# Atrial Fibrillation and Percutaneous Coronary Intervention

## A Case-based Guide to Oral Anticoagulation, Antiplatelet Therapy and Stenting

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# Preface

Atrial fibrillation (AF) is nowadays an "epidemic disease" and is associated to an increased risk of ischemic stroke. Because of that, oral anticoagulation with non-vitamin K-antagonist oral anticoagulants (NOACs, including dabigatran, rivaroxaban, apixaban and edoxaban), or vitamin K antagonists (e.g. warfarin) is warranted in the majority of cases. The recognition that AF is often associated to coronary artery disease, for which percutaneous coronary intervention with stent implantation (PCI) has become the standard of care, makes the issue of antithrombotic treatment complex as well as of great epidemiological relevance. While oral anticoagulation is the optimal therapy for stroke prevention in AF, dual antiplatelet therapy with aspirin and a $P2Y_{12}$-receptor inhibitor, including clopidogrel, prasugrel, or ticagrelor, is the most effective treatment for the prevention of stent thrombosis and/or recurrent cardiac events after PCI. No randomized, double-blind, prospective studies comparing different antithrombotic strategies in these patients are available, and current management is addressed by documents essentially based on consensus of experts.

At variance from most of the available documents, in this handbook we aim at guiding the management of AF patients who are submitted to PCI starting from individual clinical scenarios, including the stable setting and both ST-elevation and non-ST-elevation acute coronary syndromes, rather than giving an overview of the current recommendations. By doing so, we aim at more closely reproducing the clinical reasoning which is generally developed in everyday clinical practice when dealing with these patients. Also, we discuss the management of patients with AF and coronary stent implantation both when the arrhythmia is preexistent and when it develops early after PCI. Specific situations which may be commonly encountered when managing these patients, such as the need for nondeferrable surgery and the occurrence of a major bleeding event, are also discussed. Finally, the different clinical scenarios are presented for AF patients who are on oral anticoagulation both with a NOAC and warfarin.

While acknowledging that most of the recommendations given in this handbook are based on suboptimal evidence, as are those provided in the various consensus documents issued by study groups and scientific societies, we nonetheless hope to have provided a tool which can be found useful to those clinicians, including clinical and interventional cardiologists, internists, specialists in thrombosis and hemostasis, and also surgeons, who may be involved in the management of this complex

and increasing population. In hope to be successful in this task, we need to acknowledge the invaluable effort and expertise of our eminent colleagues who authored the various chapters and without whom this result could not be accomplished. Also to be acknowledged is the expert, timely, and precise assistance of the personnel at the editorial office of Springer which definitely made our endeavor less strenuous.

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# 1 Atrial Fibrillation on Vitamin K Antagonist Undergoing Elective Percutaneous Coronary Intervention for Stable Effort Angina

Raffaele Piccolo, Thomas Pilgrim, and Stephan Windecker

## 1.1 Case Presentation

### 1.1.1 Baseline Characteristics

- Gender: female.
- Age: 72 years.
- Cardiovascular risk factors: hypertension, hypercholesterolemia, previous cigarette smoker (quit 8 years earlier).
- Associated diseases: impaired fasting glucose, previous partial colectomy for colorectal cancer.
- Previous history: 12 years earlier, onset of angina on exertion, and subsequent coronary artery bypass grafting: left internal mammary artery (LIMA) to left anterior descending (LAD) and saphenous vein graft (SVG) to first obtuse marginal branch. Onset of atrial fibrillation (AF) postoperatively with selection of a rate-control strategy and oral anticoagulation (OAC) with warfarin. Four years later, hospitalization due to non-ST-segment elevation myocardial infarction (NSTEMI) with subsequent urgent coronary angiography (CORO) and percutaneous coronary intervention (PCI) with implantation of an early-generation drug-eluting stent (DES) (Table 1.1) in a significant lesion of the proximal left circumflex artery in view of the chronic occlusion of the SVG to the first obtuse marginal. Upon echocardiography, left ventricular ejection fraction was moderately depressed (35 %).

