*
Early (≤1 y) prosthetic valve placement	Coagulase-negative staphylococci *S aureus* Aerobic Gram-negative bacilli Fungi *Corynebacterium* sp *Legionella* sp
Late (>1 y) prosthetic valve placement	Coagulase-negative staphylococci *S aureus* Viridans group streptococci *Enterococcus* species Fungi *Corynebacterium* sp
Dog or cat exposure	*Bartonella* sp *Pasteurella* sp *Capnocytophaga* sp
Contact with contaminated milk or infected farm animals	*Brucella* sp *Coxiella burnetti* *Erysipelothrix* sp
Homeless, body lice AIDS	*Bartonella* sp *Salmonella* sp *S pneumoniae* *S aureus*
Pneumonia, meningitis	*S pneumoniae*
Solid organ transplantation	*S aureus* *Aspergillus fumigatus* *Enterococcus* sp *Candida* sp
Gastrointestinal lesions	*S gallolyticus (bovis)* *Enterococcus* sp *Clostridium septicum*

HACEK indicates Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species; IDU, injection drug use; and VGS, viridans group streptococci.

Infective endocarditis in adults: Diagnosis, antimicrobial therapy, and management of complications: A scientific statement for healthcare professionals from the American Heart Association. Circulation. 2015;**132**:1435–86.

Table 81.5 AHA 2015 Statement on IE. Recommendations on therapy

Infectious diseases consultation to define an optimal empirical treatment regimen	I-B
The counting of days for the duration of antimicrobial therapy should begin on the first day on which blood cultures are negative in cases in which blood cultures were initially positive	IIa-C
Obtain at least 2 sets of blood cultures every 24 to 48 hours until bloodstream infection has cleared	IIa-C
Entire antimicrobial course after valve surgery if operative tissue cultures are positive	IIa-B
Count the number of days of antimicrobial therapy administered before surgery in the overall duration of therapy if operative tissue cultures are negative	IIb-C
Time the administration of antimicrobial therapy at the same time or temporally close together for regimens that include >1 antimicrobial agent	IIa-C

Infective endocarditis in adults: Diagnosis, antimicrobial therapy, and management of complications: A scientific statement for healthcare professionals from the American Heart Association. Circulation. 2015;**132**:1435–86.

(see Appendix 2). Therapy of IE is mostly based on expert opinion since no large randomized studies exist. Bactericidal antibiotics are indicated, and the choice of an optimum regimen is based on antibiotic susceptibility testing and minimum inhibitory concentrations (MIC) of the principal drugs for the infecting pathogens. Due to the inoculum effect, ie reduced antimicrobial activity on highly dense bacterial populations, the effective MIC can be much higher than anticipated by in vitro susceptibility tests.[10] Prolonged therapy (4–6 weeks) is usually necessary for the avoidance of relapses. Therapy can be switched to oral route once fever has subsided and blood cultures are negative.[5]

Streptococci are common pathogenic agents in community-acquired native valve endocarditis. The taxonomy of these organisms is evolving, and certain species have biological characteristics that may complicate diagnosis and therapy.[10] Resistance to penicillin and other b lactams (intermediate resistance MIC: 0.12 μg/L, high resistance: MIC>0.5 μg/L) may be seen in viridans group *steptococci* (a-hemolytic) and *S gallolyticus (bovis)*-a nonenterococcal group D *streptococcus*).

Traditionally, coagulase-positive **staphylococci** (*S. aureus*) cause primarily native valve endocarditis whereas coagulase-negative staphylococci (*S. epidermidis* and various other species) cause primarily prosthetic valve endocarditis, but considerable overlap exists. *S. aureus* is now the most common cause of IE in the developed world.[4] **Methicillin-resistant staphylococci** (MRSA) are also resistant to most other antibiotics (including quinolones), and vancomycin resistance is also beginning to develop. No standard therapies exist for the treatment of *S aureus* IE caused by isolates that are not susceptible to vancomycin. Classification of these isolates has become complex and includes designations of reduced susceptibility (hVISA), intermediate resistance (VISA), and high-level resistance (VRSA). Daptomycin is an effective alternative to vancomycin/gentamicin for MRSA endocarditis, and linezolid, quinupristin-dalfopristin, telavancin, and ceftaroline may also be effective.[10]

Enterococcal IE typically occurs in older male patients with urinary tract infection or instrumentation. The morbidity and mortality of enterrococcal endocarditis are high with increasing resistance to aminoglycosides. Multidrug-resistant enterococci are also resistant to vancomycin (VRE) and cause infections of increased morbidity and mortality.

Fungal endocarditis is rare but can develop in a wide range of patients. The well-recognized risk factors associated with fungal endocarditis, such as IV dugs abuse and immunocompromised state, have become less prevalent compared with the presence of a cardiovascular device, including central venous catheters, permanent pacemakers and defibrillators, and prosthetic valves.[10] Valve replacement is usually needed (AHA 2015 statement on IE, I–B). In treated cases, chronic lifelong suppression with an oral azole is recommended (AHA 2015 statement on IE, IIa-B), especially in patients who were not suitable for valve replacement.

The management of **culture-negative endocarditis** is presented in Tables 81.6 and 81.7. Predictors of poor outcome are presented in Table 81.8.

The management of **IE related to cardiac devices** is discussed in Chapter 70 on cardiac devices.

Regardless of the source of infection, inpatients with IE should be thoroughly evaluated by a ***dentist*** familiar with the potential role of the mouth in these cases. The optimal timing for this evaluation may be after the patient's cardiac status has stabilized, and early enough that all invasive dental procedures can be accomplished during intravenous antibiotic therapy. The clinical examination should rule out periodontal inflammation and pocketing around the teeth and caries that will eventually result in pulpal infection. A full series of intraoral radiographs is required for the identification of caries and periodontal disease (eg bone loss, tooth fractures) (AHA 2015 statement on IE, I-C).

Criteria for outpatient therapy are presented in Table 81.9.

Table 81.6 AHA 2015 Statement on IE. Culture-negative endocarditis

An evaluation of epidemiological factors, history of prior infections including cardiovascular infections, exposure to antimicrobials, clinical course, severity, and extracardiac sites of infection of the current infection should be performed in all culture-negative endocarditis cases	I-C
Consultation with an infectious diseases specialist to define the most appropriate choice of therapy in patients with culture-negative endocarditis	I-C
In acute (days) clinical presentation of native valve infection, coverage for *S aureus,* β-hemolytic streptococci, and aerobic Gram-negative bacilli	IIa-C
In subacute (weeks) presentation of native valve endocarditis, coverage of *S aureus*, VGS, HACEK, and enterococci	IIa-C
In culture-negative PVE, coverage for staphylococci, enterococci, and aerobic Gram-negative bacilli if onset of symptoms is within 1 year of prosthetic valve placement	IIa-C
If symptom onset is >1 year after valve placement, then IE is more likely to be caused by staphylococci, VGS, and enterococci, and antibiotic therapy for these potential pathogens is reasonable	IIa-C
If subsequent blood culture results or other laboratory methodologies define a pathogen, then empirical therapy should be revised to focused therapy for the specific pathogen identified	I-C

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Table 81.7 ESC 2015 GL. Empirical therapy of endocarditis. Antibiotic treatment of blood culture-negative infective endocarditis

Pathogens	Proposed therapy[a]	Treatment outcome
Brucella spp.	Doxycycline (200 mg/24 h) plus co-trimoxazole (960 mg/12 h) plus rifampin (300–600/24 h for ≥3–6 months[b] orally)	Treatment success defined as an antibody titre <1:60. Some authors recommend adding gentamicin for the first 3 weeks.
C. burnetii (agent of Q fever)	Doxycycline (200 mg/24 h) plus hydroxychloroquine (200–600 mg/24 h)[c] orally (>18 months of treatment)	Treatment success defined as anti-phase 1 IgG titre <1:200, and IgA and IgM titres <1:50
Bartonella spp.[d]	Doxycycline 100 mg/24 h orally for 4 weeks plus gentamicin (3 mg/24h) IV for 2 weeks	Treatment success expected in ≥90%.
Legionella spp,	Levofloxacin (500 mg/12 h) IV or orally for ≥6 weeks or clarithromycin (500 mg/12 h IV for 2 weeks, then orally for 4 weeks plus rifampin (300–1200 mg/24 h)	Optimal treatment unknown.
Mycoplasma spp.	Levofloxacin (500 mg/12 h) IV or orally for ≥6 months[e]	Optimal treatment unknown.
T. whipplei (agent of Whipple's disease)[f]	Doxycycline (200 mg/24 h) plus hydroxychloroquine (200–600 mg/24 h)[c] orally for ≥18 months	Long-term treatment, optimal duration unknown.

Proposed antibiotic regimens for initial empirical treatment of infective endocarditis in acute severely ill patients (before pathogen identification)[g]

Antibiotic	Dosage and route	Class	Level	Comments
Community-acquired native valves or late prosthetic valves (≥12 months post surgery) endocarditis				
Ampicillin with (Flu)cloxacillin or oxacillin with gentamicin[h]	12 g/day IV in 4–6 doses 12 g/day IV in 4–6 doses 3 mg/kg/day IV or IM in 1 dose	IIa	C	Patients with BCNIE should be treated in consultation with an ID specialist.
Vancomycin[h] with gentamicin[h]	30–60 mg/kg/day IV in 2–3 doses 3 mg/kg/day IV or IM in 1 dose	IIb	C	For penicillin-allergic patients

(*continued*)

Table 81.7 (Continued)

Early PVE(<12 months post surgery) or nosocomial and non-nosocomial healthcare associated endocarditis				
Vancomycin[h] with gentamicin[h] with rifampin	30 mg/kg/day IV in 2 doses 3 mg/kg/day IV or IM in 1 dose 900–1200 mg IV or orally in 2 or 3 divided does	IIb	C	Rifampin is only recommended for PVE and it should be started 3–5 days later than vancomycin and gentamicin has been suggested by some experts. In healthcare associated native value endocarditis, some experts recommend in settings with a prevalence of MRSA infections > 5% the combination of cloxacillin plus vancomycin until they have the final *S. aureus* identification

BCNIE, blood culture-negative infective endocarditis; ID, infectious disease; IE, infective endocarditis; Ig, immunoglobulin; IM, intramuscular; IV, intravenous; PVE, prosthetic valve endocarditis; U, units.

[a] Owing to the lack of large series, the optimal duration of treatment of IE due to these pathogens is unknown. The presented durations are based on selected case reports. Consultation with an ID specialist is recommended.

[b] Addition of streptomycin (15 mg/kg/24 h in 2 doses) for the first few weeks is optional.

[c] Doxycycline plus hydroxychloroquine (with monitoring of serum hydroxychloroquine levels) is significantly superior to doxycycline.

[d] Several therapeutic regimens have been reported, including aminopenicillins (ampicillin or amoxicillin, 12 g/24 h i.v.) or cephalosporins (ceftriaxone, 2 g/24 h i.v.) combined with aminoglycosides (gentamicin or netilmicin). Dosages are as for streptococcal and enterococcal IE.

[e] Newer fluoroquinolones (levofloxacin, moxifloxacin) are more potent than ciprofloxacin against intracellular pathogens such as Mycoplasma spp., Legionella spp., and Chlamydia spp.

[f] Treatment of Whipple's IE remains highly empirical. In the case of central nervous system involvement, sulfadiazine 1.5 g/6 h orally must be added to doxycycline. An alternative therapy is ceftriaxone (2 g/24 h i.v.) for 2–4 weeks or penicillin G (2 million U/4 h) and streptomycin (1 g/24 h) i.v. for 2–4 weeks followed by co-trimoxazole (960 mg/12 h) orally.
Trimethoprim is not active against T. whipplei. Successes have been reported with long-term therapy (>1 year).

[g] If initial blood cultures are negative and there is no clinical response, consider BCNIE aetiology and maybe surgery for molecular diagnosis and treatment, and extension of the antibiotic spectrum to blood culture-negative pathogens (doxycycline, quinolones) must be considered.

[h] Monitoring of gentamicin or vancomycin dosages

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Table 81.8 ESC 2015 GL on infective endocarditis. Predictors of poor outcome in patients with infective endocarditis

Patient characteristics
Older age
Prosthetic valve IE
Diabetes mellitus
Comorbidity (e.g., frailty, immunosuppression, renal or pulmonary disease)
Clinical complications of IE
Heart failure
Renal failure
>Moderate area of ischaemic stroke
Brain haemorrhage
Septic shock
Microorganism
Staphylococcus aureus
Fungi
Non-HACEK Gram-negative bacilli
Echocardiographic findings
Periannular complications
Severe left-sided valve regurgitation
Low left ventricular ejection fraction
Pulmonary hypertension
Large vegetations
Severe prosthetic valve dysfunction
Premature mitral valve closure and other signs of elevated diastolic pressures

HACEK, *Haemophilus parainfluenzae, H. aphrophilus, H. paraphrophilus, H. influenzae, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae,* and *K. denitrificans;* IE, infective endocarditis.

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Table 81.9 ESC 2015 GL on infective endocarditis. Criteria that determine suitability of outpatient parenteral antibiotic therapy for infective endocarditis

Phase of treatment	Guidelines for use
Critical phase (weeks 0–2)	Complications occur during the phase Preferred Inpatient treatment during this phase Consider OPAT if: oral streptococci or Streptococcus bovis,[a] native value,[b] patient stable, no complications
Continuation phase (beyond week 2)	Consider OPAT if medically stable Do not consider OPAT if: HF, concerning echocardiographic features, neurological signs, or renal impairment
Essential for OPAT	Educate patient and staff Regular post-discharge evaluation (nurses 1/day physician[c] in charge 1 or 2/week)[d] Prefer physician-directed programme, not home-infusion model

AHA 2015 statement on IE. Outpatient therapy	
Patients should first be evaluated and stabilized in the hospital before being considered for outpatient therapy	I-C
Patients should be at low risk for the complications of IE, the most frequent of which are heart failure and systemic emboli	I-C

HF, heart failure; ID, infectious disease; IE, infective endocarditis; OPAT, outpatient parenteral antibiotic therapy; PVE, prosthetic valve endocarditis.

[a] For other pathogens, consultation with an ID specialist is recommended.

[b] For patients with late PVE, consultation with an ID specialist is recommended.

[c] Preferably from the Endocarditis Team.

[d] General physician can see the patient once a week, if needed.

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Complications

Heart failure due to valve destruction, **uncontrolled infection**, and **embolic phenomena** are the most common complications of IE, and constitute indications for valve replacement. Other indications for surgery are presented in Tables 81.10 and 81.11, and Figure 81.6. Surgery may also be needed for endocarditis due to organisms that are difficult to eradicate, such as *Pseudomonas aeruginosa*, *Brucella*, *Coxiella burnetii*, and fungi, and IE on prosthetic valves. Surgical mortality in active IE is 6–25%. When surgery is performed within the first week of antibiotic treatment, there may be increased risk of relapse and prosthetic-valve dysfunction.[17] However, in the recent randomized EASE trial, early surgery was beneficial in patients with left-sided infective endocarditis, severe valve disease, and large vegetations.[18] There is now evidence of an association between early surgery and lower mortality in endocarditis.[10] Valvular surgery should be deferred when cerebral haemorrhage is present.[19] Mechanical and biological prostheses have similar outcome. If blood cultures are still negative at the time of surgery, a sample of valve tissue should be obtained for culture, and a broad-range PCR assay should be performed to help identify the causative microorganism. Approximately one-quarter of patients with surgical indications did not undergo surgery in the international (ICE-PLUS) cohort. Factors associated with non-surgical treatment were a history of moderate/severe liver disease, stroke before surgical decision, and *Staphyloccus aureus* aetiology.[20]

Table 81.10 ESC 2015 GL on Endocarditis. Surgery. Indications and timing of surgery in left-sided valve infective endocarditis (native valve endocarditis and prosthetic valve endocarditis)

Indications for surgery		Timing[a]
Heart failure		
Aortic or mitral NVE or PVE with severe acute regurgitation, obstruction or fistula causing refractory pulmonary oedema or cardiogenic shock	I-B	Emergency
Aortic or mitral NVE or PVE with severe regurgitation or obstruction causing symptoms of HF or echocardiographic signs of poor haemodynamic tolerance	I-B	Urgent
Uncontrolled infection		
Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)	I-B	Urgent
Infection caused by fungi or multiresistant organisms	I-C	Urgent/elective
Persisting positive blood cultures despite appropriate antibiotic therapy and adequate control of septic metastatic foci	IIa-B	Urgent
PVE caused by staphylococci or non-HACEK gram-negative bacteria	IIa-C	Urgent/elective
Prevention of embolism		
Aortic or mitral NVE or PVE with persistent vegetations >10 mm after one or more embolic episodes despite appropriate antibiotic therapy	I-B	Urgent
Aortic or mitral NVE with vegetations >10 mm, associated with severe valve stenosis or regurgitation, and low operative risk	IIa-B	Urgent
Aortic or mitral NVE or PVE with isolated very large vegetations (>30 mm)	IIa-B	Urgent
Aortic or mitral NVE or PVE with isolated large vegetations (>15 mm) and no other indication for surgery[b]	IIb-C	Urgent
Indications for surgical treatment of right-sided infective endocarditis		
Surgical treatment should be considered in the following scenarios:	IIa-C	
Microorganisms difficult to eradicate (e.g. persistent fungi) or bacteraemia for > 7 days (e.g. S. aureus, P. aeruginosa) despite adequate antimicrobial therapy or		
Persistent tricuspid valve vegetations > 20 mm after recurrent pulmonary emboli with or without concomitant right heart failure or		
Right heart failure secondary to severe tricuspid regurgitation with poor response to diuretic therapy		

HACEK, *Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus, Haemophilus influenzae, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae* and *Kingella denitrificans;* HF, heart failure; IE, infective endocarditis; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis.

[a] Emergency surgery: surgery performed within 24 h; urgent surgery: within a few days; elective surgery: after at least 1–2 weeks of antibiotic therapy.