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- Current history: at preoperative examination for elective shoulder joint replacement surgery for chronic arthritis, typical angina on exertion (CCS II) associated with shortness of breath worsening over the previous 6 months (NYHA III) was reported. Physical examination was unremarkable with the exception of irregular heart sounds. An electrocardiogram (ECG) at rest was also unremarkable, except for the presence of AF. A subsequent exercise treadmill test (ETT) aborted after 3.5 metabolic equivalents (METs) due to fatigue and showed ST-segment depression of 2–3 mm in chest leads V5-V6 during recovery. Based on the history, clinical presentation, and ETT suspicious for ischemia, the probability of progression of coronary artery disease was deemed high, and the patient was then referred for CORO/PCI. Ongoing treatment upon admission included aspirin 100 mg once daily, rosuvastatin 10 mg once daily, lisinopril 10 mg once daily, metoprolol 25 mg twice daily, spironolactone 25 mg once daily, and warfarin according to the international normalized ratio (INR) (target 2.0–3.0).

**Table 1.1** General classification of coronary stents/scaffolds

| | | |
|---|---|---|
| BMS | | (a) Stainless steel<br>(b) Non-stainless steel, cobalt- or platinum-chrome alloy |
| DES | Early generation | (a) Durable polymer: sirolimus, paclitaxel eluting |
| | New generation | (a) Durable polymer: zotarolimus, everolimus eluting<br>(b) Biodegradable polymer: biolimus A9 and everolimus eluting<br>(c) Polymer free: biolimus A9, amphilimus eluting |
| BAS | | (a) Diamond-like carbon coated, titanium nitric oxide coated<br>(b) Endothelial progenitor cells capturing |
| BVS | | (a) Nondrug eluting<br>(b) Everolimus, myolimus, sirolimus eluting |

*BMS* bare-metal stent, *DES* drug-eluting stent, *BAS* bioactive stent, *BVS* bioresorbable vascular scaffold

## 1.2 Periprocedural Issues

The periprocedural management of OAC in patients treated with vitamin K antagonists (VKAs) who require elective CORO and/or PCI remains controversial as both OAC continuation and interruption are widely used in clinical practice. However, in 2014 the European Society of Cardiology (ESC) Working Group on Thrombosis recommended to continue OAC with VKA in a therapeutic window (i.e., INR $\geq$2.0) in patients undergoing PCI [1] (Table 1.2). This strategy has also been endorsed in the 2014 ESC Guidelines on myocardial revascularization [2]. Although there is no randomized evidence on this issue, available registries on VKAs reported no difference in the rate of bleeding or thrombotic events in patients undergoing PCI with uninterrupted OAC compared to OAC

**Table 1.2** Periprocedural management recommendations

| Issue | Recommendations |
|---|---|
| VKA anticoagulation | Uninterrupted[a,b] |
| Intra-procedural additional IV anticoagulation (UFH) | Yes (radial)/no (femoral) |
| Dose of additional IV anticoagulation (UFH) | Reduced[c] |
| Bivalirudin as additional IV anticoagulation | Not recommended |
| Vascular access site | Radial[d] |

*VKA* vitamin K antagonist, *CTO* chronic total occlusion, *IV* intravenous
[a]With the possible exception of procedures at increased risk of perforation (e.g., recanalization of CTO, rotational atherectomy, etc.)
[b]Temporary interruption, with or without heparin bridging (depending on the risk of thromboembolism), may be considered when PCI by the femoral approach is scheduled
[c]50 IU/kg
[d]When not possible and/or failed, femoral approach can be considered (provided that it is carried out with meticulous technique and possibly with ultrasound guidance)

**Table 1.3** Elimination half-life of vitamin K-dependent coagulation factors and anticoagulant proteins

| | Half-life (hours) |
|---|---|
| Factor II | 42–72 |
| Factor VII | 4–6 |
| Factor IX | 21–30 |
| Factor X | 27–48 |
| Protein C | 8–14 |
| Protein S | 30–42 |

discontinuation and bridging with unfractionated (UFH) or low-molecular-weight (LMWH) heparin [3, 4]. These findings were recently corroborated by a subgroup analysis of the WOEST study reporting the absence of significant differences in bleeding and major adverse cardiac and cerebrovascular events (MACCEs), including death, myocardial infarction, stroke, target vessel revascularization, and stent thrombosis, in patients undergoing PCI with uninterrupted OAC or bridging therapy [5]. A recent analysis from the Atrial Fibrillation undergoing Coronary Artery Stenting (AFCAS) registry reported a higher rate of major bleeding at three months in AF patients who underwent PCI and were discharged on triple therapy (TT) of VKA, aspirin, and clopidogrel in combination with bridging LMWH compared to those discharged on TT alone [6]. Thus, it is possible that the short time period of exposure to a quadruple therapy, including VKA, aspirin, clopidogrel, and LMWH, may increase the risk of bleeding without preventing MACCEs. An additional theoretical advantage of uninterrupted OAC is the elimination of the prothrombotic state occurring early after VKA initiation in relation to the transient suppression of the anticoagulant protein C and S, whose half-life is shorter than that of most of the coagulation factors targeted by VKAs (Table 1.3). Therefore, uninterrupted, effective (i.e., INR $\geq$2.0), periprocedural OAC seems as safe as, and potentially more effective than, OAC interruption plus bridging strategy, with the additional advantage of reduced length of hospitalization. The concern of bleeding events occurring during ongoing, effective (i.e., INR $\geq$2.0) OAC