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Table 81.11 AHA 2015 statement on IE. Surgery in IE (similar recommendations by ACC/AHA 2014 GL on valve disease)

Early valve surgery in left-sided native valve endocarditis	
Early surgery (during initial hospitalization and before completion of a full course of antibiotics) in valve dysfunction resulting in heart failure	I-B
IE caused by fungi or highly resistant organisms (eg, vancomycin-resistant *Enterococcus*, multidrug-resistant Gram-negative bacilli)	I-B
IE complicated by heart block, annular or aortic abscess, or destructive penetrating lesions	I-B
Persistent infection (manifested by persistent bacteremia or fever lasting >5–7 days and provided that other sites of infection and fever have been excluded) after the start of appropriate antimicrobial therapy	I-B
Recurrent emboli and persistent or enlarging vegetations despite appropriate antibiotic therapy	IIa-B
Severe valve regurgitation and mobile vegetations >10 mm	IIa-B
Mobile vegetations >10 mm, particularly when involving the anterior leaflet of the mitral valve	IIb-C
And associated with other relative indications for surgery	
Early valve surgery in prosthetic valve endocarditis	
Heart failure resulting from valve dehiscence, intracardiac fistula, or severe prosthetic valve dysfunction	I-B
Persistent bacteremia despite appropriate antibiotic therapy for 5 to 7 days in whom other sites of infection have been excluded	I-B
IE complicated by heart block, annular or aortic abscess, or destructive penetrating lesions	I-B
PVE caused by fungi or highly resistant organisms	I-B
PVE with recurrent emboli despite appropriate antibiotic treatment	IIa-B
Relapsing PVE	IIa-C
Mobile vegetations >10 mm	IIb-C
Early valve surgery in right-sided endocarditis	
Patients with certain complications	IIa-C
Valve repair rather than replacement when feasible	I-C
An individualized choice of prosthesis by the surgeon if valve replacement is performed	IIa-C
Avoid surgery when possible in patients who are IV drug abusers	IIa-C
Valve surgery in patients with prior emboli/ hemorrhage/stroke	
Stroke or subclinical cerebral emboli and residual vegetation if intracranial hemorrhage has been excluded by imaging studies and neurological damage is not severe (ie, coma)	IIb-B
Delay valve surgery for at least 4 weeks in major ischemic stroke or intracranial hemorrhage	IIa-B

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Heart failure may be seen in up to 40% of IE cases and is most commonly associated with aortic than mitral regurgitation. Urgent surgery is indicated in unstable patients; otherwise, stable AR or MR are dealt with after eradication of the infection.

Uncontrolled infection Fever associated with infective endocarditis often resolves within 2 to 3 days after the initiation of appropriate antimicrobial treatment in patients with less virulent pathogens, and defervescence occurs in the majority of patients by the end of the second week of treatment. The most common causes of persistent fever (>14 days) are infection due to resistant organisms, extension of infection beyond the valve (often with myocardial abscess, pseudoaneurysm, or fistula), other nosocomial infection, pulmonary embolism, and drug hypersensitivity (particularly if the fever resolves and then recurs). Perivalvular extension is suspected in cases of persistent fever or new AV block. Perivalvular abscess is more common in aortic IE, and especially in prosthetic valve IE (50–100%). The presence of persistent positive blood cultures is an independent risk factor for in-hospital mortality which doubles the risk of death of patients with left-sided endocarditis.[21]

Embolic events are related to migration of vegetations. They are more often seen with large vegetations (>10 mm) and *S. aureus* or *Candida* IE. Age, diabetes, AF and embolism before antibiotics are also associated with embolism.[22] Reported incidence is 20–40% but much lower after initiation of suitable antibiotic therapy (6–12%). Aspirin does not reduce the risk of embolization.[23] The risk is during the first 2 weeks of treatment and with large (>10 mm and especially >15 mm) and mobile vegetations. The role of anticoagulants in IE is

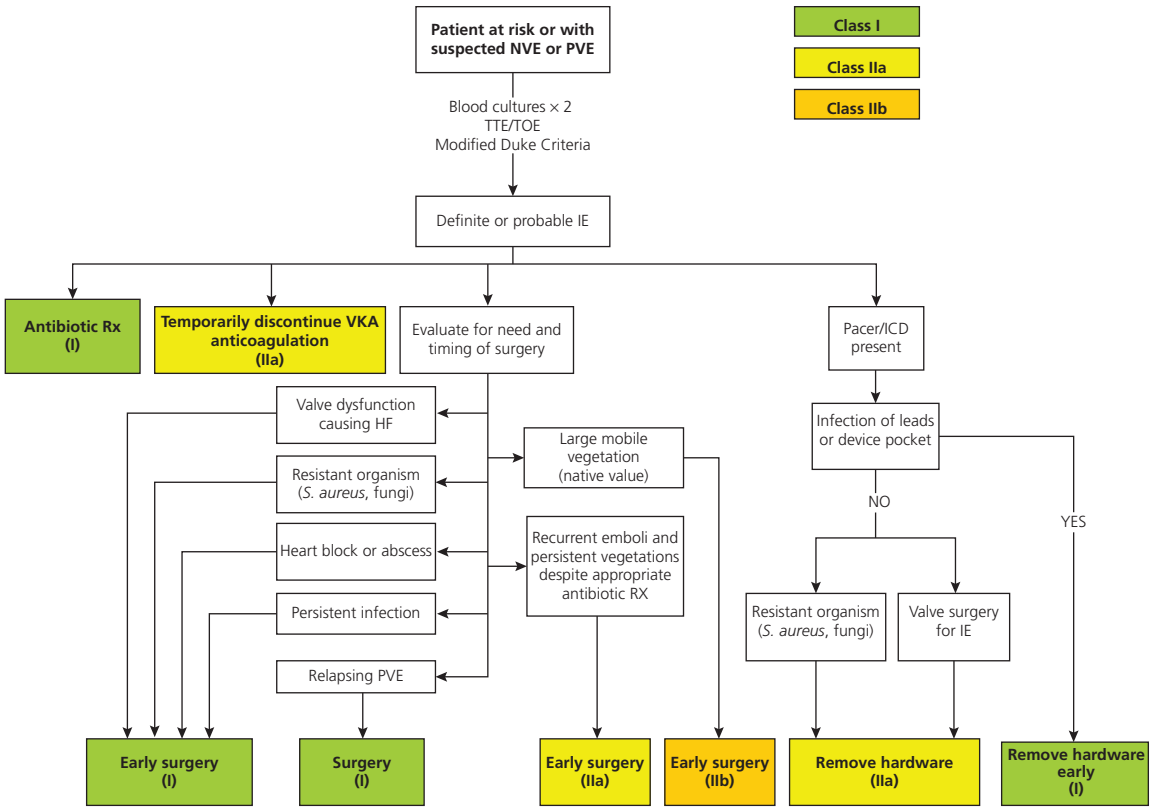

Figure 81.6 AHA/ACC 2014 GL on VHD. Diagnosis and treatment of IE.

* Early surgery defined as during initial hospitalization before completion of a full therapeutic course of antibiotics.
HF indicates heart failure; ICD, implantable cardioverter-defibrillator; IE, infective endocarditis; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis; Rx, therapy; *S. aureus*, *Staphylococcus aureus*; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography; and VKA, vitamin K antagonist.
AHA/ACC 2014 Guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol.* 2014;**63**:2438–88 with permission from Elsevier.

controversial. Temporary discontinuation of anticoagulation until the septic phase of the disease is overcome may be useful in cases of *S. aureus* endocarditis.[19] Recommendations are provided in Table 81.12.

Neurological complications may be due to emboli (usually middle cerebral artery), intracranial haemorrhage due to mycotic aneurysms that result from septic embolization of vegetations to the arterial vasa vasorum, or due to rupture of an artery related to septic arteritis at the site of embolism. Vegetation size ≥3 cm, *Staphylococcus aureus* as the causative microorganism, and involvement of the mitral valve are risk factors related to the development of neurological complications, whereas early and appropriate antimicrobial treatment reduce their incidence.[19] Unruptured aneurysms may resolve with antibiotic therapy alone, and patients should be followed with serial angiography performed to document the resolution of the aneurysm. Endovascular treatment should be pursued only if the aneurysm is very large (e.g. >10 mm) or if it is not resolving or is enlarging despite treatment with antibiotics. The management of neurological complications is presented in Table 81.13.

Glomerulonephritis is immune complex-mediated (15% of patients with IE). Renal embolism may cause haematuria (25% of patients) but rarely azotaemia. Antibiotic-induced interstitial nephritis (mainly with aminoglycosides and vancomycin), or severe haemodynamic impairment may also contribute.

Pyogenic spondylodiscitis, **peripheral arthritis**, and **myopericarditis** may also be seen. Splenic emboli are common, but **splenic abscess** is rare. CT angiography, magnetic resonance angiography, or digital subtraction angiography can be used for detection of intracranial or extracranial **mycotic aneurysms** (AHA 2015 statement on IE, IIa-B). Cerebrospinal imaging can be used to detect intracranial mycotic aneurysms or CNS bleeding in all patients with IE or contiguous spread of infection who develop severe, localized headache, neurological deficits, or meningeal signs (AHA 2015 statement on IE, I-B).

Table 81.12 Anticoagulation and antithrombotic therapy in IE

AHA 2015 Statement on IE (similar recommendations by ACC/AHA 2014 GL on valve disease)	
Discontinuation of all forms of anticoagulation in patients with mechanical valve IE who have experienced a CNS embolic event for at least 2 weeks	IIa-C
Continuation of long-term antiplatelet therapy at the time of development of IE with no bleeding complications may be considered	IIb-B
Aspirin or other antiplatelet agents as adjunctive therapy in IE is not recommended	III-B
ESC 2015 GL on infective endocarditis. Recommendations for the use of antithrombotic therapy	
Interruption of antiplatelet therapy in the presence of major bleeding	I-B
In intracranial haemorrhage, interruption of all anticoagulation	I-C
In ischaemic stroke without haemorrhage, replacement of oral anticoagulant (anti-vitamin K) therapy by UFH or LMWH for 1–2 weeks under close monitoring[a]	IIa-C
Reinitiate as soon as possible UFH or LMWH in patients with intracranial haemorrhage and a mechanical valve following multidisciplinary discussion	IIa-C
In the absence of stroke, replacement of oral anticoagulant therapy by UFH or LMWH for 1–2 weeks, in the case of Staphylococcus aureus IE under close monitoring	IIa-C
Thrombolytic therapy is not recommended in patients with IE	III-C

IE, infective endocarditis; UFH, unfractionated heparin; LMWH, low molecular weight heparin.
[a] There is very limited experience with new oral anticoagulant treatment in the field of IE.
AHA/ACC 2014 Guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:2438–88 with permission from Elsevier.
ESC 2015 Guidelines for the management of infective endocarditis. *Eur Heart J*. 2015;**36**:3075–128 with permission from Oxford University Press.

Table 81.13 ESC 2015 GL on endocarditis. Management of neurological complications

After a silent embolism or transient ischaemic attack, cardiac surgery, if indicated, without delay	I-B
Neurosurgery or endovascular therapy for very large, enlarging or ruptured intracranial infectious aneurysms	I-C
Postopone surgery for ≥1 month following intracranial haemorrhage	IIa-B
After a stroke, as long as coma is absent and the presence of cerebral haemorrhage has been excluded by cranial CT or MRI, surgery indicated for HF, uncontrolled infection, abscess, or persistent high embolic risk, without any delay	IIa-B
Look for intracranial infectious aneurysms in patients with IE and neurological symptoms. CT or MR angiography for diagnosis. Conventional angiography if non-invasive techniques are negative and the suspicion of intracranial aneurysm remain	IIa-B

CT, computed tomography; HF, heart failure; IE, infective endocarditis; MR, magnetic resonance; MRI, magnetic resonance imaging.
ESC 2015 Guidelines for the management of infective endocarditis. *Eur Heart J*. 2015;**36**:3075–128 with permission from Oxford University Press.

Prognosis

Increased age, pulmonary oedema, paravalvular complications, prosthetic valve IE, and staphylococcal IE are prognostic factors for in-hospital mortality.[2] Mortality rates vary according to the offending organism and range from approximately 10% with viridans streptococci, 25–45% with *S. aureus*, to >50% with fungi (mainly *Candida* and *Aspergillus*) and *P. aeruginosa*. Q fever IE also carries a high mortality. Overall mortality is 15–25%, ranging from 10% for right-sided, to up to 40% for left-sided IE, whereas operative mortality again depends on the underlying condition and varies between 5 and 15%.[1,4] Relapses usually occur within 2 months of discontinuation of therapy, in 2–6% of patients. Main risk factors are inadequate duration of antibiotic therapy or the presence of resistant organisms, persistent focus of infection (i.e. abscess), and prosthetic valve endocarditis (Table 81.14).[24,25] In a recent report of the ENDOREA Study Group, factors associated with adverse long-term outcomes were the severity of multiorgan failure (the strongest independent predictor), prosthetic mechanical valve IE, vegetation size ≥15 mm, and surgical treatment, but not surgical timing.[24] It is estimated that the average long-term survival rates after the completion of treatment for IE is 80–90% at 1 year, 70–80% at 2 years and 60–70% at 5 years.[5] Thus, endocarditis survivors have an increased morbidity and mortality after successful therapy, and long-term surveillance is recommended.

Table 81.14 ESC 2015 GL on endocarditis. Factors associated with an increased rate of relapse

Inadequate antibiotic treatment (agent, dose, duration)
Resistant microorganisms, i.e. Brucella spp., Legionella spp., Chlamydia spp., Mycoplasma spp., Mycobacterium spp., Bartonella spp., Coxiella Burnetii, fungi
Polymicrobial infection in an IVDA
Empirical antimicrobial therapy for BCNIE
Periannular extension
Prosthetic valve IE
Persistent metastatic foci of infection (abscesses)
Resistance to conventional antibiotic regimens
Positive valve culture
Persistence of fever at the seventh postoperative day
Chronic dialysis

BCNIE, blood culture-negative infective endocarditis; IE, infective endocarditis; IVDA, intravenous drug abuser.
ESC 2015 Guidelines for the management of infective endocarditis. *Eur Heart J.* 2015;**36**:3075–128 with permission from Oxford University Press.

Pregnancy

The incidence of IE during pregnancy has been reported to be 0.006%[3] and is either a complication of a pre-existing cardiac lesion or the result of intravenous drug abuse. Maternal and foetal mortality are approximately 30%, with most deaths relating to heart failure or an embolic event. Close attention should be paid to any pregnant woman with unexplained fever and a cardiac murmur since rapid detection and appropriate treatment are important in reducing the risk of both maternal and foetal mortality.

Prophylaxis

Turbulent blood flow produced by congenital or valve disease may traumatize the endocardium and endothelial surfaces. Invasion of the bloodstream by microbes that can colonize this damaged site may result in clinical infection. Transient bacteraemia may occur after invasive procedures, such as gastrointestinal and genitourinary, particularly at a site of pre-existing infection. It is also very common during dental procedures and during daily activities, such as toothbrushing or defecation. Oral mucosal surfaces, and particularly the gingival crevice around teeth, are populated by a dense endogenous microflora, including species, such as streptococci, and at least 126 individual bacteria have been isolated in blood cultures after extractions or toothbrushing.[26,27] The rationale for endocarditis prophylaxis, therefore, was that antibiotics by limiting bacteraemia should be effective in preventing infective endocarditis following invasive procedures.

However, up to now, there has been no consistent association between interventional procedures, dental or non-dental, and the development of IE, and no controlled randomized study has proven the efficacy of prophylaxis. Recent studies have shown that most cases of infective endocarditis are not attributable to an invasive procedure and that the protective efficacy of antibiotic prophylaxis was not significant.[28,29] Bacteraemia resulting from daily activities, such as chewing food, brushing teeth, flossing, use of water irrigation devices and other activities, is much more likely to cause infective endocarditis than bacteraemia associated with a dental procedure.[27] The presence of dental disease may increase the risk of bacteraemia associated with these routine activities. Maintenance of optimal oral health and hygiene may reduce the incidence of bacteraemia from daily activities and is more important than prophylactic antibiotics for a dental procedure in reducing the risk of infective endocarditis.[27] Finally, the risk of a serious allergic reaction to amoxicillin may be greater than the risk of contracting infective endocarditis. For these reasons, both the ACC/AHA and the ESC recommend that prophylaxis is no longer mandatory in any patient. It is still recommended as a Class IIa in high-risk patients only, as indicated in Table 81.15. Recommended antibiotics are presented in Table 81.16. See also http://www.heart.org/idc/groups/heartpublic/@wcm/@hcm/documents/downloadable/ucm_307644.pdf.

Thus, antibiotic infective endocarditis prophylaxis should be given only to high-risk patients prior to dental procedures that involve manipulation in gingival tissue or periapical region of the teeth or perforation of the oral mucosa. Prophylaxis is no longer needed for routine anaesthetic injections through non-infected tissue, dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth, or bleeding from trauma to the lips or oral mucosa.

Antibiotic infective endocarditis prophylaxis is also no longer indicated in patients with native valve disease, such as aortic stenosis, mitral stenosis, or mitral valve prolapse. However, for patients with cardiac conditions about which data are virtually lacking, such as bicuspid aortic valves, coarctation of the aorta, significant native valve disease, or severe hypertrophic obstructive cardiomyopathy, and who are subjected to dental procedures as indicated, or to other procedures in the presence of active infection, or before vaginal delivery, the situation should be discussed and patient preferences should be assessed. If doctors and patients feel more comfortable, they can continue using prophylaxis with the antibiotic schemes proposed by ACC/AHA and ESC. These new recommendations have not resulted in a higher incidence of streptococcal endocarditis in France,[7] but this finding was not verified in a subsequent US study that demonstrated a significant rise

Table 81.15 IE prophylaxis

AHA/ACC 2014 GL on VD.	
Recommendations for IE prophylaxis	
Prophylaxis against infective endocarditis for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa:	
Patients with prosthetic cardiac valves	IIa-B
Patients with previous infective endocarditis.	IIa-B
Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve	IIa-B
Patients with CHD with: • Unrepaired cyanotic CHD, including palliative shunts and conduits. • Completely repaired congenital heart defect repaired with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure. • Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (both of which inhibit endothelialization).	IIa-B
Prophylaxis against infective endocarditis is not recommended for nondental procedures (such as transesophageal echocardiogram, esophagogastroduodenoscopy, colonoscopy or cystoscopy) in the absence of active infection.	III-B
ESC 2015 GL on infective endocarditis.	
Cardiac conditions at highest risk of infective endocarditis for which prophylaxis is recommended when a high risk procedure is performed	
Antibiotic prophylaxis for patients at highest risk for IE:	IIa-C
(1) Patients with any prosthetic valve, including a transcatheter valve, or those in whom any prosthetic material was used for cardiac valve repair.	
(2) Patients with a previous episode of IE.	
(3) Patients with CHD:	
(a) Any type of cyanotic CHD.	
(b) Any type of CHD repaired with a prosthetic material, whether placed surgically or by percutaneous techniques, up to 6 months after the procedure or lifelong if residual shunt or valvular regurgitation remains.	
Antibiotic prophylaxis is not recommended in other forms of valvular or CHD.	III-C
Recommendations for prophylaxis of infective endocarditis in the highest risk patients according to the type of procedure at risk	
Dental procedures	
Antibiotic prophylaxis only for dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa	IIa-C
Antibiotic prophylaxis is not recommended for local anaesthetic injections in non-infected tissues, treatment of superficial caries, removal of sutures, dental X-rays, placement or adjustment of removable prosthodontic or orthodontic appliances or braces or following the shedding of deciduous teeth or trauma to the lips and oral mucosa	III-C
Respiratory tract procedures	
Antibiotic prophylaxis is not recommended for respiratory tract procedures, including bronchoscopy or laryngoscopy, or transnasal or endotracheal intubation	III-C
Gastrointestinal or urogenital procedures or TOE	
Antibiotic prophylaxis is not recommended for gastroscopy, colonoscopy, cystoscopy, vaginal or caesarean delivery or TOE	III-C
Skin and soft tissue procedures	
Antibiotic prophylaxis is not recommended for any procedure	III-C
Recommendations for antibiotic prophylaxis for the prevention of local and systemic infections before cardiac or vascular interventions	
Preoperative screening of nasal carriage of Staphylococcus aureus before elective cardiac surgery in order to treat carriers	I-A
Perioperative prophylaxis before placement of a pacemaker or implantable cardioverter defibrillator	I-B
Eliminate potential sources of sepsis ≥2 weeks before implantation of a prosthetic valve or other intracardiac or intravascular foreign material, except in urgent procedures	IIa-C
Perioperative antibiotic prophylaxis for surgical or transcatheter implantation of a prosthetic valve, intravascular prosthetic or other foreign material	IIa-C
Systematic local treatment without screening of S. aureus is not recommended	III-C

CHD, congenital heart disease; IE, infective endocarditis.