should be considered in the context of rapid reversal of the effect of VKAs with the administration of several therapies, including prothrombin complex concentrates, fresh frozen plasma, and recombinant factor VII, in combination or not with oral or intravenous vitamin K [7].

As regards the intra-procedural anticoagulation, additional heparin in patients undergoing PCI (mostly by the femoral approach) during effective OAC has been reported to increase the risk of vascular access site complications with no benefit on the risk of MACCEs [6]. In contrast, a significantly higher rate of radial occlusion in patients undergoing CORO/PCI by the radial route and receiving OAC without additional UFH compared to patients receiving UFH has been recently reported [8]. The intra-procedural administration of additional UFH, at the reduced dose of 50 IU/kg currently recommended for radial procedures [9], is therefore an option to be routinely considered (Table 1.2). Although the use of bivalirudin is considered to be associated with a lower risk of bleeding than UFH [10], a recent randomized trial comparing bivalirudin vs. UFH in patients at high risk of bleeding undergoing elective PCI reported similar rates of major in-hospital bleeding [11]. Therefore, while having been reported more effective and safer than the combination of UFH and glycoprotein IIb/IIIa inhibitors in small cohorts [12], the use of bivalirudin in patients with uninterrupted OAC undergoing CORO/PCI may not afford a greater prevention of bleeding compared with UFH and is therefore currently not recommended (Table 1.2). Moreover, the anticoagulant effect of UFH may be rapidly reverted by the use of protamine. In a meta-analysis of 6,762 patients undergoing PCI, the use of protamine after coronary stenting was safe, by allowing early sheath removal and reducing the risk of bleeding complications [13].

As regards the choice of the vascular access site in patients on uninterrupted OAC with VKA undergoing CORO/PCI, there is broad agreement to prefer the radial approach over the standard femoral route [1] (Table 1.2). Several randomized trials and meta-analyses demonstrated that the radial approach reduces the risk of vascular complications and major bleeding compared to the femoral approach [14, 15]. Similar results have also been reported in a small, single-center experience with patients on OAC with VKA [16]. However, an important caveat is that the radial approach may have several shortcomings in patients with previous coronary artery bypass graft surgery (CABG). Indeed, a randomized trial, comparing radial vs. femoral approach in patients who had previously undergone CABG, showed that radial diagnostic CORO is associated with greater contrast use, longer procedure time, and greater access crossover and operator radiation exposure compared with femoral angiography [17]. Thus, in these patients, as in other patients where the radial approach is not feasible or has failed, the puncture of the femoral artery, provided that it is carried out with the proper technique (i.e., puncture of the anterior wall only) and possibly with ultrasound guidance, may be considered. When the femoral approach has been used, the routine use of vascular closure devices (VCD) is advised, even though data on VKA patients undergoing PCI are currently not available. In patients at increased risk of periprocedural bleeding and/or submitted to

aggressive antithrombotic therapy, VCD have indeed been shown to reduce the time to ambulation, and hence hospital discharge, while appearing comparably effective and safe [18].

### 1.2.1 Periprocedural Management

- CORO was scheduled without interruption of VKA (INR on the morning of procedure: 2.4).
- Ongoing aspirin treatment was continued at a dose of 100 mg once daily, and clopidogrel 600 mg loading was performed.
- Left radial access was chosen and a cocktail including nitroglycerine and UFH at the dose of 4,000 IU (corresponding to about 50 IU/kg) was given through the arterial 5 French sheath.
- Coronary angiography was performed using Judkins left 3.5 and Judkins right 4.5 French catheters for the native coronary arteries and the SVG. The LIMA graft to the LAD was selectively intubated with an IMA 4 French catheter. Angiography showed a right dominant system with a significant stenosis of the mid-RCA (Fig. 1.1). There was a good result in the stented segment of the circumflex coronary artery; the SVG to the first obtuse marginal was occluded as documented previously. The LIMA graft to the native LAD was patent with thrombolysis in myocardial infarction (TIMI) 3 flow to the apex (Figs. 1.2 and 1.3).