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ESC 2015 Guidelines for the management of infective endocarditis. *Eur Heart J*. 2015;**36**:3075–128 with permission from Oxford University Press.

Table 81.16 Regimens before dental procedures when endocarditis prophylaxis is indicated.

AHA/ACC 2014 GL on VHD. Antibiotic Prophylactic regimens for dental procedures

Situation	Agent	Regimen—Single dose 30–60 minutes before procedure	
		Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin **or**	2 g IM or IV*	50 mg/kg IM or IV
	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin–Oral regimen	Cephalexin**†	2 g	50 mg/kg
	or		
	Clindamycin	600 mg	20 mg/kg
	or		
	Azithromycin or clarithromycin	500 mg	15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone†	1 g IM or IV	50 mg/kg IM or IV
	or Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

* IM—intramuscular, IV—intravenous

** Or other first or second generation oral cephalosporin in equivalent adult or pediatric dosage.

† Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema or urticaria with penicillins or ampicillin.

ESC 2015 GL on infective endocarditis

Situation	Antibiotic	Single-dose 30–60 minutes before procedure	
		Adults	Children
No allergy to penicillin or ampicillin	Amoxicillin or ampicillin[a]	2 g orally or IV	50 mg/kg orally or IV
Allergy to penicillin or ampicillin	Clindamycin	600 mg orally or IV	20 mg/kg orally or IV

[a] Alternatively, cephalexin 2 g i.v. for adults or 50 mg/kg i.v. for children, cefazolin or ceftriaxone 1 g i.v. for adults or 50 mg/kg i.v. for children.

Cephalosporins should not be used in patients with anaphylaxis, angio-oedema, or urticaria after intake of penicillin or ampicillin due to cross-sensitivity.

AHA/ACC 2014 Guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:2438–88 with permission from Elsevier.

ESC 2015 Guidelines for the management of infective endocarditis. *Eur Heart J*. 2015;**36**:3075–128 with permission from Oxford University Press.

in the incidence of *Streptococcus* IE since the 2007 guideline revisions.[30]

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Part XVIII

Rheumatic fever

Relevant guidelines

AHA 1992 Guidelines for diagnosis of rheumatic fever

Guidelines for the diagnosis of rheumatic fever. Jones Criteria, 1992 update. *JAMA*. 1992;**268**:2069–73.

ACC/AHA 2009 Statement on prevention of rheumatic fever

AHA Scientific statement: prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis. *Circulation*. 2009;**119**:1541–51.

2014 AHA/ACC Guideline for the management of patients with valvular heart disease

2014 AHA/ACC Guideline for the management of patients with valvular heart disease: executive summary. *J Am Coll Cardiol*. 2014;**63**:2438–88.

Chapter 82

Rheumatic fever

Definition

Acute rheumatic fever (ARF) results from an autoimmune response to infection with group A *Streptococcus*. Although the acute illness causes considerable morbidity and even mortality, the major clinical and public health effects derive from the long-term damage to heart valves, i.e. rheumatic heart disease.[1]

Epidemiology

In developing areas of the world, acute rheumatic fever and rheumatic heart disease are estimated to affect nearly 20 million people, with an incidence exceeding 50 per 100 000 children, and are the leading causes of cardiovascular death during the first five decades of life.[2] Rheumatic heart disease is one of the leading noncommunicable diseases in low- and middle-income countries and accounts for up to 1.4 million deaths per year.[3] In contrast, the incidence of acute rheumatic fever has decreased dramatically in most developed countries.[2] The prevalence of rheumatic heart disease increases with age, peaking in adults aged 25–34 years and being higher in women.

Aetiology

Infections of the pharynx with group A *beta-haemolytic streptococci* (GAS) are the precipitating cause of rheumatic fever. However, only one third of pharyngitis in young children is associated with GAS.[4] Streptococcal skin infections (impetigo or pyoderma) have not been proven to lead to acute rheumatic fever, at least in non-tropical countries. Some strains of group A streptococci belonging to certain M serotypes are more likely to cause rheumatic fever, and HLA types and B cell alloantigens have been associated with increased susceptibility to rheumatic fever and rheumatic carditis.[1] Up to 0.3–3% of untreated streptococcal pharyngitis are followed by rheumatic fever, 40–60% of patients with rheumatic fever end-up with carditis, and 60% of those with rheumatic heart disease.[4] Appropriate therapy prevents rheumatic fever, but at least one-third of episodes of the disease result from inapparent streptococcal infections.[2]

Pathophysiology

The autoimmune response that causes ARF is supposed to be triggered by molecular mimicry between epitopes on the pathogen (group A *Streptococcus*) and specific human tissues. The structural and immunological similarities between streptococcal M protein and myosin are essential to the development of rheumatic carditis. The initial damage to the valve might be due to laminin that is present in the valvular basement membrane and around endothelium, and which is recognized by T cells against myosin and M protein.[5]

In young patients, mitral valve regurgitation is the predominant cardiac lesion, but mitral stenosis becomes progressively more common with increasing age.[1]

Presentation

Group A streptococcal pharyngitis is primarily a disease of children 5–15 years of age, usually occuring in winter and early spring. Acute pharyngitis is caused considerably more often by viruses than by bacteria. Viruses that commonly cause pharyngitis include influenza virus, parainfluenza virus, rhinovirus, coronavirus, adenovirus, respiratory syncytial virus, Epstein–Barr virus, enteroviruses, and herpesviruses. Other causes of acute pharyngitis include *groups C and G streptococci, Neisseria gonorrhoeae, Mycoplasma pneumoniae, Chlamydia pneumoniae, Arcanobacterium haemolyticum*, and human immunodeficiency virus (HIV).[2]

There is typically sudden-onset sore throat, pain on swallowing, fever, headache, and possibly nausea or vomiting. Polyarthralgia and carditis follow afterwards.

Clinical forms

The main features of ARF are described in the modified Jones criteria,[6] as presented, together with the WHO criteria,[7] in Table 82.1.

Carditis, associated with a murmur of valvulitis, occurs in 50–70% of patients and is the most specific manifestation of ARF.

Polyarthritis is the most common, but the least specific, major manifestation. The classic migratory polyarthritis of the major joints of rheumatic fever should be distinguished from the post-streptococcal reactive arthritis of the small joints of the hand that does not carry a risk of carditis.

Chorea (Sydenham's chorea, St. Vitus dance, or chorea minor) occurs in about 20% of cases. It is a delayed manifestation of ARF, usually appearing ≥3 months after the onset of the precipitating streptococcal infection.

Erythema marginatum and **subcutaneous nodules** in the elbows, knees, and the occipital portion of the scalp are rare (<5%).

Table 82.1 Diagnosis of ARF

Jones criteria (1992)
Two major or one major and two minor manifestations must be present, plus evidence of antecedent group A Streptococcus infection
Chorea and indolent carditis do not require evidence of antecedent group A Streptococcus infection
Recurrent episode requires only one major or several minor manifestations, plus evidence of antecedent group A Streptococcus infection
Major manifestations
Carditis
Polyarthritis
Chorea
Erythema marginatum
Subcutaneous nodules
Minor manifestations
Arthralgia
Fever
Raised erythrocyte sedimentation rate or C-reactive protein concentrations
Prolonged PR interval on electrocardiogram
Evidence of antecedent group A *Streptococcus* infection
Positive throat culture or rapid antigen test for group A *Streptococcus*
Raised or rising streptococcal antibody titre
WHO criteria (2001)
Chorea and indolent carditis do not require evidence of antecedent group A *Streptococcus* infection
First episode
As per Jones criteria
Recurrent episode
In a patient without established RHD: as per first episode
In a patient with established RHD: requires two minor manifestations, plus evidence of antecedent group A *Streptococcus* infection. Evidence of antecedent group A *Streptococcus* infection as per Jones criteria, but with addition of recent scarlet fever

Table 82.2 AHA 2009 Statement on rheumatic fever prevention

Clinical and epidemiological findings and diagnosis of group A streptococci (GAS) pharyngitis
Features suggestive of GAS as causative agent
Sudden-onset sore throat
Pain on swallowing
Fever
Scarlet fever rash
Headache
Nausea, vomiting, and abdominal pain
Tonsillopharyngeal erythema
Tonsillopharyngeal exudates
Soft palate petechiae ('doughnut' lesions)
Beefy, red, swollen uvula
Tender, enlarged anterior cervical nodes
Patient 5–15 years of age
Presentation in winter or early spring (in temperate climates)
History of exposure
Features suggestive of viral origin
Conjunctivitis
Coryza
Hoarseness
Cough
Diarrhoea
Characteristic exanthems
Characteristic enanthems

AHA 2009 Scientific statement: prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis. *Circulation*. 2009;**119**:1541–51 with permission from Wolters Kluwer.

Diagnosis

Differentiation of group A streptococcal pharyngitis from pharyngitis caused by other pathogens is impossible on clinical grounds. However, several clues may be helpful (Table 82.2).

Throat culture

Microbiological confirmation, with either a throat culture or a rapid antigen detection test (RADT), is required for the diagnosis (Class I-B, AHA 2009 statement).[2] In untreated patients with group A streptococci (GAS) pharyngitis, a properly obtained throat culture (by vigorous swabbing of both tonsils and posterior pharynx) is almost always positive. A positive throat culture may reflect chronic colonization by GAS and cannot be used to differentiate carriage from infection. A negative throat culture permits the physician to withhold antibiotic therapy from the large majority of patients with sore throats.

When deciding whether to perform a microbiological test for a patient with acute pharyngitis, the clinical and epidemiological findings in Table 82.2 need to be considered (Class I-B, AHA 2009 statement).

For patients with acute pharyngitis and clinical and epidemiological findings suggestive of a viral origin, the pretest

probability of GAS is low, and testing usually does not need to be performed (Class IIb-B, AHA 2009 statement).

The use of a clinical algorithm without microbiological confirmation has been recently recommended as an acceptable strategy for diagnosing GAS pharyngitis in adults. This approach could result in inappropriate antimicrobial therapy of an unacceptably large number of adults with non-streptococcal pharyngitis and is not recommended (Class III-B, AHA 2009 statement).

However, a strategy of culture for all patients may be prohibitively expensive. Treating all children presenting with pharyngitis in urban primary care clinics in South Africa with intramuscular penicillin was the least costly.[8] It seems that a strategy of using a clinical decision rule without culturing may be the preferred strategy.

Antigen detection tests

Most of these tests have a high degree of specificity, but their sensitivity in clinical practice can be unacceptably low. Treatment is indicated for the patient with acute pharyngitis who has a positive RADT (Class I-B, AHA 2009 statement). However, as with the throat culture, a positive test may reflect chronic colonization instead of active infection. A negative test does not exclude the presence of GAS, and a throat culture should be performed (Class I-B, AHA 2009 statement).

Newer tests with improved sensitivity are developed. Physicians who use newer tests without culture backup in children and adolescents should compare the results of that specific RADT with those of blood agar plate cultures to confirm adequate sensitivity in their practice (Class IIa-C, AHA 2009 statement). However, because of the low incidence of GAS infections and extremely low risk of acute rheumatic fever in adults, diagnosis of GAS pharyngitis on the basis of an antigen detection test alone, without confirmation of negative RADT results by a negative throat culture, is reasonable and an acceptable alternative to diagnosis on the basis of throat culture results (Class IIa-C, AHA 2009 statement).

Streptococcal antibody tests

Anti-streptococcal antibody titres reflect past, and not present, immunological events and, therefore, cannot be used to determine whether an individual with pharyngitis and GAS in the pharynx is truly infected or merely a streptococcal carrier.

Table 82.3 AHA 2009 Statement on rheumatic fever prevention.* Primary prevention of rheumatic fever (treatment of streptococcal tonsillopharyngitis)

Agent	Dose	Mode	Duration	Rating
Penicillins				
Penicillin V (phenoxymethylpenicillin)	Children: 250 mg 2–3 times daily for ≤27 kg (60 lb); children >27 kg (60 lb), adolescents, and adults: 500 mg 2–3 times daily	Oral	10 days	I-B
	or			
Amoxicillin	50 mg/kg once daily (maximum 1 g)	Oral	10 days	I-B
	or			
Benzathine penicillin G	600 000 U for patients ≤27 kg (60 lb); 200 000 U for patients >27 kg (60 lb)	Intramuscular	Once	I-B
For individuals allergic to penicillin				
Narrow-spectrum cephalosporin† (cephalexin, cefadroxil)	Variable	Oral	10 days	I-B
	or			
Clindamycin	20 mg/kg per day divided in three doses (maximum 1.8 g/d)	Oral	10 days	IIa-B
	or			
Azithromycin	12 mg/kg once daily (maximum 500 mg)	Oral	5 days	IIa-B
	or			
Clarithromycin	15 mg/kg per day divided bd (maximum 250 mg bd)	Oral	10 days	IIa-B

† To be avoided in those with immediate (type I) hypersensitivity to a penicillin.
Sulfonamides, trimethoprim, tetracyclines, and fluoroquinolones are not acceptable alternatives.
* Similar recommendations have been provided by ACC/AHA GL on valve disease.
AHA 2009 Scientific statement: prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis. *Circulation*. 2009;**119**:1541–51 with permission from Wolters Kluwer.

Table 82.4 AHA/ACC 2014 GL on valvular heart disease. Secondary prevention of rheumatic fever (prevention of recurrent attacks)

Agent	Dosage
Penicillin G benzathine	1.2 million units IM every 4 wk*
Penicillin V potassium	250 mg orally BID
Sulfadiazine	1 g orally once daily
Macrolide or azalide antibiotic (for patients allergic to penicillin and sulfadiazine)*	Varies

* Administration every 3 wk is recommended in certain high-risk situations.
† Macrolide antibiotics should not be used in persons taking other medications that inhibit cytochrome *P450 3A*, such as azole antifungal agents, HIV protease inhibitors, and some selective serotonin reuptake inhibitors.
BID indicates twice daily; HIV, human immunodeficiency virus; and IM, intramuscularly.
AHA/ACC 2014 Guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:2438–88 with permission from Elsevier.

Table 82.5 AHA/ACC 2014 GL on valvular heart disease. Duration of secondary prophylaxis for rheumatic fever

Type	Duration after last attack
Rheumatic fever with carditis and residual heart disease (persistent VHD*)	10 y or until patient is 40 y of age (whichever is longer)
Rheumatic fever with carditis but no residual heart disease (no valvular disease*)	10 y or until patient is 21 y of age (whichever is longer)
Rheumatic fever without carditis	5 y or until patient is 21 y of age (whichever is longer)

* Clinical or echocardiographic evidence.
AHA/ACC 2014 Guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2014;**63**:2438–88 with permission from Elsevier.

Therapy

The 2009 AHA recommendations are presented in Table 82.3.[2] Streptococcal infections that occur in family members of patients with current or previous rheumatic fever should also be treated promptly (Class I-B, AHA 2009 statement).

Prophylaxis

An individual with a previous attack of rheumatic fever in whom GAS pharyngitis develops is at high risk for a recurrent attack of rheumatic fever. A recurrent attack can be associated with worsening of the severity of rheumatic heart disease that developed after a first attack or, less frequently, with the new onset of rheumatic heart disease in individuals who did not develop cardiac manifestations during the first attack.[2,9]

Continuous prophylaxis is recommended for patients with well-documented histories of rheumatic fever (including cases manifested solely by Sydenham chorea) and those with definite evidence of rheumatic heart disease, and especially mitral stenosis.[2,9] The ACCF/AHA recommendations on antibiotics and duration of prophylaxis are presented in Tables 82.4 and 82.5. Such prophylaxis should be initiated as soon as acute rheumatic fever or rheumatic heart disease is diagnosed. A full therapeutic course of penicillin first should be given to patients with acute rheumatic fever to eradicate residual GAS, even if a throat culture is negative at that time.

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9. Nishimura RA, *et al*. 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;**63**:2438–88

Part XIX

Athlete's heart

Relevant guidelines

AHA/ACC 2014 Statement on screening in the young

Assessment of the 12-lead ECG as a screening test for detection of cardiovascular disease in healthy general populations of young people (12–25 years of age): A scientific statement from the American Heart Association and the American College of Cardiology. *Circulation*. 2014;**130**:1303–34.

AHA/ACC 2015 Statement on athletes

Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Preamble, principles, and general considerations: A scientific statement from the American Heart Association and American College of Cardiology. *J Am Coll Cardiol*. 2015;**66**:2343–9.

2015 ESC 2015 Guidelines on ventricular arrhythmias and prevention of sudden cardiac death

2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015;**36**:2793–867.

Chapter 83

Athlete's heart

Exercise-induced cardiac remodelling

Isotonic exercise, i.e. endurance exercise with activities such as long-distance running, cycling, and swimming, results in sustained elevations in cardiac output with normal or reduced peripheral vascular resistance. It represents primarily a volume challenge for the heart that affects all four chambers.[1,2]

Isometric exercise, i.e. strength training, results in increased peripheral vascular resistance and normal, or only slightly elevated, cardiac output. This increase in peripheral vascular resistance causes transient, but potentially marked, systolic hypertension and LV afterload.[1]

Left ventricular hypertrophy and dilatation may be seen in isotonic, and hypertrophy in isometric, exercise. Mild reductions of LVEF might be seen, although there is evidence that both systolic and diastolic LV function may improve with exercise.

Right ventricular dilatation and increased free wall thickness have been seen in athletes with isotonic or isometric exercise. Electrocardiographic RV hypertrophy does not indicate underlying pathology.[3,4] In black athletes, training-related RV enlargement may even mimic ARVC.[3] Intensive endurance exercise of increased duration (i.e. marathon runners) has also been reported to result in transient RV dysfunction that is usually reversible, although septal fibrosis was seen in athletes with intensive training for prolonged periods.[5] In athletes with normal cardiac function at rest, echocardiographic and CMR measures of RV function performed during exercise reveal RV contractile dysfunction among athletes with RV arrhythmias, and may assist risk-stratification.[6]

Table 83.1 Common cardiovascular conditions associated with sudden death in athletes

HCM
Congenital coronary anomalies
Genetic channelopathies (Brugada, early repolarization syndrome, LQTS, SQTS, CPVT)
Blunt trauma
Commotio cordis
Coronary artery disease
ARVC
Myocarditis
Bicuspid aortic valve with stenosis or dilated aortic root
WPW syndrome
Heat stroke

Aortic root may be slightly dilated (up to 1.6 mm compared to controls), but marked aortic root dilatation represents a pathological process and not a physiological adaptation to exercise.[7] A slightly larger **left atrium** has also been detected in trained athletes.