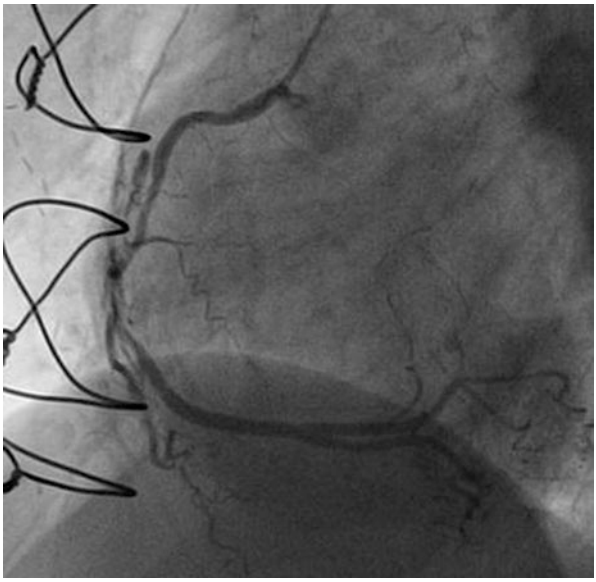

**Fig. 1.1** Significant stenosis in the right coronary artery (LAO view)

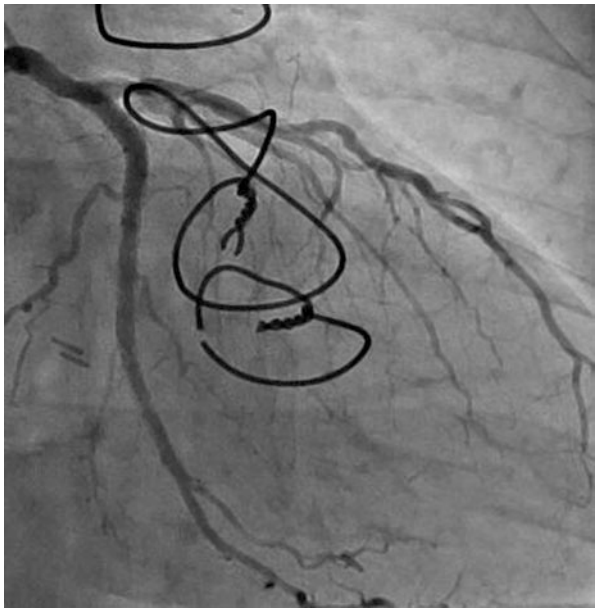

**Fig. 1.2** Selective angiography of the native left coronary system (RAO view)

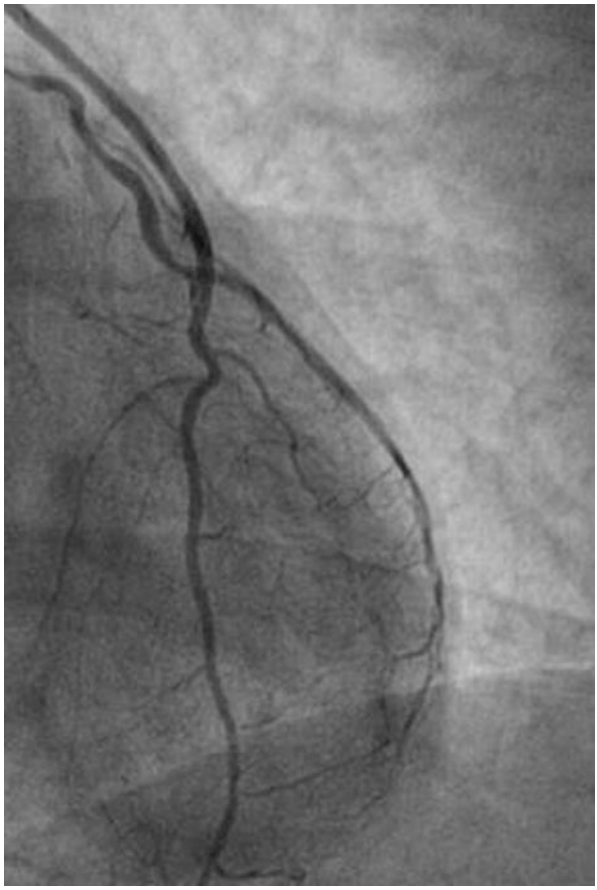

**Fig. 1.3** Selective angiography of the left internal mammary artery (RAO view cranial)

## 1.3 Procedural Issues

The advent of bare-metal stents (BMSs) resolved the threat of abrupt vessel closure following balloon angioplasty, thus eliminating the need for standby surgical backup. Subsequently, DESs with release of antiproliferative drugs during the first months after implantation successfully addressed the problem of restenosis inherent to BMSs due to potent suppression of neointimal hyperplasia [19] (Table 1.1). A relevant shortcoming of early-generation DESs was a delayed healing response of the stented coronary vessel that was associated with a small but notable increase in late thrombotic events [20] (Table 1.4). New-generation DESs were developed featuring thinner stent struts, novel-durable or biodegradable polymer coatings or even no coating, and various antiproliferative agents at lower dosages [21]. These refinements resulted not only in a 50 % reduction in the risk of definite or probable stent thrombosis compared to early-generation DESs during long-term follow-up but also in improved efficacy (10–20 % lower risk of repeat revascularization) and safety (lower risk of death and myocardial infarction). A network meta-analysis of 76 trials with 117,762 patient-years of follow-up comparing DESs with BMSs revealed a lower risk (18–37 %) of myocardial infarction among patients treated with DESs (except early-generation, paclitaxel-eluting stents) compared to those treated with BMSs [22]. A pooled analysis of 26 randomized trials in 11,557 women showed a significantly lower rate of death or myocardial infarction in patients treated with new-generation DESs compared with early-generation DESs and BMSs at 3 years [23]. Therefore, new-generation DESs represent the standard of care in patients undergoing PCI and are currently indicated in nearly all patient and lesion subsets [2]. No data are available regarding the use of bioresorbable vascular scaffolds (BVSs) in patients on VKA