Intensive and long-lasting endurance exercise, such as a full-distance marathon, results in high cardiovascular strain whose clinical relevance, especially for middle-aged and older athletes, is unclear and remains a matter of controversy.[8]

Common cardiovascular conditions associated with sudden death in athletes are presented in Table 83.1.

Interpretation of the ECG in athletes

Differentiation between adaptive and pathological ECG changes in athletes is not always easy. Recommendations have been published by the ESC,[9] and a group of US experts[10] and an international group of experts in sports cardiology and sports medicine (Seattle criteria).[11]

Recently, a refinement of current ECG screening criteria that may reduce the false positive ECGs in athletes, and particularly black athletes, has been proposed.[12] African athletes display a large proportion of ECG abnormalities, including an increase in R/S-wave voltage, ST-segment elevation, and inverted or diffusely flat T waves.[13] ECG patterns seen in athletes are presented in Tables 83.2 to 83.5. There has been evidence that isolated QRS voltage criteria (Sokolow–Lyon) for RV hypertrophy may be a non-pathologic adaptive change, whereas left or right axis deviation and left or right atrial enlargement may be considered minor training-unrelated abnormalities, as indicated in Table 83.2.[4,14] Points for differentiating between adaptive changes and truly pathological findings are:

1. Sinus bradycardia is normal. Only heart rates <30 bpm and pauses ≥3 s during wake suggest sick sinus syndrome.
2. First- and second-degree type 1 (Wenckebach) blocks are benign and usually resolve with hyperventilation or exercise.
3. Isolated axis deviation does not indicate further investigation, unless there is a history of pulmonary disease or systemic hypertension.
4. LV hypertrophy needs further evaluation only in the presence of family history of sudden cardiac death or non-voltage ECG criteria suggesting pathological ECG hypertrophy.

Table 83.2 Classification of abnormalities of the athlete's electrocardiogram

Group 1: common and training-related ECG changes	Group 2: uncommon and training-unrelated ECG changes
Sinus bradycardia	T wave inversion
First-degree AV block	ST segment depression
Incomplete RBBB	Pathological Q waves
Early repolarization	Left atrial enlargement
Isolated QRS voltage criteria for left ventricular hypertrophy	Left axis deviation/left anterior hemiblock
	Right axis deviation/left posterior hemiblock
	Right ventricular hypertrophy
	Ventricular pre-excitation
	Complete LBBB or RBBB
	Long or short QT interval
	Brugada-like early repolarization

EACPR 2010 Recommendations for interpretation of 12-lead electrocardiogram in the athlete. *Eur Heart J*. 2010;**31**:243–59 with permission from Oxford University Press.

5. Q waves >3 mm in depth and/or >40 ms duration in any lead, except aVR, III, and V_1, suggest hypertrophic cardiomyopathy (HCM) (Figure 83.1). Standard criteria for MI in athletes should also be considered in those >40 years of age.
6. Inferolateral early repolarization patterns may be seen in young athletes and is a dynamic phenomenon caused by exercise.[15] Two types predominate. An elevated ST segment with upward concavity and positive T wave is seen in Caucasians, and an elevated ST segment with upward convexity and negative T wave in Afro-Caribbean athletes (Figures 83.2 and 83.3, and Figure 62.1 in Chapter 62). Pathological early repolarization patterns are discussed in Chapter 61. ST elevation should be differentiated from Brugada syndrome (see Figure 60.3 of Chapter 60).
7. T wave inversion, seen in leads aVR, III, and V_1 and in V_1–V_4, when preceded by domed ST segments, in asymptomatic Afro-Caribbean athletes is considered physiological.[12] It has to be differentiated from pathological T wave inversion that is associated with cardiac pathology in up to 45% of other athletes as detected by CMR.[16] HCM was the commonest pathology (81%) in this series, and echocardiography did not identify pathology in up to 50% of the cases.[16]
8. Incomplete RBBB (QRS <120 ms) is common. However, it should be differentiated from ARVC and Brugada syndrome (Figure 83.4). Complete LBBB or RBBB with hemiblock necessitates cardiological work-up, including myocardial imaging. ECG of siblings should also be obtained to exclude genetically determined AV conduction disease.
9. Suspicion of long QT (>470 ms in men and >480 ms in women) or short QT (<340 ms) should lead to evaluation by a specialist. A QT_C ≤380 ms may also be a marker of abuse of anabolic androgenic steroids.
10. WPW needs ablation for the elimination of the very low risk of sudden death, particularly since athletes may develop AF. Exclusion of conditions, such as Ebstein disease, HCM, and glycogen storage cardiomyopathy, should be undertaken.

Table 83.3 Seattle Criteria: normal ECG variants in athletes. Common training-related ECG alterations that are physiological adaptations to regular exercise, considered normal variants in athletes and do not require further evaluation in asymptomatic athletes

1. Sinus bradycardia (≥30 bpm)
2. Sinus arrhythmia
3. Ectopic atrial rhythm
4. Junctional escape rhythm
5. 1° AV block (PR interval >200 ms)
6. Mobitz Type 1 (Wenckebach) 2° AV block
7. Incomplete RBBB
8. Isolated QRS voltage for LVH Except: QRS voltage criteria for LVH occurring with any non-voltage criteria for LVH such as left atrial enlargement, left axis deviation, ST segment depression, T-wave inversion or pathological Q waves
9. Early repolarization (ST elevation, J-point elevation, J-waves or terminal QRS slurring)
10. Convex ('domed') ST segment elevation combined with T-wave inversion in leads V1–V4 in black/African athletes

AV, atrioventricular; bpm, beats per minute; LVH, left ventricular hypertrophy; ms, milliseconds; RBBB, right bundle branch block.
Drezner JA, *et al*. Electrocardiographic interpretation in athletes: the 'Seattle Criteria'. *Br J Sports Med*. 2013;**47**:122–4 with permission from BMJ Publishing Group.

Table 83.4 Seattle Criteria: abnormal ECG findings in athletes. ECG findings unrelated to regular training or expected physiological adaptation to exercise that may suggest the presence of pathological cardiovascular disease, and require further diagnostic evaluation

Abnormal ECG finding	Definition
T-wave inversion	>1 mm in depth in two or more leads V2–V6, II and aVF, or I and aVL (excludes III, aVR and V1)
ST segment depression	≥0.5 mm in depth in two or more leads
Pathological Q waves	>3 mm in depth or >40 ms in duration in two or more leads (except for III and aVR)
Complete left bundle branch block	QRS ≥120 ms, predominantly negative QRS complex in lead V1 (QS or rS), and upright monophasic R wave in leads I and V6
Intraventricular conduction delay	Any QRS duration ≥140 ms
Left axis deviation	–30° to –90°
Left atrial enlargement	Prolonged P wave duration of >120 ms in leads I or II with negative portion of the P wave ≥1 mm in depth and ≥40 ms in duration in lead V1
Right ventricular hypertrophy pattern	R–V1+S–V5 >10.5 mm and right axis deviation >120°
Ventricular pre-excitation	PR interval <120 ms with a delta wave (slurred upstroke in the QRS complex) and wide QRS (>120 ms)
Long QT interval*	QTc ≥470 ms (male) QTc ≥480 ms (female) QTc ≥500 ms (marked QT prolongation)
Short QT interval*	QTc ≤320 ms
Brugada-like ECG pattern	High take-off and downsloping ST segment elevation followed by a negative T wave in ≥2 leads in V1–V3
Profound sinus bradycardia	<30 BPM or sinus pauses ≥3 s
Atrial tachyarrhythmias	Supraventricular tachycardia, atrial fibrillation, atrial flutter
Premature ventricular contractions	≥2 PVCs per 10 s tracing
Ventricular arrhythmias	Couplets, triplets and non-sustained ventricular tachycardia

* The QT interval corrected for heart rate is ideally measured with heart rates of 60–90 bpm. Consider repeating the ECG after mild aerobic activity for borderline or abnormal QTc values with a heart rate <50 bpm.

Drezner JA, *et al*. Electrocardiographic interpretation in athletes: the 'Seattle Criteria'. *Br J Sports Med.* 2013;**47**:122–4 with permission from BMJ Publishing Group.

Table 83.5 Electrocardiographic parameters used to define various ECG abnormalities in the European Society of Cardiology recommendations, Seattle Criteria, and refined criteria

ECG abnormality	ESC recommendations	Seattle Criteria	Refined criteria
Left atrial enlargement	Negative portion of the P wave in lead V1 ≥0.1 mV in depth and ≥40 ms in duration	Prolonged P wave duration of >120 ms in leads I or II with negative portion of the P wave ≥1 mm in depth and ≥40 ms in duration in lead V1	As ESC
Right atrial enlargement	P-wave amplitude ≥2.5 mm in leads II, III or aVF	As ESC	As ESC
Left QRS-axis deviation	–30° to –90°	As ESC	As ESC
Right QRS-axis deviation	>115°	>120°	As ESC
Right ventricular hypertrophy	Sum of R wave in V1 and S wave in V5 or V6 ≥10.5 mm	Sum of R wave in V1 and S wave in V5 >10.5 mm and right axis deviation >120°	As ESC
Complete left bundle branch block	QRS ≥120 ms predominantly negative QRS complex in lead V1 (QS or rS), and upright monophasic R wave in leads I & V6	As ESC	As ESC
Complete right bundle branch block	RSR' pattern in anterior precordial leads with QRS duration ≥120 ms	Not relevant	As ESC
Intraventricular conduction delay	Any QRS duration >120 ms including RBBB and LBBB	Any QRS duration ≥140 ms or complete LBBB	As ESC
Pathological Q-wave	>4 mm deep in any lead except III, aVR	>3 mm deep and/or >40 ms duration in ≥2 leads except III and aVR	≥40 ms in duration or ≥25% of the height of the ensuing R-wave
Significant T-wave inversion	≥2 mm in ≥2 adjacent leads (deep) or 'minor' in ≥2 leads	>1 mm in depth in two or more leads V2–6, II and aVF or I and aVL (excludes III, aVR and V1)	As Seattle
ST-segment depression	≥0.5 mm deep in ≥2 leads	As ESC	As ESC

(*continued*)

Table 83.5 continued

ECG abnormality	ESC recommendations	Seattle Criteria	Refined criteria
Ventricular pre-excitation	PR interval <120 ms with or without delta wave	PR interval <120 ms with delta wave	As Seattle

Sheikh N, *et al*. Comparison of electrocardiographic criteria for the detection of cardiac abnormalities in elite black and white athletes. *Circulation*. 2014;**129**:1637–49 with permission from Wolters Kluwer.

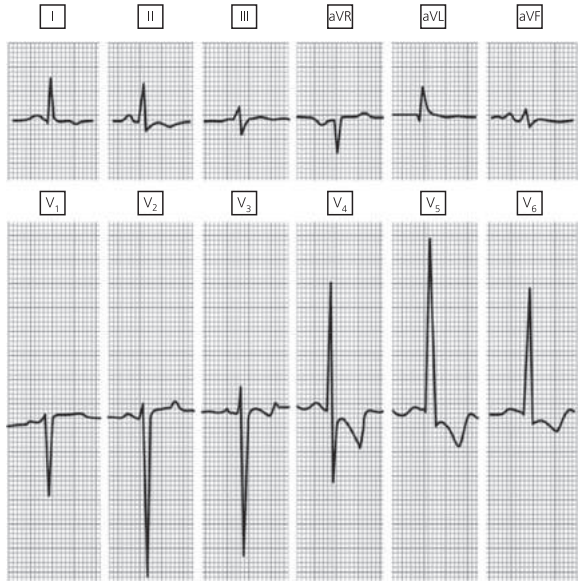


Figure 83.1 Twelve-lead ECG of an asymptomatic athlete with HCM. The disease was suspected at pre-participation evaluation from ECG abnormalities consisting of increased QRS voltages and inverted T waves in lateral leads. HCM was diagnosed by echocardiography afterwards.

EACPR 2010 Recommendations for interpretation of 12-lead electrocardiogram in the athlete. *Eur Heart J*. 2010;**31**:243–59 with permission from Oxford University Press.

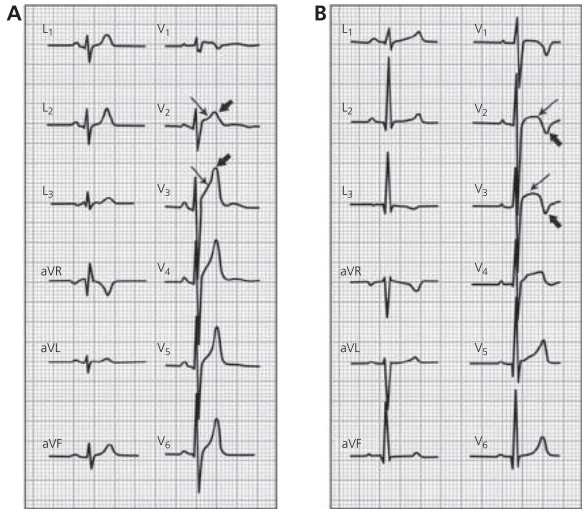


Figure 83.2 Different patterns of precordial early repolarization in two healthy athletes. (A) ST segment elevation with upward concavity (arrows), followed by a positive T wave (arrowheads). (B) ST segment elevation with upward convexity (arrows), followed by a negative T wave (arrowheads). European Association of Cardiovascular Prevention and Rehabilitation.

EACPR 2010 Recommendations for interpretation of 12-lead electrocardiogram in the athlete. *Eur Heart J*. 2010;**31**:243–59 with permission from Oxford University Press.

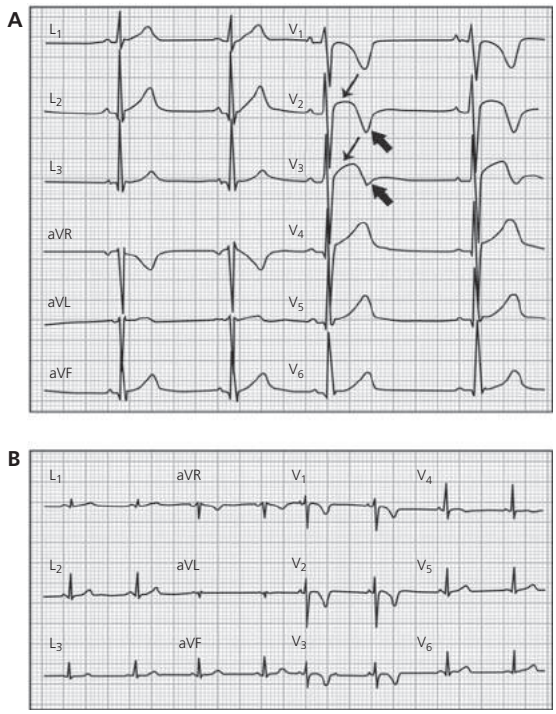


Figure 83.3 (A) Early repolarization pattern in a healthy black athlete characterized by right precordial T wave inversion (arrowhead), preceded by ST segment elevation (arrow). (B) Right precordial T wave inversion in a patient with ARVC. Note that, unlike early repolarization, in ARVC the right precordial leads do not demonstrate any elevation of the ST segment.

EACPR 2010 Recommendations for interpretation of 12-lead electrocardiogram in the athlete. *Eur Heart J*. 2010;**31**:243–59 with permission from Oxford University Press.

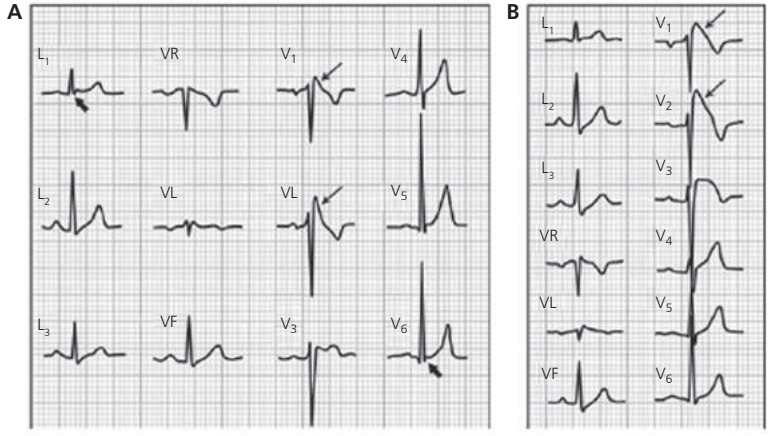


Figure 83.4 (A) Borderline Brugada ECG pattern mimicking incomplete RBBB. Unlike the 'R wave' of RBBB, the 'J wave' (arrows) of Brugada ECG is confined to right precordial leads (V_1 and V_2) without reciprocal 'S wave' (of comparable voltage and duration) in leads L_1 and V_6 (arrowhead). (B) In this case, definitive diagnosis of Brugada ECG was achieved by a drug challenge with sodium channel blockers which unmasked diagnostic 'coved-type' (arrows) pattern (V_1 and V_2). European Association of Cardiovascular Prevention and Rehabilitation.

EACPR 2010 Recommendations for interpretation of 12-lead electrocardiogram in the athlete. *Eur Heart J*. 2010;**31**:243–59 with permission from Oxford University Press.

Arrhythmias in athletes

Sudden cardiac death in athletes is discussed in Chapter 68. Other arrhythmias in athletes (SVT, AF, VT) are discussed in the relevant chapters.

Classification of sports

Classification of sports from the 36th Bethesda Conference and by the ESC are presented in Figures 83.5 and 83.6.[17–19]

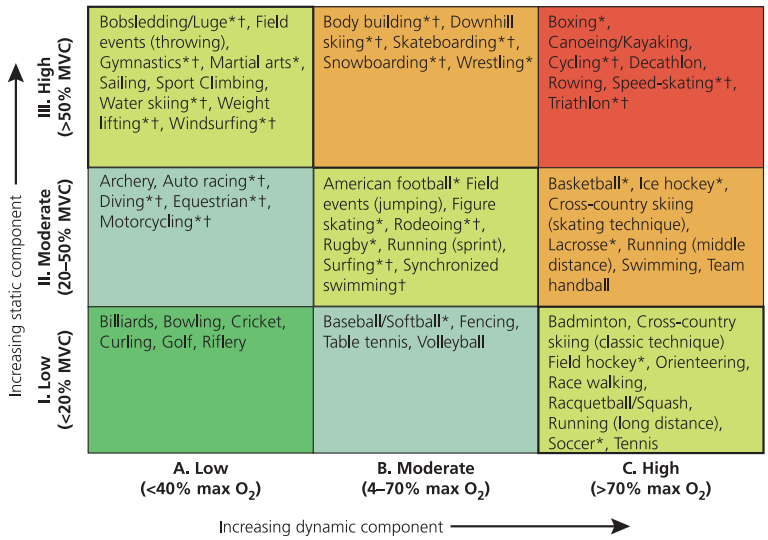


Figure 83.5 Classification of sports (36th Bethesda Conference). This classification is based on peak static and dynamic components achieved during competition. It should be noted, however, that higher values may be reached during training. The increasing dynamic component is defined in terms of the estimated percentage of maximal oxygen uptake ($MaxO_2$) achieved and results in an increasing cardiac output. The increasing static component is related to the estimated percentage of maximal voluntary contraction (MVC) reached and results in an increasing blood pressure load. The lowest total cardiovascular demands (cardiac output and blood pressure) are shown in green and the highest in red. Blue, yellow, and orange depict low moderate, moderate, and high moderate total cardiovascular demands, respectively.

* Danger of bodily collision. † Increased risk if syncope occurs.
Mitchell JH, *et al*. Task Force 8: Classification of sports. *J Am Coll Cardiol*. 2005;**45**:1364–7 with permission from Elsevier.

	A. Low dynamic	B. Moderate dynamic	C. High dynamic
I. Low static	Bowling Cricket Golf Riflery	Fencing Table tennis Tennis (doubles) Volleyball Baseball[a]/softball[a]	Badminton Race walking Running (marathon) Cross-country skiing (classic) Squash[a]
II. Moderate static	Auto racing[a,b] Diving[b] Equestrian[a,b] Motorcycling[a,b] Gymnastics[a] Karate/Judo[a] Sailing Archering	Field events (jumping) Figure skating[a] Lacrosse[a] Running (sprint)	Basketball[a] Biathlon Ice hockey[a] Field hockey[a] Rugby[a] Soccer[a] Cross-country skiing (skating) Running (mid/long) Swimming Tennis (single)
III. High static	Bobsledding[a,b] Field events (throwing) Luge[a,b] Rock climbing[a,b] Waterskiing[a,b] Weight lifting[a] Windsurfing[a,b]	Body building[a] Downhill skiing[a,b] Wrestling[a] Snow boarding[a,b]	Team handball[a] Boxing[a] Canoeing, Kayaking Cycling[a,b] Decathlon Rowing Speed skating Triathlon[a,b]

Figure 83.6 Classification of sports (ESC).

[a] Danger of bodily collision. [b] Increased risk if syncope occurs.

Pre-participation screening, and recommendations for eligibility and disqualification

A mandatory national preparticipation screening strategy with routine ECGs is recommended by the European Society of Cardiology,[9] and the International Olympic Committee,[20] mainly based on the beneficial results of screening observed in the Veneto region of Italy.[21] The American Heart Association has expressed reservations about the cost efficiency and effectiveness of such screening, that has been adopted by the ESC (Tables 83.6 to 83.8 and Figure 83.7).[22,23] Although debatable,[24] recent data argue for a closer scrutiny, especially since cardiac symptoms before death are often found.[16,25–27]

Recommendations for eligibility and disqualification have been recently published by AHA/ACC.[28]

Table 83.6 The 14-element AHA recommendations for preparticipation cardiovascular screening of competitive athletes

Medical history*
Personal history
1. Chest pain/discomfort/tightness/pressure related to exertion
2. Unexplained syncope/near-syncope†
3. Excessive and unexplained dyspnoea/fatigue or palpitations, associated with exercise
4. Prior recognition of a heart murmur
5. Elevated systemic blood pressure
6. Prior restriction from participation in sports
7. Prior testing for the heart, ordered by a physician
Family history
8. Premature death (sudden and unexpected, or otherwise) before 50y of age attributable to heart disease in ≥1 relative
9. Disability from heart disease in close relative <50y of age
10. Hypertrophic or dilated cardiomyopathy, long-QT syndrome, or other ion channelopathies, Marfan syndrome, or clinically significant arrhythmias; specific knowledge of genetic cardiac conditions in family members
Physical examination
11. Heart murmur‡
12. Femoral pulses to exclude aortic coarctation
13. Physical stigmata of Marfan syndrome
14. Brachial artery blood pressure (sitting positions) §

*Parental verification is recommended for high school and middle school athletes.
†Judged not to be of neurocardiogenic (vasovagal) origin; of particular concern when occurring during or after physical exertion.
‡Refers to heart murmurs judged likely to be organic and unlikely to be innocent; auscultation should be performed with the patient in both the supine and standing positions (or with Valsalva manoeuvre), specifically to identify murmurs of dynamic left ventricular outflow tract obstruction.
§Preferably taken in both arms.
Assessment of the 12-lead ECG as a screening test for detection of cardiovascular disease in healthy general populations of young people (12–25 years of age): A scientific statement from the American Heart Association and the American College of Cardiology. *Circulation*. 2014;**130**:1303–34 with permission from Wolters Kluwer.

Table 83.7 AHA recommendations for screening of healthy young people

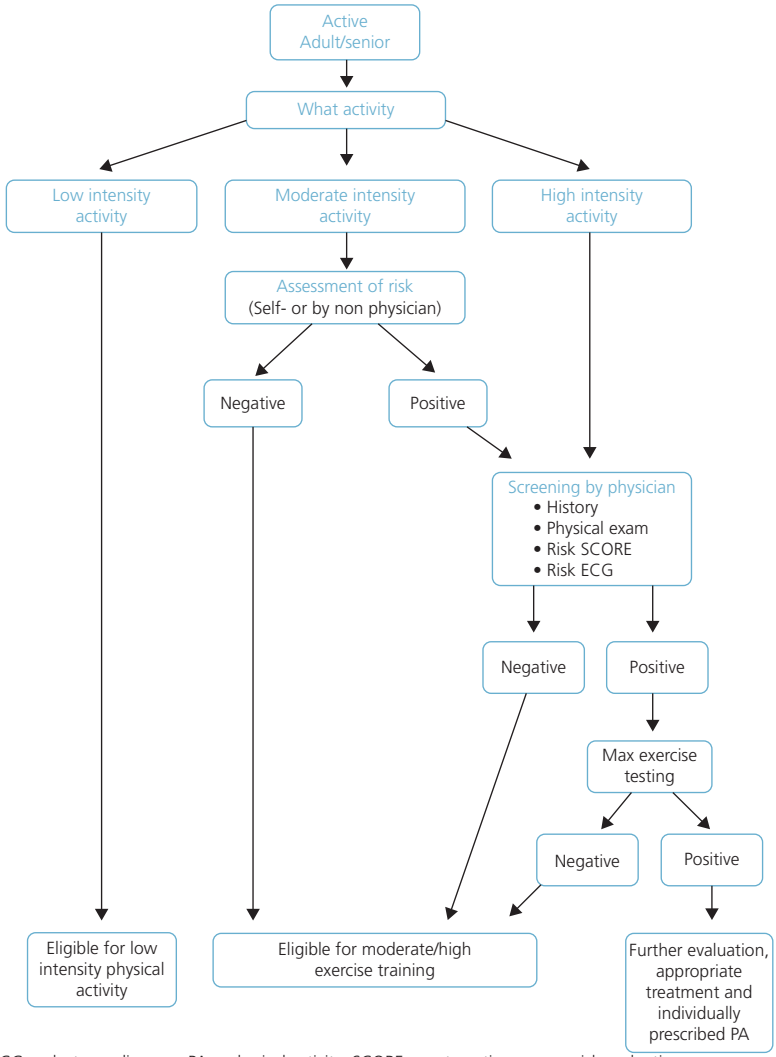
The AHA 14-point screening guidelines and those of other societies, such as the Preparticipation Physical Evaluation monograph should be used by examiners as part of a comprehensive history-taking and physical examination to detect or raise suspicion of genetic/congenital and other cardiovascular abnormalities.	I-C
Standardization of the questionnaire forms used as guides for examiners of high school and college athletes in the United States should be pursued	I-C
Screening with 12-lead ECGs (or echocardiograms) in association with comprehensive history-taking and physical examination to identify or raise suspicion of genetic/congenital and other cardiovascular abnormalities may be considered in relatively small cohorts of young healthy people 12 to 25 years of age, not necessarily limited to athletes (e.g., in high schools, colleges/universities, or local communities), provided that close physician involvement and sufficient quality control can be achieved. If undertaken, such initiatives should recognize the known and anticipated limitations of the 12-lead ECG as a population screening test, including the expected frequency of false-positive and false-negative test results, as well as the cost required to support these initiatives over time	IIb-C
Mandatory and universal mass screening with 12-lead ECGs in large general populations of young healthy people 12 to 25 years of age to identify genetic/congenital (including on a national basis in the United States) and other cardiovascular abnormalities is not recommended for athletes and nonathletes alike	III-C (no benefit)
Consideration for large-scale, general population, and universal cardiovascular screening in the age group 12 to 25 years with history-taking and physical examination alone is not recommended (including on a national basis in the United States)	III-C (no benefit)

Assessment of the 12-lead ECG as a screening test for detection of cardiovascular disease in healthy general populations of young people (12–25 years of age): a scientific statement from the American Heart Association and the American College of Cardiology. *Circulation*. 2014;**130**:1303–34 with permission from Wolters Kluwer.

Table 83.8 ESC 2015 GL on VA and SCD. Prevention of sudden cardiac death in athletes

Careful history taking to uncover underlying cardiovascular disease, rhythm disorder, syncopal episodes or family history of SCD.	I-C
Upon identification of ECG abnormalities suggestive of structural heart disease, echocardiography and/or CMR imaging.	I-C
Physical examination and resting 12-lead ECG for pre-participation screening in younger athletes.	IIa-C
Middle-aged individuals engaging in high-intensity exercise should be screened with history, physical examination, SCORE and resting ECG.	IIa-C
Staff at sporting facilities should be trained in cardiopulmonary resuscitation and on the appropriate use of automatic external defibrillators.	IIa-C

SCORE: systematic coronary risk evaluation
2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015; **36**: 2793–867



ECG = electrocardiogram; PA = physical activity; SCORE = systematic coronary risk evaluation.

Figure 83.7 ESC 2015 GL on VA and SCD. Proposed pre-participation evaluation protocol for asymptomatic active adult or senior individuals.

ESC 2015 Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015;**36**:2793–867 with permission from Oxford University Press.

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Part XX

Cardiac tumours and pseudoaneurysms

Chapter 84

Cardiac tumours

Primary cardiac tumours

Primary cardiac tumours are a rare entity across all age groups, with a reported prevalence of 0.001–0.03% in autopsy series.[1] Primary tumours consist 0.3% to 0.7% of all cardiac tumours, whereas metastasis to the heart from other primary cancers is 30 times more common.[2] Approximately 75% of primary cardiac tumours are benign, and, of those, the majority are myxomas.[3,4] Cardiac lipomas and papillary fibroelastomas occur in adults and are usually asymptomatic. Of the malignant tumours which often occur in the young, 75% are sarcomas.[2] Malignant primary cardiac sarcomas are usually located in the right atrium and are most commonly angiosarcomas. In the left atrium, the most common malignant tumours are pleomorphic sarcoma (also known as malignant fibrous histiocytoma) and leiomyosarcoma.[2] Rhabdomyomas and fibromas are seen in infants.

Aetiology

The genetics of primary cardiac tumours is poorly understood, especially for those that occur sporadically. Myxomas are familial in 10% of cases. **Carney's syndrome** (or complex) is an autosomal dominant syndrome characterized by familial recurrent cardiac and mucocutaneous myxomas arising from mesenchymal cells, pigmented lesions over the lips, conjunctiva, and genitalia, adenomas of the breast and thyroid, and endocrine abnormalities, including Cushing's syndrome and acromegaly. Genetic studies have identified mutations in the gene encoding protein kinase A, regulatory subunit 1-α (PRKAR1α).[5] There are no demonstrable associations with malignant sarcomas.

Presentation

Systemic or pulmonary embolization, congestive heart failure from intracardiac obstruction, and arrhythmias may occur. Cardiac myxoma is the most common primary cardiac tumour to produce emboli to virtually any organ or tissue.[6] Cerebral aneurysm, secondary to embolic tumour fragments, is a life-threatening complication. Left atrial sarcomas tend to be more solid and less infiltrative than right-sided sarcomas, and they tend to metastasize later. They usually present with symptoms of blood flow obstruction and severe congestive heart failure. Right-sided cardiac tumours are usually malignant and appear as bulky, infiltrative masses that grow in an outward pattern. These are usually fast-growing tumours that metastasize early and do not present with congestive heart failure until late in the disease.[2]

Investigations

Cardiac magnetic resonance (CMR) and 3D echocardiography are the investigations of choice for intracardiac tumours.[4] A CT of the chest with contrast agent is needed to exclude lung metastasis of malignant tumours. Two-dimensional transthoracic and transoesophageal echocardiography underestimate tumour mass by as much as 24%.[2]

Therapy

Myxomas are completely excised under cardiopulmonary bypass; this may not always be feasible.[3] Recurrence occurs in 3% of the cases and may be local or in extracardiac locations, such as the brain, lung, and other tissues. Thus, follow-up for more than 10 years is advisable.[1] Malignant primary cardiac tumours have a dismal prognosis, and, without surgical resection, the survival rate at 9 to 12 months is only 10%.[2]

Cardiac metastases

Cardiac metastases are much more common than primary tumours. The frequency of secondary metastatic tumours to the pericardium, myocardium, great vessels, or coronary arteries is between 0.7% and 3.5% at autopsy in the general population, and up to 9.1% in patients with known malignancies.[7,8] In a post-mortem survey of 7289 malignant neoplasms, the highest rate was reported in pleural mesothelioma (48.4%), melanoma (27.8%), lung adenocarcinoma (21%), undifferentiated carcinoma (19.5%), lung squamous cell carcinoma (18.2%), and breast carcinoma (15.5%). Approximately 14% of patients with multiple distant metastases also have cardiac involvement.[7]

Pathophysiology

Tumours can reach the heart via haematogenous or lymphatic spread, and transvenous or direct extension. The pericardium is the most frequently involved site comprising 64 to 69 of all cardiac metastases.[7,9] Epicardial and myocardial involvement (25–30%) and endocardial and intracavitary metastases (3–5%) are more rare.[8]

Table 84.1 Potential clinical manifestations of cardiac metastasis

Pericardial metastasis
Pericarditis, pericardial effusions, and cardiac tamponade
Pericardial adhesions and constrictive pericarditis
Epicardial and myocardial metastasis
Atrial and ventricular arrhythmias and conduction disturbances, including atrial fibrillation with RVR, atrial flutter, complete AV block, PVCs, and ventricular fibrillation
CHF with systolic or diastolic dysfunction
Myocardial ischaemia or infarction from perivascular coronary artery compression, tumour embolism, or coronary invasion
Cardiac rupture
Endocardial and intracavitary metastasis
Intracavitary obstruction, left and right heart failure, cardiogenic shock
Pulmonary tumour emboli from right-sided metastasis
Stroke from tumour emboli from left-sided metastasis
Superior or inferior vena cava metastasis
Superior vena cava syndrome
Inferior vena cava syndrome
Right heart metastasis

AV indicates atrioventricular; CHF, congestive heart failure; PVC, premature ventricular contraction; and RVR, rapid ventricular response.
Goldberg AD, *et al*. Tumors metastatic to the heart. *Circulation*. 2013;**12**:1790–4 with permission from Wolters Kluwer.

Presentation

Potential clinical manifestations are presented in Table 84.1. The most common sign is pericardial effusion. The possibility of cardiac metastasis should be considered in any patient with a malignancy and new cardiac symptoms.

Investigations

Echocardiography is essential but CMR provides additional tissue characterization with a higher resolution than CT. Positron emission tomography/CT may assist differentiation of malignant tumours from benign ones, and allows imaging of the entire body to detect distant extracardiac metastatic disease.[8] Malignant cells can be identified in the majority of pericardial effusions. Exploratory thoracotomy and open or endomyocardial biopsy may also be needed.

Therapy

Cardiac tamponade requires immediate pericardiocentesis. Recurrent effusions may need subxiphoid or transthoracic pericardial windows and percutaneous tube pericardiostomy. Surgical resection is indicated for intracardiac obstruction or when it allows complete removal of the tumour in the context of good prognosis. Radiotherapy and chemotherapy may also be indicated.[9]

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Chapter 85

Pseudoaneurysms of the heart

Introduction

A pseudoaneurysm is a rupture of a blood vessel or of the myocardial wall that is contained by the pericardium, thrombus, or adhesions and has typically a narrow neck.[1] A true aneurysm is contained by all layers of the myocardium or vessel and displays a paradoxical movement, bulging outward during systole. Although their natural history is not well defined, pseudoaneurysms usually have a greater risk of rupture (30–45%) and should thus be considered for immediate repair.[2]

Aetiology

Myocardial infarction is the most common cause of LV pseudoaneurysms. Aortic valvular surgery and endocarditis (pseudoaneurysms at the mitral-aortic intervalvular fibrosa), blunt or penetrating trauma, and radiofrequency ablation are less common causes.[1,2] Pseudoaneurysms of the native coronary arteries may occur after stenting or after spontaneous coronary arterial dissection, whereas pseudoaneurysms of bypass grafts tend to occur at suture line sites or after stenting.[1,2]

Diagnosis

Patients may be asymptomatic or present with a murmur and/or heart failure. Systemic embolism may also occur. Rupture results in tamponade, shock, or sudden death. Transthoracic echocardiography has low sensitivity to detect pseudoaneurysms; transoesophageal echocardiography, cardiac CT, and MRI offer a higher diagnostic yield.[3]

Treatment

Ventricular pseudoaneurysms are more likely to rupture when they are relatively acute (<3 months), large, or located within the anterior or lateral ventricular wall.[4] Saphenous vein graft pseudoaneurysm should be considered for repair if large (>1 cm) or if associated with symptoms.[5] For LV pseudoaneurysms, surgical repair or percutaneous closure may be used.[6] Conservative management may be considered in high-risk patients with chronic pseudoaneurysms. The use of anticoagulation is controversial since it may increase the risk of rupture.

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Part XXI

Cardiovascular disease in pregnancy

Relevant guidelines

ESC 2011 Guidelines on pregnancy

ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**:3147–97.

Chapter 86

Cardiovascular disease in pregnancy

Overview

General issues on cardiovascular disease in pregnancy are discussed. The implications of pregnancy for individual disease entities are also discussed in relevant chapters.

Pregnancy is associated by an increase in blood volume (50%), cardiac output, and heart rate, combined with a decrease in systemic vascular resistance.[1,2] Risk factors (before pregnancy) have been estimated by the CARPEG score (heart disease in general) and the ZAHARA and Khairy *et al*. studies (Table 86.1).[3–5]

In general they are:

- LVEF <40%
- NYHA > II or cyanosis
- Left heart obstruction (mitral valve area <2 cm^2, aortic valve area <1.5 cm^2 with gradient >30 mmHg)
- Prior cardiac event or arrhythmia and use of cardiac medication
- Mechanical valve replacement
- Systemic or pulmonary AV valve regurgitation.

The most prevalent cardiac complications during pregnancy are arrhythmias, heart failure, and hypertensive complications. Spontaneous coronary dissection is rare, but potentially lethal. Neonatal complications increase with:

- Poor functional class or cyanosis
- Left heart obstruction
- Anticoagulation
- Smoking
- Mechanical valve replacement
- Multiple gestations

Women experiencing common pregnancy complications, such as gestational diabetes mellitus, preeclampsia and other hypertensive disorders, intrauterine growth restriction, and preterm delivery, are at increased risk of cardiovascular disease.[6] These complications are prevalent (36%), and provide an opportunity for early identification of women at increased risk of cardiovascular disease later in life. Women with congenital or acquired heart disease may also be at increased risk or unable to tolerate pregnancy.[7] Risks are discussed in relevant chapters.