undergoing PCI. Although undergoing progressive reabsorption to complete disappearance, the time required for such process (i.e., approximately 2 years) and the recommended duration of dual antiplatelet therapy (DAPT) (i.e., at least 6 months) [24] currently make these devices of limited applicability for this patient subset. Similarly, no data are available with drug-eluting balloons (DEBs), whose indication for a short duration of DAPT (i.e., 1–3 months) [25] makes these devices attractive for patients on OAC. Whereas they may be considered when accepted indications (i.e., in-stent restenosis and possibly small vessel

**Table 1.4** Academic Research Consortium (ARC) definitions of stent thrombosis [43]

| | |
|---|---|
| Event certainty | (a) Definite: acute coronary syndrome with angiographic or autopsy confirmation of stent thrombosis |
| | (b) Probable: |
| | (i) Unexplained death within 30 days of stent implantation without autopsy |
| | (ii) Acute myocardial infarction in the territory of target vessel where stent was implanted without angiographic confirmation |
| Time frame | (a) Early: |
| | (i) Acute – within 24 h of stent implantation |
| | (ii) Subacute – between 24 h and 30 days of stent implantation |
| | (b) Late: between 30 days and 1 year of stent implantation |
| | (c) Very late: after 1 year of stent implantation |

**Table 1.5** HAS-BLED score and associated risk of major bleeding/year [42]

| | Condition | Points | Total score | Risk of major bleeding/year (%) |
|---|---|---|---|---|
| H | Hypertension (uncontrolled blood pressure above 160/90 mmHg) | 1 | 0 | <1 |
| A | Renal (dialysis, transplant, creatinine >2.6 mg/dL or >200 μmol/L) and/or liver (cirrhosis, bilirubin >2× normal or AST/ALT/AP >3× normal) disease | 1 or 2 | 1–2 | 2–3 |
| S | Stroke | 1 | ≥3 | 4–12 |
| B | Bleeding (previous or predisposition to) | 1 | | |
| L | Labile INR (unstable/high or TTR <60 %) | 1 | | |
| E | Elderly (i.e., age >65 years) | 1 | | |
| D | Drug usage predisposing to bleeding (antiplatelet agents, NSAIDs) and/or alcohol (≥8 drinks a week) | 1 or 2 | | |

*INR* international normalized ratio, *TTR* time in therapeutic range, *NSAID* nonsteroidal anti-inflammatory drugs, *AST* aspartate aminotransferase, *ALT* alanine transaminase, *AP* Alkaline phosphatase