Tables 86.2 and 86.3 present the ESC recommendations and WHO modified classification for maternal cardiovascular risks.[1,8]

Table 86.1 Predictors of maternal cardiovascular events

Predictors of maternal cardiovascular events and risk score in patients with cardiovascular disease
CARPREG study
Prior cardiac event (heart failure, transient ischaemic attack, stroke before pregnancy or arrhythmia).
Baseline NYHA functional class > II or cyanosis.
Left heart obstruction (mitral valve area <2 cm^2, aortic valve area <1.5 cm^2, peak LV outflow tract gradient >30 mmHg by echocardiography).
Reduced systemic ventricular systolic function (ejection fraction <40%).
CARPREG risk score: for each CARPREG predictor that is present, a point is assigned. Risk estimation of cardiovascular maternal complications
0 point 5%
1 point 27%
>1 point 75%.
Predictors of maternal cardiovascular events identified in congenital heart diseases
ZAHARA 1 study
History of arrhythmia event.
Baseline NYHA functional class > II.
Left heart obstruction (aortic valve peak gradient >50 mm Hg).
Mechanical valve prosthesis.
Moderate/severe systemic atrioventricular valve regurgitation (possibly related to ventricular dysfunction).
Moderate/severe subpulmonary atrioventricular valve regurgitation (possibly related to ventricular dysfunction).
Use of cardiac medication pre-pregnancy.
Repaired or unrepaired cyanotic heart disease.
Khairy *et al*. study
Smoking history.
Reduced subpulmonary ventricular function and/or severe pulmonary regurgitation.

The ESC general recommendations are presented in Table 86.4. Recommendations for specific disorders are presented in the relevant chapters. Table 86.5 presents estimated fetal and maternal effective doses for various diagnostic and interventional radiology procedures, and

Table 86.2 ESC 2011 GL on pregnancy. Modified World Health Organization (WHO) classification of maternal cardiovascular risk: principles

Risk class	Risk of pregnancy by medical condition
I	No detectable increased risk of maternal mortality and no/mild increase in morbidity.
II	Small increased risk of maternal mortality or moderate increase in morbidity.
III	Significantly increased risk of maternal mortality or severe morbidity. Expert counselling required. If pregnancy is decided upon, intensive specialist cardiac and obstetric monitoring needed throughout pregnancy, childbirth, and the puerperium.
IV	Extremely high risk of maternal mortality or severe morbidity; pregnancy contraindicated. If pregnancy occurs, termination should be discussed. If pregnancy continues, care as for class III.

ESC 2011 Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**:3147–97 with permission from Oxford University Press.

Table 86.3 ESC 2011 GL on pregnancy. Modified World Health Organization (WHO) classification of maternal cardiovascular risk: application

Conditions in which pregnancy risk is WHO I
Uncomplicated, small, or mild
Pulmonary stenosis
Patent ductus arteriosus
Mitral valve prolapse
Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous drainage)
Atrial or ventricular ectopic beats, isolated
Conditions in which pregnancy risk is WHO II or III
WHO II (if otherwise well and uncomplicated)
Unoperated atrial or ventricular septal defect
Repaired tetralogy of Fallot
Most arrhythmias
WHO II–III (depending on individual)
Mild left ventricular impairment
Hypertrophic cardiomyopathy
Native or tissue valvular heart disease not considered WHO I or IV
Marfan's syndrome without aortic dilatation
Aorta <45 mm in aortic disease associated with bicuspid aortic valve
Repaired coarctation
WHO III
Mechanical valve
Systemic right ventricle
Fontan circulation
Cyanotic heart disease (unrepaired)
Other complex congenital heart disease
Aortic dilatation 40–45 mm in Marfan's syndrome
Aortic dilatation 45–50 mm in aortic disease associated with bicuspid aortic valve
Conditions in which pregnancy risk is WHO IV (pregnancy contraindicated)
Pulmonary arterial hypertension of any cause
Severe systemic ventricular dysfunction (LVEF <30%, NYHA III/IV)
Previous peripartum cardiomyopathy with any residual impairment of left ventricular function
Severe mitral stenosis, severe symptomatic aortic stenosis
Marfan's syndrome with aorta dilated >45 mm
Aortic dilatation >50 mm in aortic disease associated with bicuspid aortic valve
Native severe coarctation

ESC 2011 Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**:3147–97 with permission from Oxford University Press.

Table 86.4 ESC 2011 on pregnancy. General recommendations

Pre-pregnancy risk assessment and counselling in all women with known or suspected congenital or acquired cardiovascular and aortic disease.	I-C
Risk assessment in all women with cardiac diseases of childbearing age and after conception.	I-C
High-risk patients should be treated in specialized centres by a multidisciplinary team.	I-C
Genetic counselling to women with congenital heart disease or congenital arrhythmia, cardiomyopathies, aortic disease or genetic malformations associated with CVD.	I-C
Echocardiography should be performed in any pregnant patient with unexplained or new cardiovascular signs or symptoms.	I-C
Before cardiac surgery, a full course of corticosteroids should be administered to the mother, whenever possible.	I-C
For the prevention of infective endocarditis in pregnancy, the same measures as in non-pregnant patients should be used.	I-C
Vaginal delivery is recommended as first choice in most patients.	I-C
MRI (without gadolinium) should be considered if echocardiography is insufficient.	IIa-C
In patients with severe hypertension, vaginal delivery with epidural analgesia and elective instrumental delivery should be considered.	IIa-C
When gestational age is at least 28 weeks, delivery before necessary surgery should be considered.	IIa-C
Caesarean delivery for obstetric indications or for patients with dilatation of the ascending aorta >45 mm, severe aortic stenosis, preterm labour while on oral anticoagulants, Eisenmenger's syndrome, or severe heart failure.	IIa-C
Caesarean delivery in Marfan's patients with an aortic diameter 40–45 mm.	IIb-C
Chest radiography, with shielding of the fetus, may be considered if other methods are not successful in clarifying the cause of dyspnoea.	IIb-C
Cardiac catheterization may be considered with very strict indications, timing, and shielding of the fetus.	IIb-C
CT and electrophysiological studies, with shielding of the fetus, may be considered in selected patients for vital indications.	IIb-C
CABG or valvular surgery may be considered when conservative and medical therapy has failed, in situations that threaten the mother's life and that are not amenable to percutaneous treatment.	IIb-C
Prophylactic antibiotic therapy during delivery is not recommended.	III-C

CT, computed tomography; CVD, cardiovascular disease; MRI, magnetic resonance imaging.
ESC 2011 Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**:3147–97 with permission from Oxford University Press.

Table 86.5 ESC 2011 on pregnancy. Estimated fetal and maternal effective doses for various diagnostic and interventional radiology procedures

Procedure	Fetal exposure		Maternal exposure	
Chest radiograph (PA and lateral)	<0.01 mGy	<0.01 mSv	0.1 mGy	0.1 mSv
CT chest	0.3 mGy	0.3 mSv	7 mGy	7 mSv
Coronary angiography[a]	1.5 mGy	1.5 mSv	7 mGy	7 mSv
PCI or radiofrequency catheter ablation[a]	3 mGy	3 mSv	15 mGy	15 mSv

[a] Exposure depends on the number of projections or views.
CT, computed tomography; PA, posteroanterior; PCI, percutaneous coronary intervention.
ESC 2011 Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2011;**32**:3147–97 with permission from Oxford University Press.

Appendix 3 the ESC 2011 recommendations on drug use in pregnancy and breastfeeding.

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Part XXII

Cardiovascular drugs

Relevant guidelines

AHA/ESC 2013 Consensus document on sexual counselling

Sexual counselling for individuals with cardiovascular disease and their partners: A consensus document from the American Heart Association and the ESC Council on Cardiovascular Nursing and Allied Professions (CCNAP). *Eur Heart J.* 2013;**34**:3217–35.

Chapter 87

Cardiovascular drugs

Drug interactions

The cytochrome P450 superfamily (CYP) is a large and diverse group of enzymes that catalyze the oxidation of organic substances, and they are the major enzymes involved in drug metabolism. Permeability glycoprotein (P-gp) mediates the export of drugs from cells located in the small intestine, blood-brain barrier, hepatocytes, and kidney proximal tubule, serving a protective function for the body against foreign substances. Intestinal absorption, biliary excretion, and urinary excretion of P-gp substrates can therefore be altered by either the inhibition or induction of P-gp. A wide spectrum of drugs including cardiovascular drugs are known CYP or P-gp substrates and/or inhibitors, and may interfere with each other's concentrations.[1]

Digoxin, amiodarone, warfarin and new oral anticoagulant agents (thrombin and Xa inhibitors), calcium channel blockers, beta blockers, and antiplatelet agents may be affected by the concomitant administration of anticancer drugs, antibiotics, and steroids. Interactions are discussed in relevant chapters.

Antiarrhythmic drugs

Beta blockers are discussed in Chapter 25 on hypertension and Chapter 32 on heart failure. Other antiarrhythmic agents are discussed in Chapter 50 on tachycarrhythmias.

Antiplatelet agents

Aspirin and $P2Y_{12}$ receptor blockers are discussed mainly in Chapter 28 on UA/NSTEMI.

Anticoagulants

Heparins, fondaparinux, warfarin, and new anticoagulants, such as thrombin and Xa inhibitors, are mainly discussed in Chapter 28 on UA/NSTEMI, Chapter 23 on valve disease, and Chapter 53 on AF.

Beta blockers, diuretics, ACEIs, ARBs, CCBs

They are discussed in the Chapter 25 on hypertension and Chapter 32 on heart failure.

Statins, fibrates

These are mainly discussed in Chapter 30 on stable CAD.

Drugs for erectile dysfunction

Erectile dysfunction is common, affecting almost 40% of men over 40 years of age (with varying degrees of severity) and increases in frequency with age.[2,3] It can be psychogenic, organic, or mixed. The most common causes of organic erectile dysfunction are cardiovascular risk factors (diabetes, hypertension, dyslipidemia, obesity) and testosterone deficiency. Erectile dysfunction is a predictor of coronary artery disease, especially in men >60 years of age.[3]

Phosphodiesterase-5 inhibitors (PDE5Is) (sildenafil [Viagra®], vardenafil [Levitra®], and tadalafil [Cialis®]) are used for erectile dysfunction. Sildenafil (Revatio®) and tadalafil (Adcirca®) are also prescribed for pulmonary hypertension (see Chapter 79). There is now evidence that PDE5Is do not significantly affect the incidence of adverse cardiovascular events.[4] Tadalafil, in particular, has fewer effects on the cardiovascular system than the other PDE5Is, as exemplified by its minimal effects on BP in healthy control subjects.

Sildenafil (50–100 mg) and vardenafil (10–20 mg) lead to peak plasma levels in 60 min and have a half-life of 3–5 hours. Tadalafil (10–20 mg) peaks at 2 hours and has a half-life of 17.5 h, and its absorption is not influenced by food. Reduced initial doses are required for patients with hepatic impairment, creatinine clearance <30 mL/min, and age >65 years.

PDE5Is improve erectile function by enhancing nitric oxide availability in the penis and its supplying vasculature, resulting in vasodilation and increased blood flow. Since phosphodiesterase-5 is also located elsewhere in the body, including the pulmonary and systemic vasculature, and in hypertrophied myocardium, PDE5Is are also used for pulmonary arterial hypertension. Initial evidence also suggests beneficial effects in congestive heart failure, secondary pulmonary hypertension, high-altitude pulmonary oedema, high-altitude pulmonary hypertension, and Raynaud's phenomenon.[5]

Side effects and precautions

Most common side effects are mild headache and flushing. Priapism is rare. A direct link between PDE5Is and optic neuropathy could not be established, but a possible link between

Table 87.1 AHA Statement on sexual activity and cardiovascular disease 2012. Use of PDE5 inhibitors

PDE5 inhibitors are useful for the treatment of erectile dysfunction in patients with stable CVD.	I-A
The safety of PDE5 inhibitors is unknown in patients with severe aortic stenosis or HCM.	IIb-C
PDE5 inhibitors should not be used in patients receiving nitrate therapy.	III-B
Nitrates should not be administered to patients within 24 hours of sildenafil or vardenafil administration or within 48 hours of tadalafil administration.	III-B

Sexual activity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2012;**125**:1058–72 with permission from Wolters Kluwer.

these drugs, especially sildenafil, and hearing impairment has been reported.[2] A potential association of sildenafil with melanoma has also been reported.[6] In a Swedish cohort of men, the use of PDE5 inhibitors was associated with a modest but statistically significant increased risk of malignant melanoma. However, the pattern of association (eg, the lack of association with multiple filled prescriptions) raises questions about whether this association is causal.[7]

PDE5I can be safely given with antihypertensive medications.

Care is needed with nitrates and alpha blockers (Table 87.1).[8]

Nitrates

Penile erections and endothelium-mediated vasodilation are mediated through cGMP, which promotes trabecular and vascular smooth muscle relaxation. PDE5Is prevent the breakdown of cGMP. Nitric oxide donors (i.e. nitrates) increase the production of cGMP. Because both PDE5Is and nitrates increase cGMP, co-administration can generate excess accumulation of cGMP and can trigger marked vasodilation and severe hypotension. Thus, all nitrates are contraindicated for at least 24 h after sildenafil/vardenafil and 48 h after tadalafil.

In case of hypotension due to concomitant administration of nitrates, placing the patient in the Trendelenburg position, aggressive fluid resuscitation, and, if necessary, an α-agonist (phenylephrine) or a β-agonist (norepinephrine) are recommended.[5] There is no antidote to PDE5Is.

α-blockers

'Uroselective' α-blockers (tamsulosin, alfuzosin) preferentially inhibit $\alpha 1_A$ and $\alpha 1_D$ receptors, found primarily in the prostate, and benefit patients with benign prostatic hypertrophy. Other α-blockers (terazosin) are less selective, and some (doxazosin) are used as third-line agents for hypertension because of their higher affinity for $\alpha 1_B$ receptors, which are abundant in the peripheral vasculature. All α-blockers can cause vasodilation and orthostatic hypotension, and co-administration with PDE5Is increases the risk of a clinically significant decrease in BP. This risk is reduced with tadalafil, with uroselective α-blockers, when low doses of α-blockers are used, when dosing is separated by several hours (instead of simultaneously), and when patients are on stable therapy with one agent before the other drug class is administered.[4]

Other drug interactions

PDE5I are metabolized mainly by the cytochrome P450 (mainly 3A4 cytochrome) pathway, and their concentrations may be increased by drugs, such as cimetidine, erythromycin, clarithromycin, and ciprofloxacin (mainly sildenafil), ketoconazole (mainly vardenafil and tadalafil), and ritonavir. Rifampin and bosentan may reduce their levels. QT prolongation is minimal with PDE5Is. Vardenafil and sildenafil have been studied and produced no increase of absolute QT and only similar small increases of the QTc interval, with a shallow dose–response curve.[9]

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Appendix 1

Recommendation classes and levels of evidence used in guidelines

Conversion of units

Cholesterol	mg/dL	x 0.026	to	mmol/L
Creatinine	mg/dL	x 88.4	to	µmol/L
Digoxin	ng/mL	x 1.28	to	nmol/L
Glucose	mg/dL	x 0.055	to	mmol/L

ESC

CLASSES OF RECOMMENDATIONS

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

LEVELS OF EVIDENCE

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

ACC/AHA

Applying class of recommendation and level of evidence to clinical strategies, interventions, treatments, or diagnostic testing in patient care*

CLASS (STRENGTH) OF RECOMMENDATION

Class I (Strong)	**Benefit >>> Risk**
Suggested phrases for writing recommendations:	
Is recommended	
Is indicated/useful/effective/beneficial	
Should be performed/administered/other	
Comparative-Effectiveness Phrases†:	
• Treatment/strategy A is recommended/indicated in preference to treatment B	
• Treatment A should be chosen over treatment B	
Class IIa (Moderate)	**Benefit >> Risk**
Suggested phrases for writing recommendations:	
Is reasonable	
Can be useful/effective/beneficial	
Comparative-Effectiveness Phrases†:	
• Treatment/strategy A is probably recommended/indicated in preference to treatment B	
• It is reasonable to choose treatment A over treatment B	
Class IIb (Weak)	**Benefit ≥ Risk**
Suggested phrases for writing recommendations:	
May/might be reasonable	
May/might be considered	
Usefulness/effectiveness is unknown/unclear/uncertain or not well established	
Class III: No Benefit (Moderate) *(Generally, LOE A or B use only)*	**Benefit = Risk**
Suggested phrases for writing recommendations:	
Is not recommended	
Is not indicated/useful/effective/beneficial	
Should not be performed/administered/other	
Class III: Harm (Strong)	**Risk > Benefit**
Suggested phrases for writing recommendations:	
Potentially harmful	
Causes harm	
Associated with excess morbidity/mortality	
Should not be performed/administered/other	

LEVEL (QUALITY) OF EVIDENCE‡

Level A	
High-quality evidence‡ from more than 1 RCTs.	
Meta-analyses of high-quality RCTs	
One or more RCTs corroborated by high-quality registry studies	
Level B-R	**(Randomized)**
Moderate-quality evidence‡ from 1 or more RCTs	
Meta-analyses of moderate-quality RCTs	
Level B-NR	**(Nonrandomized)**
Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies	
Meta-analyses of such studies	
Level C-LD	**(Limited Data)**
Randomized or nonrandomized observational or registry studies with limitations of design or execution	
Meta-analyses of such studies	
Physiological or mechanistic studies in human subjects	
Level C-EO	**(Expert Opinion)**
Consensus of expert opinion based on clinical experience	

COR and LOE are determined independently (any COR may be paired with any LOE). **SR**, used as level of evidence, indicates systematic review.
A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.
* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).
† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.
‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools: and for systematic reviews, the incorporation of an Evidence Review Committee.
COR indicates class of recommendation; EO, expert opinion; LD, limited data; LOE, level of evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

Appendix 2

Specific therapy of endocarditis

Recent recommendations by AHA (2015) and ESC (2015) are presented. See also http://www.idsociety.org/IDSA_Practice_Guidelines.

AHA 2015 Statement on IE. Therapy of Native Valve Endocarditis Caused by Highly Penicillin-Susceptible VGS and *Streptococcus gallolyticus (bovis)*

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Aqueous crystalline penicillin G sodium	12–18 million U/24 h IV either continuously or in 4 or 6 equally divided doses	4	IIa-B	Preferred in most patients >65 y or patients with impairment of eighth cranial nerve function or renal function.
Or				Ampicillin 2 g IV every 4 h is a reasonable alternative to penicillin if a penicillin shortage exists.
Ceftriaxone sodium	2 g/24 h IV/IM in 1 dose	4	IIa-B	
Aqueous crystalline penicillin G sodium	12–18 million U/24 h IV either continuously or in 6 equally divided doses	2	IIa-B	2-wk regimen not intended for patients with known cardiac or extracardiac abscess or for those with creatinine clearance of <20 mL/min, impaired eighth cranial nerve function, or *Abiotrophia, Granulicatella,* or *Gemella* spp infection; gentamicin dose should be adjusted to achieve peak serum concentration of 3–4 µg/mL and trough serum concentration of <1 µg/mL when 3 divided doses are used; there are no optimal drug concentrations for single daily dosing.†
Or				
Ceftriaxone sodium	2 g/24 h IV or IM in 1 dose	2	IIa-B	
Plus				
Gentamicin sulfate‡	3 mg/kg per 24 h IV or IM in 1 dose	2		
Vancomycin hydrochloride§	30 mg/kg per 24 h IV in 2 equally divided doses	4	IIa-B	Vancomycin therapy is reasonable only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dose should be adjusted to a trough concentration range of 10–15 µg/mL

IM indicates intramuscular; IV, intravenous; and VGS, viridans group streptococci. Minimum inhibitory concentration is ≤0.12 µg/mL. The subdivisions differ from Clinical and Laboratory Standards Institute-recommended break points that are used to define penicillin susceptibility.