**Table 1.6** Procedural management recommendations

| Issue | Recommendations |
|---|---|
| Type of stent | New-generation DES[a] |
| Adjunct IV glycoprotein IIb/IIIa inhibitors | Not recommended[b] |
| Antiplatelet therapy | Aspirin[c,d], clopidogrel[e], VKA |

*DES* drug-eluting stent, *BMS* bare-metal stent, *IV* intravenous, *UFH* unfractionated heparin, *VKA* vitamin K antagonist

[a]In patients at low bleeding risk, i.e., HAS-BLED score ≤2, whereas in those at high bleeding risk, i.e., HAS-BLED score ≥3 the choice between BMS and new-generation DES to be made on an individual basis

[b]May be considered only as a bailout treatment in selected situations (e.g., threatened acute vessel closure, no reflow/slow flow, etc.)

[c]75–100 mg once daily

[d]May be omitted in selected patients at highly increased risk of bleeding and low risk of stent thrombosis

[e]Use of newer, more potent $P2Y_{12}$ receptor inhibitors, including prasugrel and ticagrelor, is not approved nor recommended

disease) in non-OAC patients are present, DEBs are currently not routinely recommended in OAC patients undergoing PCI.

In AF patients undergoing PCI, current guidelines recommend the use of new-generation DES over BMSs in patients requiring OAC who are at low bleeding risk (i.e., HAS-BLED score ≤2) (Table 1.5) [1, 2] (Tables 1.5 and 1.6). In contrast, among patients undergoing PCI who require OAC and have a high bleeding risk (i.e., HAS-BLED score ≥3) (Tables 1.5 and 1.6), the choice between BMSs and new-generation DESs needs to be decided on an individual basis [1, 2]. However, in patients with uncertain indication for DESs, the Zotarolimus-eluting Endeavor Sprint Stent in Uncertain DES Candidates (ZEUS) trial reported a significantly lower rate of major adverse events in patients randomly allocated to the new-generation zotarolimus-eluting stent compared to those treated with BMSs, driven by reductions in target

vessel revascularization, myocardial infarction, and definite/probable stent thrombosis [26]. Of note, among 1,606 patients included in the ZEUS trial, 52 % were deemed at high risk of bleeding, while 45 % and 63 % of patients discontinued DAPT at 1 and 2 months, respectively [26]. At variance with the clinical context of acute coronary syndrome (ACS), where there is indication to prolong DAPT up to 12 months irrespective of the type (i.e., BMS or DES) of stent implanted, and even regardless of whether a stent has been implanted or not, the duration of DAPT in the elective setting is driven by the type of stent, with 1 and 6 (or even 1–3 only) months being required in the case of BMSs or new-generation DESs implantation, respectively [2].

In elective PCI patients on OAC with VKA, antiplatelet therapy should include aspirin and clopidogrel [1, 27, 28] (Table 1.6). Although there is no guideline-based recommendation, the choice of clopidogrel loading dose (300 vs. 600 mg) should be carefully evaluated in patients who are going to be treated with triple therapy (TT). ESC Guidelines on myocardial revascularization strongly recommend the higher 600 mg clopidogrel loading [2], given the more rapid and intense antiplatelet effect. Indeed, the Intracoronary Stenting and Antithrombotic Regimen: Choose between 3 high Oral doses for immediate Clopidogrel Effect (ISAR-CH) trial did not find an additional suppression of platelet function with single doses of clopidogrel higher than 600 mg [29], while meta-analysis data showed a greater protection from ischemic events with a loading dose >300 mg [30]. Therefore, it seems reasonable to use a high clopidogrel loading dose (600 mg) in the majority of cases and reserve the standard loading dose (300 mg) to patients with very high risk of bleeding. At the same time, the risk of periprocedural myocardial infarction and stent thrombosis should be also weighted, again favoring the 600 mg loading dose in lesion and patient subsets at increased risk of periprocedural thrombotic events. Because of the time required for clopidogrel to be effective (i.e., approximately 2–4 and 6–8 h with 600 and 300 mg, respectively), timely pretreatment should generally be considered in elective patients referred for CORO/PCI. Newer $P2Y_{12}$ ADP-receptor inhibitors such as prasugrel and ticagrelor are currently not approved for elective patients, and their use as part of TT should be avoided due to the excessive risk of bleeding [1] (Table 1.6). In a series of 377 patients who underwent DES implantation (for both stable and unstable coronary artery disease) and had indication for OAC, the use of prasugrel compared with clopidogrel significantly increased the risk of bleeding at 6 months, without differences in terms of ischemic events [31]. At variance, in a small retrospective study, the use of ticagrelor in combination with VKA in patients with ACS was not associated with an increased risk of bleeding compared to TT including VKA, aspirin, and clopidogrel [32], possibly making this combination an option needing however still to be proven.

Glycoprotein IIb/IIIa inhibitors (abciximab, tirofiban, and eptifibatide) should be avoided as an adjunct to PCI in patients with uninterrupted, effective (i.e., INR $\geq$2.0) OAC due to the excessive risk of bleeding (Table 1.6). In a cohort of 377 patients on VKA undergoing PCI, the use of glycoprotein IIb/IIIa inhibitors was associated with a significant increase in the rate of in-hospital major bleeding [33]. Glycoprotein IIb/IIIa inhibitors may only be given for bailout situations, where nonetheless the use of small molecules, like tirofiban and eptifibatide, may be preferred to abciximab due to the shorter half-life.

### 1.3.1 Procedural Management

- PCI of the stenosis in the mid-RCA was planned.
- Given the pre-procedural INR of 2.4, a weight of 85 kg, and an ACT of 190 s after administration of a bolus of 4,000 IU UFH for diagnostic angiography, an additional bolus of 1,000 IU UFH, therefore reaching a total dose of approximately 60 IU UFH/kg, was given prior to PCI.
- The diagnostic catheter was exchanged to a 6.5 French sheathless JR 4 guiding catheter, and after pre-dilatation, a new-generation everolimus-eluting stent (XIENCE PRIME, Abbott Vascular, 2.5 × 38 mm) (Table 1.1) was implanted in the mid-RCA with good angiographic result after subsequent post-dilatation in its proximal part with a 3.0 × 12 mm non-compliant balloon (NC TREK, Abbott Vascular) (Fig. 1.4).
- After removal of the sheathless catheter, local compression was applied using a dedicated device (TR band, Terumo).

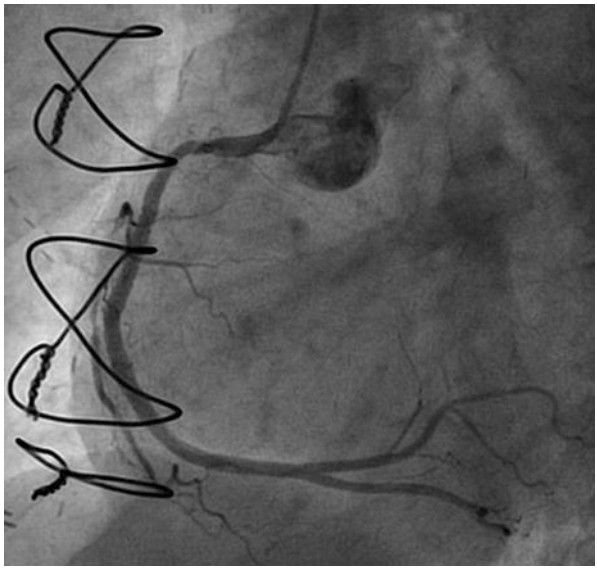

**Fig. 1.4** Final angiographic result after PCI (LAO view)

## 1.4 Post-procedural Issues

The management of antithrombotic therapy after PCI should take into consideration three main aspects: the risk of stroke (i.e., $CHA_2DS_2$-VASc score) (Table 1.7), the risk of bleeding (i.e., HAS-BLED score) (Table 1.5), and the clinical setting in which PCI has been performed (i.e., stable coronary artery disease vs. acute coronary syndrome, which are associated with a low and, respectively, high risk of

**Table 1.7** $CHA_2DS_2$-VASc score and associated risk of stroke/year [42]

| | Condition | Points | Total score | Stroke risk/ year (%) |
|---|---|---|---|---|
| C | Congestive heart failure (or left ventricular ejection fraction ≤35 %) | 1 | 0 | 0 |
| H | Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication) | 1 | 2 | 1.3 |
| $A_2$ | Age ≥75 years | 2 | 2 | 2.2 |
| D | Diabetes mellitus | 1 | 3 | 3.2 |
| $S_2$ | Prior stroke or TIA or thromboembolism | 2 | 4 | 4.0 |
| V | Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque) | 1 | 5 | 6.7 |
| A | Age 65–74 years | 1 | 6 | 9.8 |
| Sc | Sex category (i.e., female sex) | 1 | 7 | 9.6 |
| | | | 8 | 6.7 |
| | | | 9 | 15.2 |