*Doses recommended are for patients with normal renal function.

†Data for once-daily dosing of aminoglycosides for children exist, but no data for treatment of IE exist.

‡Other potentially nephrotoxic drugs (e.g., nonsteroidal anti-inflammatory drugs) should be used with caution in patients receiving gentamicin therapy. Although it is preferred that gentamicin (3 mg/kg) be given as a single daily dose to adult patients with endocarditis caused by viridans group streptococci, as a second option, gentamicin can be administered daily in 3 equally divided doses.

§Vancomycin dosages should be infused during the course of at least 1 hour to reduce the risk of histamine-release "red man" syndrome.

AHA 2015 Statement on IE. Therapy of Native Valve Endocarditis Caused by Strains of VGS and *Streptococcus gallolyticus (bovis)* Relatively Resistant to Penicillin

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Aqueous crystalline penicillin G sodium	24 million U/24 h IV either continuously or in 4–6 equally divided doses	4	IIa-B	It is reasonable to treat patients with IE caused penicillin-resistant (MIC ≥0.5 μg/mL) VGS strains with a combination of ampicillin or penicillin plus gentamicin as done for enterococcal IE with infectious diseases consultation (*Class IIa; Level of Evidence C*). Ampicillin 2 g IV every 4 h is a reasonable alternative to penicillin if a penicillin shortage exists.
Plus				
Gentamicin sulfate†	3 mg/kg per 24 h IV or IM in 1 dose	2		Ceftriaxone may be a reasonable alternative treatment option for VGS isolates that are susceptible to ceftriaxone (*Class IIb; Level of Evidence C*).
Vancomycin hydrochloride‡	30 mg/kg per 24 h IV in 2 equally divided doses	4	IIa-B	Vancomycin therapy is reasonable only for patients unable to tolerate penicillin or ceftriaxone therapy.

MIC is >0.12 to <0.5 μg/mL for penicillin. The subdivisions differ from Clinical and Laboratory Standards Institute-recommended break points that are used to define penicillin susceptibility.
*Doses recommended are for patients with normal renal function.
†See previous Table for appropriate dose of gentamicin. Although it is preferred that gentamicin (3 mg/kg) be given as a single daily dose to adult patients with endocarditis caused by viridans group streptococci, as a second option, gentamicin can be administered daily in 3 equally divided doses.
‡See previous Table for appropriate dosage of vancomycin.

AHA 2015 Statement on IE. Therapy for Endocarditis Involving a Prosthetic Valve or Other Prosthetic Material Caused by VGS and *Streptococcus gallolyticus (bovis)*

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Penicillin-susceptible strain (≤0.12 μg/mL)				
Aqueous crystalline penicillin G sodium	24 million U/24 h IV either continuously or in 4–6 equally divided doses	6	IIa-B	Penicillin or ceftriaxone together with gentamicin has not demonstrated superior cure rates compared with monotherapy with penicillin or ceftriaxone for patients with highly susceptible strain; gentamicin therapy should not be administered to patients with creatinine clearance <30 mL/min.
Or				
Ceftriaxone	2 g/24 h IV or IM in 1 dose	6	IIa-B	
With or without				
Gentamicin sulfate†	3 mg/kg per 24 h IV or IM in 1 dose	2		Ampicillin 2 g IV every 4 h is a reasonable alternative to penicillin if a penicillin shortage exists.
Vancomycin hydrochloride‡	30 mg/kg per 24 h IV in 2 equally divided doses	6	IIa-B	Vancomycin is reasonable only for patients unable to tolerate penicillin or ceftriaxone.
Penicillin relatively or fully resistant strain (MIC >0.12 μg/mL)				
Aqueous crystalline penicillin sodium	24 million U/24 h IV either continuously or in 4–6 equally divided doses	6	IIa-B	Ampicillin 2 g IV every 4 h is a reasonable alternative to penicillin if a penicillin shortage exists.
Or				

(*Continued*)

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Ceftriaxone	2 g/24 h IV/IM in 1 dose	6	IIa-B	
Plus				
Gentamicin sulfate	3 mg/kg per 24 h IV/IM in 1 dose	6		
Vancomycin hydrochloride	30 mg/kg per 24 h IV in 2 equally divided doses	6	IIa-B	Vancomycin is reasonable only for patients unable to tolerate penicillin or ceftriaxone.

*Doses recommended are for patients with normal renal function.
†See previous Table for appropriate dose of gentamicin. Although it is preferred that gentamicin (3 mg/kg) be given as a single daily dose to adult patients with endocarditis resulting from VGS, as a second option, gentamicin can be administered daily in 3 equally divided doses.
‡See previous Table for appropriate dose of vancomycin.

ESC 2015 GL on Endocarditis. Antibiotic treatment of IE due to oral streptococci and *Streptococcus* bovis group

Antibiotic	Dosage and route	Duration, wk	Strength of Recommendation	Comments
Strains penicillin-susceptible (MIC ≤ 0.125 mg/L) or al and digestive streptococci				
Standard treatment: 4-week duration				
Penicillin G	12–18 million U/day i.v. either in 4–6 doses or continuously	4	I-B	Preferred in patients > 65 years or with impaired renal or VIII (vestibulocochlear) cranial nerve functions.
or				
Amoxicillin[a]	100–200 mg/kg/day i.v. in 4–6 doses	4	I-B	
or				
Ceftriaxone[b]	2 g/day i.v. or i.m. in 1 dose	4	I-B	6-week therapy recommended for patients with PVE
	Paediatric doses:[c]			
	Penicillin G 200,000 U/kg/day i.v. in 4–6 divided doses			
	Amoxicillin 300 mg/kg/day i.v. in 4–6 equally divided doses			
	Ceftriaxone 100 mg/kg/day i.v. or i.m. in 1 dose			
Standard treatment: 2-week duration				
Penicillin G	12–18 million U/day i.v. either in 4–6 doses or continuously	2	I-B	Only recommended in patients with non-complicated NVE with normal renal function.
or				
Amoxicillin[a]	100–200 mg/kg/day i.v. in 4–6 doses	2	I-B	
or				
Ceftriaxone[b]	2 g/day i.v. or i.m. in 1 dose	2	I-B	
combined with				
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 doses	2	I-B	
or				

(*Continued*)

Antibiotic	Dosage and route	Duration, wk	Strength of Recommendation	Comments
Netilmicin	4–5 mg/kg/day i.v. in 1 dose	2	I-B	Netilmicin is not available in all European countries.
	Paediatric doses:[c]			
	Penicillin G, amoxicillin, and ceftriaxone as above			
	Gentamicin 3 mg/kg/day i.v. or i.m. in 1 dose or 3 equally divided doses			
In beta-lactam allergic patients[e]				
Vancomycin[j]	30 mg/kg/day i.v. in 2 doses	4	I-C	6-week therapy recommended for patients with PVE
	Paediatric doses:[c]			
	Vancomycin 40 mg/kg/day i.v. in 2 or 3 equally divided doses			
Strains relatively resistant to penicillin (MIC 0.250–2 mg/l)[k]				
Standard treatment				
Penicillin G	24 million U/day i.v. either in 4–6 doses or continuously	4	I-B	6-week therapy recommended for patients with PVE
or				
Amoxicillin[e]	200 mg/kg/day i.v. in 4–6 doses	4	I-B	
or				
Ceftriaxone[b]	2 g/day i.v. or i.m. in 1 dose	4	I-B	
combined with				
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose	2	I-B	
In beta-lactam allergic patients[e]				
Vancomycin[f]	30 mg/kg/day i.v. in 2 doses	4	I-C	6-week therapy recommended for patients with PVE
with				
Gentamicin[g]	3 mg/kg/day i.v. or i.m. in 1 dose	2	I-C	
	Paediatric doses:[c]			
	As above			

C_{min}, minimum concentration; MIC, minimum inhibitory concentration; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis; U, units.

[a] Or ampicillin, same dosages as amoxicillin.

[b] Preferred for outpatient therapy.

[c] Paediatric doses should not exceed adult doses.

[d] Renal function and serum gentamicin concentrations should be monitored once a week. When given in a single daily dose, pre-dose (trough) concentrations should be < 1 mg/L and post-dose (peak; 1 hour after injection) serum concentrations should be 10–12 mg/L.

[e] Penicillin desensitization can be attempted in stable patients.

[f] Serum vancomycin concentrations should achieve 10–15 mg/L at pre-dose (trough) level, although some experts recommend to increase the dose of vancomycin to 45–60 mg/kg/day i.v. in 2 or 3 divided doses to reach serum trough vancomycin levels (C_{min}) of 15– 20 mg/L as in staphylococcal endocarditis. However, vancomycin dose should not exceed 2 g/d unless serum levels are monitored and can be adjusted to obtain a peak plasma concentration of 30–45 mg/mL 1 hour after completion of the i.v. infusion of the antibiotic.

[g] Patients with penicillin-resistant strains (MIC >2 mg/L) should be treated as enterococcal endocarditis.

AHA 2015 Statement on IE. Therapy for Native Valve Endocarditis caused by staphylococci

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Oxacillin-susceptible strains				
Nafcillin or oxacillin	12 g/24 h IV in 4–6 equally divided doses	6	I-C	For complicated right-sided IE and for left-sided IE; for uncomplicated right-sided IE, 2 wk.
For penicillin-allergic (nonanaphylactoid type) patients				Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin.
Cefazolin*	6 g/24 h IV in 3 equally divided doses	6	I-B	Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to β-lactams; vancomycin should be used in these cases.
Oxacillin-resistant strains				
Vancomycin§	30 mg/kg per 24 h IV in 2 equally divided doses	6	I-C	Adjust vancomycin dose to achieve trough concentration of 10–20 μg/mL.
Daptomycin	≥8 mg/kg/dose	6	IIb-B	Await additional study data to define optimal dosing.

*Doses recommended are for patients with normal renal function.
§For specific dosing adjustment and issues concerning vancomycin, see previous Tables

AHA 2015 Statement on IE. Therapy for Endocarditis Involving a Prosthetic Valve or Other Prosthetic Material Caused by Staphylococci

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Oxacillin-susceptible strains				
Nafcillin or oxacillin	12 g/24 h IV in 6 equally divided doses	≥6	I-B	Vancomycin should be used in patients with immediate-type hypersensitivity reactions to β-lactam antibiotics; cefazolin may be substituted for nafcillin or oxacillin in patients with non-immediate-type hypersensitivity reactions to penicillins.
Plus				
Rifampin	900 mg per 24 h IV or orally in 3 equally divided doses	≥6		
Plus				
Gentamicin†	3 mg/kg per 24 h IV or IM in 2 or 3 equally divided doses	2		
Oxacillin-resistant strains				
Vancomycin	30 mg/kg 24 h in 2 equally divided doses	≥6	I-B	Adjust vancomycin to a trough concentration of 10–20 μg/mL.
Plus				
Rifampin	900 mg/24 h IV/PO in 3 equally divided doses	≥6		
Plus				
Gentamicin	3 mg/kg per 24 h IV/IM in 2 or 3 equally divided doses	2		

*Doses recommended are for patients with normal renal function.
†Gentamicin should be administered in close proximity to vancomycin, nafcillin, or oxacillin dosing. See previous Tables for appropriate dose of gentamicin.

ESC 2015 GL on endocarditis. Antibiotic treatment of IE due to *Staphylococcus* spp.

Antibiotic	Dosage and route	Duration, wk	Strength of Recommendation	Comments
Native valves				
Methicillin-susceptible staphylococci				
(Flu)cloxacillin or oxacillin	12 g/day i.v. in 4–6 doses	4–6	I-B	Gentamicin addition is not recommended because clinical benefit has not been demonstrated and there is increased renal toxicity
	Paediatric doses:[g] 200–300 mg/kg/day i.v. in 4–6 equally divided doses			
Alternative therapy*				
Co-trimoxazole[a] with Clindamycin	Sulfamethoxazole 4800 mg/day and Trimethoprim 960 mg/day (i.v. in 4–6 doses)	1 i.v. + 5 oral intake	IIb-C	*for *Staphylococcus aureus*
	1800mg/day i.v. in 3 doses	1	IIb-C	
	Paediatric doses:[g] Sulfamethoxazole 60 mg/kg/day and Trimethoprim 12 mg/kg/day (i.v. in 2 doses) Clindamycin 40 mg/kg/day (i.v. in 3 doses)			
Penicillin-allergic patients[h] or methicillin-resistant staphylococci				
Vancomycin[b] **	30–60 mg/kg/day i.v. in 2–3 doses	4–6	I-B	**Cephalosporins** (cefazolin 6 g/day or cefotaxime 6 g/day i.v. in 3 doses) are recommended for penicillin-allergic patients with non-anaphylactic reactions with methicillin-susceptible endocarditis
	Paediatric doses:[g] 40 mg/kg/day i.v. in 2–3 equally divided doses			
Alternative therapy*				
Daptomycin[c,d]	10 mg/kg/day i.v. once daily	4–6	IIa-C	**Daptomycin** is superior to vancomycin for MSSA and MRSA bacteraemia with vancomycin MIC > 1 mg/L
	Paediatric doses:[g] 10 mg/kg/day i.v. once daily			
Alternative therapy*				
Co-trimoxazole[a] with Clindamycin	Sulfamethoxazole 4800 mg/day and Trimethoprim 960 mg/day (i.v. in 4–6 doses) 1800mg/day IV in 3 doses	1 i.v. + 5 oral intake	IIb-C	*for *Staphylococcus aureus*
		1	IIb-C	
Prosthetic valves				
Methicillin-susceptible staphylococci				
(Flu)cloxacillin *or* oxacillin with Rifampin[e] and Gentamicin[f]	12 g/day i.v. in 4–6 doses	≥ 6	I-B	
	900–1200 mg i.v. or orally in 2 or 3 divided doses	≥ 6	I-B	Starting rifampin 3–5 days later than vancomycin and gentamicin has been suggested by some experts.
	3 mg/kg/day i.v. or i.m. in 1 or 2 doses	2	I-B	Gentamicin can be given in a single daily dose in order to reduce renal toxicity
	Paediatric doses:[g] Oxacillin and (flu)cloxacillin as above Rifampin 20 mg/kg/day i.v. or orally in 3 equally divided doses			

(*Continued*)

Antibiotic	Dosage and route	Duration, wk	Strength of Recommendation	Comments
Penicillin-allergic patients[h] and methicillin-resistant staphylococci				
Vancomycin[b]	30–60 mg/kg/day i.v. in 2–3 doses	≥ 6	I-B	**Cephalosporins** (cefazolin 6 g/day or cefotaxime 6 g/day i.v. in 3 doses) are recommended for penicillin-allergic patients with non-anaphylactic reactions with methicillin-susceptible endocarditis. Starting rifampin 3–5 days later than vancomycin and gentamicin has been suggested by some experts. Gentamicin can be given in a single daily dose in order to reduce renal toxicity
with	900–1200 mg i.v. or orally in 2 or 3 divided doses	≥ 6	I-B	
Rifampin[*]	3 mg/kg/day i.v. or i.m. in 1 or 2 doses	2	I-B	
and				
Gentamicin[f]				
	Paediatric dosing:[g] As above			

AUC, area under the curve; C_{min}, minimum concentration; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-susceptible S. aureus; PVE, prosthetic valve endocarditis.

[a] Renal function, serum co-trimoxazole concentrations should be monitored once/week (twice/week in patients with renal failure).

[b] Serum trough vancomycin levels (C_{min}) should be ≥20 mg/L. A vancomycin AUC/MIC >400 is recommended for MRSA infections.

[c] Monitor plasma CPK levels at least once a week. Some experts recommend adding cloxacillin (2 g/4 h i.v.) or fosfomycin (2 g/6 h i.v.) to daptomycin in order to increase activity and avoid the development of daptomycin resistance.

[d] Daptomycin and fosfomycin are not available in some European countries.

[e] Rifampin is believed to play a special role in prosthetic device infection because it helps eradicate bacteria attached to foreign material. The sole use of rifampin is associated with a high frequency of microbial resistance and is not recommended. Rifampin increases the hepatic metabolism of warfarin and other drugs.

[f] Renal function and serum gentamicin concentrations should be monitored once/week (twice/week in patients with renal failure).

[g] Paediatric doses should not exceed adult doses.

[h] Penicillin desensitization can be attempted in stable patients.

[**] No clinical benefit of adding rifampicin or gentamicin.

AHA 2015 Statement on IE. Therapy for Endocarditis Involving a Native or Prosthetic Valve or Other Prosthetic Material Resulting From *Enterococcus* Species Caused by Strains Susceptible to Penicillin and Gentamicin in Patients Who Can Tolerate β-lactam Therapy*

Regimen	Dose† and Route	Duration, wk	Strength of Recommendation	Comments
Either			IIa-B	Native valve: 4-wk therapy recommended for patients with symptoms of illness <3 mo; 6-wk therapy recommended for native valve symptoms >3 mo and for patients with prosthetic valve or prosthetic material. Recommended for patients with creatinine clearance >50 mL/min.
Ampicillin sodium	2 g IV every 4 h	4–6		
Or		4–6	IIa-B	
Aqueous penicillin G sodium	18–30 million U/24 h IV either continuously or in 6 equally divided doses	4–6		
Plus				
Gentamicin sulfate‡	3 mg/kg ideal body weight in 2–3 equally divided doses			
Or			IIa-B	Recommended for patients with initial creatinine clearance <50 mL/min or who develop creatinine clearance <50 mL/min during therapy with gentamicin-containing regimen.
Double β-lactam Ampicillin	2 g IV every 4 h	6		
Plus				
Ceftriaxone	2 g IV every 12 h	6		

*For patients unable to tolerate a β-lactam, see following Tables.

†Doses recommended are for patients with normal renal and hepatic function.

‡Dose of gentamicin should be adjusted to achieve a peak serum concentration of 3 to 4 μg/mL and a trough concentration of <1 μg/mL.

AHA 2015 Statement on IE. Therapy for Endocarditis Involving a Native or Prosthetic Valve or Other Prosthetic Material Resulting From *Enterococcus* Species Caused by a Strain Susceptible to Penicillin and Resistant to Aminoglycosides or Streptomycin-Susceptible Gentamicin-Resistant in Patients Able to Tolerate β-lactam Therapy*

Regimen	Dose† and Route	Duration, wk	Strength of Recommendation	Comments
Double β-lactam			IIa-B	Double β-lactam is reasonable for patients with normal or impaired renal function abnormal cranial nerve VIII function or if the laboratory is unable to provide rapid results of streptomycin serum concentration; native valve infection with symptoms of infection <3-mo duration may be treated for 4 wk with the streptomycin-containing regimen. PVE, NVE with symptoms >3 mo, or treatment with a double β-lactam regimen require a minimum of 6 wk of therapy.
Ampicillin	2 g IV every 4 h	6		
Plus				
Ceftriaxone	2 g IV every 12 h			
Alternative for streptomycin susceptible/ gentamicin resistant				
Either		4–6	IIa-B	Use is reasonable only for patients with availability of rapid streptomycin serum concentrations. Patients with creatinine clearance <50 mL/min or who develop creatinine clearance <50 mL/min during treatment should be treated with double–β-lactam regimen. Patients with abnormal cranial nerve VIII function should be treated with double–β-lactam regimen.
Ampicillin sodium	2 g IV every 4 h			
Or				
Aqueous penicillin G sodium	18–30 million U/24 h IV either continuously or in 6 equally divided doses			
Plus				
Streptomycin sulfate‡	15 mg/kg ideal body weight per 24h IV or IM in 2 equally divided doses			

NVE, native valve infective endocarditis; PVE, prosthetic valve infective endocarditis.
*For patients unable to tolerate a β-lactam, see following Table.
†Doses recommended for patients with normal renal and hepatic function.
‡Streptomycin dose should be adjusted to obtain a serum peak concentration of 20 to 35 μg/mL and a trough concentration of <10 μg/mL.

Vancomycin-Containing Regimens for Vancomycin- and Aminoglycoside-Susceptible Penicillin-Resistant *Enterococcus* Species for Native or Prosthetic Valve (or Other Prosthetic Material) IE in Patients Unable to Tolerate β-lactam

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Unable to tolerate β-lactams				
Vancomycin†	30 mg/kg per 24 h IV in 2 equally divided doses	6	IIa-B	
Plus				
Gentamicin‡	3 mg/kg per 24 h IV or IM in 3 equally divided doses	6		
Penicillin resistance; intrinsic or β-lactamase producer				
Vancomycin	30 mg/kg per 24 h IV in 2 equally divided doses	6	IIb-C	For β-lactamase–producing strain, if able to tolerate a β-lactam antibiotic, ampicillin-sulbactam§ plus aminoglycoside therapy may be used.
Plus				
Gentamicin‡	3 mg/kg per 24 h IV or IM in 3 equally divided doses	6		

*Doses recommended are for adults with normal renal function.
†Dose of vancomycin should be adjusted to obtain a serum trough concentration of 10 to 20 μg/mL.
‡Dose of gentamicin should be adjusted to obtain serum peak and trough concentrations of 3 to 4 and <1 μg/mL, respectively.
§Ampicillin-sulbactam dosing is 3 g/6 hour IV.

Therapy for Endocarditis Involving a Native or Prosthetic Valve or Other Prosthetic Material Resulting from *Enterococcus* Species Caused by Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin

Regimen	Dose* and Route	Durating, wk	Strength of Recommendation	Comments
Linezolid	600 mg IV or orally every 12 h	>6	IIb-C	Linezolid use may be associated with potentially severe bone marrow suppression, neuropathy, and numerous drug interactions. Patients with IE caused by these strains should be treated by a care team including specialists in infectious diseases, cardiology, cardiac surgery, clinical pharmacy, and, in children, pediatrics. Cardiac valve replacement may be necessary for cure.
Or				
Daptomycin	10–12 mg/kg per dose	>6	IIb-C	

*Doses recommended are for patients with normal renal and hepatic function.

ESC 2015 GL on endocarditis. Antibiotic treatment of IE due to *Enterococcus* spp.

Antibiotic	Dosage and route	Duration, wk	Strength of Recommendation	Comments
Beta-lactam and gentamicin-susceptible strains (for resistant isolates see[a,b,c])				
Amoxicillin[*] with Gentamicin[d]	200 mg/kg/day i.v. in 4–6 doses	4–6	I-B	6-week therapy recommended for patients with > 3 months symptoms or PVE
	3 mg/kg/day i.v. or i.m. in 1 dose	2–6[**]	I-B	
	Paediatric doses:[e] Ampicillin 300 mg/kg/day i.v. in 4–6 equally divided doses Gentamicin 3 mg/kg/day i.v. or i.m. in 3 equally divided doses			
Ampicillin with	200 mg/kg/day i.v. in 4–6 doses	6	I-B	This combination is active against *Enterococcus faecalis* strains with and without HLAR, being the combination of choice in patients with HLAR *E. faecalis* endocarditis.
Ceftriaxone	4 g/day i.v. or i.m. in 2 doses	6	I-B	
	Paediatric doses:[e] Amoxicillin as above Ceftriaxone 100 mg/kg/12 h i.v. or i.m.			This combination is not active against *E. faecium*
Vancomycin[f] with	30 mg/kg/day i.v. in 2 doses	6	I-C	
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose	6	I-C	
	Paediatric doses:[e] Vancomycin 40 mg/kg/day i.v. in 2–3 equally divided doses. Gentamicin as above			

HLAR, high-level aminoglycoside resistance; MIC, minimum inhibitory concentration; PBP, penicillin binding protein; PVE, prosthetic valve endocarditis.

[a] High level resistance to gentamicin (MIC >500 mg/L): if susceptible to streptomycin, replace gentamicin with streptomycin 15 mg/kg/day in two equally divided doses (I, A). Otherwise, use more prolonged course of β-lactam therapy. The combination of ampicillin with ceftriaxone was recently suggested for gentamicin-resistant E. faecalis (IIa, B).

[b] β-Lactam resistance: (i) if due to β-lactamase production, replace ampicillin with ampicillin–sulbactam or amoxicillin with amoxicillin–clavulanate (I, C); (ii) if due to PBP5 alteration, use vancomycin-based regimens.

[c] Multiresistance to aminoglycosides, β-lactams, and vancomycin: suggested alternatives are (i) daptomycin 10 mg/kg/day plus ampicillin 200 mg/kg/day i.v. in four to six doses; (ii) linezolid 2 × 600 mg/day i.v. or orally for ≥8 weeks (IIa, C) (monitor haematological toxicity); (iii) quinupristin–dalfopristin 3 × 7.5 mg/kg/day for ≥8 weeks. Quinupristin–dalfopristin is not active against *E. faecalis*; (iv) for other combinations (daptomycin plus ertapenem or ceftaroline), consult infectious diseases.

[d] Monitor serum levels of aminoglycosides and renal function.

[e] Paediatric doses should not exceed adult doses.

[f] Monitor serum vancomycin concentrations as stated previously.

[*] Or ampicillin, same dosages as amoxicillin.

[**] Some experts recommend giving gentamicin for only 2 weeks (IIa, B).

AHA 2015 Statement on IE. Therapy for Endocarditis Involving a Native or Prosthetic Valve or Other Prosthetic Material Caused by HACEK Microorganisms

Regimen	Dose and Route	Duration, wk	Strength of Recommendation	Comments
Ceftriaxone sodium*	2 g/24 h IV or IM in 1 dose	4	IIa-B	Preferred therapy: cefotaxime or another third- or fourth-generation cephalosporin may be substituted.
Or				
Ampicillin sodium	2 g IV every 4 h		IIa-B	Ampicillin sodium may be an option if the growth of the isolate is sufficient to permit in vitro susceptibility results.
Or				
Ciprofloxacin†	1000 mg/24 h orally or 800 mg/24 h IV in 2 equally divided doses		IIb-C	Fluoroquinolone therapy‡ may be considered for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin or moxifloxacin may be substituted; fluoroquinolones generally is not recommended for patients <18 y old. Treatment for 6 wk is reasonable in patients with PVE (*Class IIa; Level of Evidence C*).

HACEK indicates *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species.
*Patients should be informed that intramuscular injection of ceftriaxone is painful.
†Dose recommended for patients with normal renal function.
‡Fluoroquinolones are highly active in vitro against HACEK microorganisms. Published data on the use of fluoroquinolones for endocarditis caused by HACEK are minimal.

ESC 2011 Guidelines on pregnancy

Recommendations on drug use in pregnancy and breastfeeding

A The Guideline Committee added acenocoumarol and phenprocoumon in analogy to warfarin to this list. The necessity for risk assessment also applies to these two OAC. Previously, the risk category X was attributed to warfarin. In the opinion of the Task Force, available evidence suggests that risk category D is more appropriate for warfarin and other vitamin K antagonists.

B Adenosine: most of the experiences with this drug are in the second and third trimesters. Its short half-life may prevent it from reaching the fetus.

C Atenolol is classified D by FDA; nevertheless, some authors classify it as C.

D The available data on first-trimester use do not strongly support teratogenic potential.

Because ACE inhibitors, angiotensin II receptor blockers, aldosterone antagonists, and renin inhibitors should be avoided during pregnancy and breastfeeding, the risk category is D. Positive outcomes with ACE inhibitors have been described, and pregnancy does not have to be terminated if the patient was exposed to these medications but should be followed up closely.

E Breastfeeding is possible if the mother is treated with the drug.

F Digoxin: the experience with digoxin is extensive, and it is considered to be the safest antiarrhythmic drug during pregnancy. A prophylactic antiarrhythmic efficacy has never been demonstrated.

G Statins: should not be prescribed in pregnancy and during breastfeeding since their harmlessness is not proven, and disadvantages to the mother are not to be expected by a temporary interruption of the therapy for the time period of pregnancy.

Drugs	Classification (Vaughan Williams for AA drugs)	FDA category	Placenta permeable	Transfer to breast milk (fetal dose)	Adverse effects
Abciximab	Monoclonal antibody with antithrombotic effects	C	Unknown	Unknown	Inadequate human studies; should be given only if the potential benefit outweighs the potential risk to the fetus
Acenocoumarol[a]	Vitamin K antagonist	D	Yes	Yes (no adverse effects reported)	Embryopathy (mainly first trimester), bleeding
Acetylsalicylic acid (low dose)	Antiplatelet drug	B	Yes	Well-tolerated	No teratogenic effects known (large datasets)
Adenosine[b]	Antiarrhythmic	C	No	No	No fetal adverse effects reported (limited human data)
Aliskiren	Renin inhibitor	D	Unknown	Unknown	Unknown (limited experience)
Amiodarone	Antiarrhythmic (class III)	D	Yes	Yes	Thyroid insufficiency (9%), hyperthyroidism, goitre, bradycardia, growth retardation, premature birth
Ampicillin, amoxicillin, cephalosporins, erythromycin, mezlocillin, penicillin	Antibiotics	B	Yes	Yes	No fetal adverse effects reported
Imipenem, rifampicin, telcoplanin, vancomycin	Antibiotics	C	Unknown	Unknown	Risk cannot be excluded (limited human data)
Aminoglycosides, quinolones, tetracyclines	Antibiotics	D	Unknown	Unknown	Risk to the fetus exists (reserved for vital indications)
Atenolol[c]	β-blocker (class II)	D	Yes	Yes	Hypospadias (first trimester); birth defects, low birthweight, bradycardia, and hypoglycaemia in fetus (second and third trimester)

(*Continued*)

Drugs	Classification (Vaughan Williams for AA drugs)	FDA category	Placenta permeable	Transfer to breast milk (fetal dose)	Adverse effects
Benazepril[d]	ACE inhibitor	D	Yes	Yes[e] (maximum 1.6%)	Renal or tubular dysplasia, oligohydramnios, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, intrauterine fetal death
Bisoprolol	β-blocker (class II)	C	Yes	Yes	Bradycardia and hypoglycaemia in fetus
Candesartan	Angiotensin II receptor blocker	D	Unknown	Unknown; not recommended	Renal or tubular dysplasia, oligohydramnios, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, intrauterine fetal death
Captopril[d]	ACE inhibitor	D	Yes	Yes[e] (maximum 1.6%)	Renal or tubular dysplasia, oligohydramnios, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, intrauterine fetal death
Clopidogrel	Antiplatelet drug	C	Unknown	Unknown	No information during pregnancy available
Colestipol, cholestyramine	Lipid-lowering drugs	C	Unknown	Yes, lowering fat-soluble vitamins	May impair absorption of fat-soluble vitamins, e.g. vitamin K > cerebral bleeding (neonatal)
Danaparoid	Anticoagulant	B	No	No	No side effects (limited human data)
Digoxin[f]	Cardiac glycoside	C	Yes	Yes[e]	Serum levels unreliable, safe
Diltiazem	Calcium channel blocker (class IV)	C	No	Yes[e]	Possible teratogenic effects
Disopyramide	Antiarrhythmic (class IA)	C	Yes	Yes[e]	Uterus contraction
Enalapril[d]	ACE inhibitor	D	Yes	Yes[e] (maximum 1.6%)	Renal or tubular dysplasia, oligohydramnios, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, intrauterine fetal death
Eplerenone	Aldosterone antagonist	–	Unknown	Unknown	Unknown (limited experience)
Fenofibrate	Lipid-lowering drug	C	Yes	Yes	No adequate human data
Flecainide	Antiarrhythmic (class IC)	C	Yes	Yes[e]	Unknown (limited experience)
Fondaparinux	Anticoagulant	–	Yes (maximum 10%)	No	New drug, (limited experience)
Furosemide	Diuretic	C	Yes	Well-tolerated; milk production can be reduced	Oligohydramnios
Gemfibrozil	Lipid-lowering drug	C	Yes	Unknown	No adequate human data
Glyceryl trinitrate	Nitrate	B	Unknown	Unknown	Bradycardia, tocolytic
Heparin (low molecular weight)	Anticoagulant	B	No	No	Long-term application: seldom osteoporosis and markedly less thrombocytopenia than UF heparin
Heparin (unfractionated)	Anticoagulant	B	No	No	Long-term application: osteoporosis and thrombocytopenia
Hydralazine	Vasodilator	C	Yes	Yes[e] (maximum 1%)	Maternal side effect: lupus-like symptoms; fetal tachyarrhythmias (maternal use)
Hydrochlorothiazide	Diuretic	B	Yes	Yes, milk production can be reduced	Oligohydramnios

(*Continued*)

Drugs	Classification (Vaughan Williams for AA drugs)	FDA category	Placenta permeable	Transfer to breast milk (fetal dose)	Adverse effects
Irbesartan[d]	Angiotensin II receptor blocker	D	Unknown	Unknown	Renal or tubular dysplasia, oligohydramnios, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, intrauterine fetal death
Isosorbide dinitrate	Nitrate	B	Unknown	Unknown	Bradycardia
Isradipine	Calcium channel blocker	C	Yes	Unknown	Potential synergism with magnesium sulfate may induce hypotension
Labetalol	-/-blocker	C	Yes	Yes[e]	Intrauterine growth retardation (second and third trimester), neonatal bradycardia and hypotension (used near term)
Lidocaine	Antiarrhythmic (class IB)	C	Yes	Yes[e]	Fetal bradycardia, acidosis, central nervous system toxicity
Methyldopa	Central -agonist	B	Yes	Yes[e]	Mild neonatal hypotension
Metoprolol	-blocker (class II)	C	Yes	Yes[e]	Bradycardia and hypoglycaemia in fetus
Mexiletine	Antiarrhythmic (class IB)	C	Yes	Yes[e]	Fetal bradycardia
Nifedipine	Calcium channel blocker	C	Yes	Yes[e] (maximum 1.8%)	Tocolytic; sublingual application and potential synergism with magnesium sulfate may induce hypotension (mother) and fetal hypoxia
Phenprocoumon[a]	Vitamin K antagonist	D	Yes	Yes (maximum 10%), well tolerated as inactive metabolite	Coumarin embryopathy, bleeding
Procainamide	Antiarrhythmic (class IA)	C	Yes	Yes	Unknown (limited experience)
Propafenone	Antiarrhythmic (class IC)	C	Yes	Unknown	Unknown (limited experience)
Propranolol	-blocker (class II)	C	Yes	Yes[e]	Bradycardia and hypoglycaemia in fetus
Quinidine	Antiarrhythmic (class IA)	C	Yes	Yes[e]	Thrombopenia, premature birth, 8th cranial nerve toxicity.
Ramipril[d]	ACE inhibitor	D	Yes	Yes (maximum 1.6%)	Renal or tubular dysplasia, oligohydramnios, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, intrauterine fetal death
Sotalol	Antiarrhythmic (class III)	B	Yes	Yes[e]	Bradycardia and hypoglycaemia in fetus (limited experience)
Spironolactone	Aldosterone antagonist	D	Yes	Yes[e] (maximum 1.2%); milk production can be reduced	Antiandrogenic effects, oral clefts (first trimester)
Statins[g]	Lipid-lowering drugs	X	Yes	Unknown	Congenital anomalies
Ticlopidine	Antiplatelet	C	Unknown	Unknown	Unknown (limited experience)
Valsartan[d]	Angiotensin II receptor blocker	D	Unknown	Unknown	Renal or tubular dysplasia, oligohydramnios, growth retardation, ossification disorders of skull, lung hypoplasia, contractures, large joints, anaemia, intrauterine fetal death
Verapamil oral	Calcium channel blocker (class IV)	C	Yes	Yes[e]	Well tolerated (limited experience during pregnancy)

(*Continued*)

Drugs	Classification (Vaughan Williams for AA drugs)	FDA category	Placenta permeable	Transfer to breast milk (fetal dose)	Adverse effects
Verapamil IV	Calcium channel blocker (class IV)	C	Yes	Yes[e]	Intravenous use may be associated with a greater risk of hypotension and subsequent fetal hypoperfusion
Vernakalant	Antiarrhythmic (class III)	–	Unknown	Unknown	No experience of use in pregnancy
Warfarin[a]	Vitamin K antagonist	D	Yes	Yes (maximum 10%), well tolerated as inactive metabolite	Coumarin embryopathy, bleeding

ACE, angiotensin-converting enzyme; UF, unfractionated.
[a]The Guideline Committee added acenocoumarol and phenprocoumon in analogy to warfarin to this list. The necessity for risk assessment also applies to these two OAC. Previously the risk category X was attributed to warfarin. In the opinion of the Task Force available evidence suggests that risk category D is more appropriate for warfarin and other vitamin K antagonists.
[b]Adenosine: most of the experiences with this drug are in the second and third trimesters. Its short half-life may prevent it from reaching the fetus
[c]Atenolol is classified D by FDA, nevertheless some authors classify as C.
[d]The available data on first-trimester use do not strongly support teratogenic potential. Because ACE inhibitors, angiotensin II receptor blockers, aldosterone antagonists, and renin inhibitors should be avoided during pregnancy and breastfeeding the risk category is D. Positive outcomes with ACE inhibitors have been described and pregnancy does not have to be terminated if the patient was exposed to these medications, but should be followed-up closely.
[e]Breastfeeding is possible if the mother is treated with the drug.
[f]Digoxin: the experience with digoxin is extensive, and it is considered to be the safest antiarrhythmic drug during pregnancy. A prophylactic antiarrhythmic efficacy has never been demonstrated.
[g]Statins: should not be prescribed in pregnancy and during breastfeeding since their harmlessness is not proven and disadvantages to the mother are not to be expected by a temporary interruption of the therapy for the time period of pregnancy.
ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J.* 2011;**32**:3147–97, with permission from Oxford University Press.

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