*TIA* transient ischemic attack

recurrent events) [1]. In general, TT of OAC (with VKA), aspirin, and clopidogrel should be prescribed, given the observed superiority on various ischemic end points compared to other regimens, at the price however of an increase in bleeding events. Both in patients at low (i.e., HAS-BLED score 0–2) and high (i.e., HAS-BLED score ≥3) risk of bleeding, TT of OAC, aspirin, and clopidogrel should be prescribed [1] (Table 1.8). In the latter however, a number of bleeding avoidance strategies that are generally recommended in the setting of TT [1, 28] should be even more strictly implemented. Thus, together with targeting the INR to the lower end of the therapeutic range (i.e., 2.0–2.5), the shortest duration possible of TT should be pursued (Table 1.9). In the elective setting therefore, 1 month only of TT should be carried out after BMS implantation (Table 1.8). After new-generation DES implantation, 6 months would be the duration usually recommended [2] and should generally be confirmed in the OAC patient at low bleeding risk (i.e., HAS-BLED score 0–2) [1, 2, 28]. In patients at increased risk of bleeding (i.e., HAS-BLED score ≥3), a shorter duration of 3 months, or even 1, may be considered from the beginning [1, 2, 28]. It should be noted, however, that even if the initial prescription of TT after new-generation DES implantation was 6 months, such duration might likely be safely reduced (by interrupting one antiplatelet agent) in the event that a need arises (e.g., because of bleeding) before the full course has been completed. Extensive use of gastric protection with proton pump inhibitors (PPIs) that also should be routinely considered given that the gastrointestinal tract is the most frequent source of bleeding in patients on TT [1, 34]. In the Bern PCI registry, including 6,212 patients undergoing PCI, gastrointestinal bleeding had a profound effect on prognosis and was an independent predictor of 1-year mortality [35]. In addition to patient-related risk factors, TT emerged as the single drug-related predictor of gastrointestinal bleeding [35].

In selected patients at increased risk of bleeding (i.e., HAS-BLED score ≥3), and low risk of atherothrombotic events, including stent thrombosis and recurrence of

**Table 1.8** Medium- to long-term (i.e., up to 12 months after PCI) management recommendations

| Issue | Recommendations |
|---|---|
| Initial antithrombotic treatment | Triple therapy (VKA + aspirin[a,b] + clopidogrel) |
| Duration of triple therapy | BMS in elective setting: 1 month<br>DES in elective setting: 3–6 months[c]<br>Either BMS or DES in ACS setting: 3–6 months[d] |
| Intensity of OAC throughout triple therapy | Reduced[e] |
| Special care throughout triple therapy | Frequent INR monitoring[f]<br>Attention to high-quality OAC[g]<br>Routine gastric protection[h] |
| Subsequent antithrombotic treatment[i] | VKA[j] + either clopidogrel[k] or aspirin |

*PCI* percutaneous coronary intervention, *BMS* bare-metal stent, *DES* drug-eluting stent, *ACS* acute coronary syndrome, *OAC* oral anticoagulation, *INR* international normalized ratio, *VKA* vitamin K antagonist

[a]75–100 mg once daily

[b]May be omitted in selected patients at high risk of bleeding and concomitant low risk of stent thrombosis

[c]1 month only may be considered when the risk of bleeding is high, and new-generation DES has been implanted

[d]1 month only may be considered when the risk of bleeding is high, and either a BMS or a new-generation DES has been implanted

[e]Target INR 2.0–2.5

[f]Every 2 weeks

[g]Aiming at an average INR >70 %

[h]Preferably with proton pump inhibitors (PPIs) not interfering with clopidogrel metabolism (e.g., pantoprazole, dexlansoprazole)

[i]After the initial course of 1 to 3–6 months of triple therapy (TT) has been completed

[j]Standard intensity of OAC, that is, INR 2.0–3.0, should be resumed

[k]Preferred due to its superior gastric tolerability

**Table 1.9** Long-term (i.e., >12 months after PCI, in the absence of recurrent events) management recommendations

| Issue | Recommendation |
|---|---|
| Antithrombotic treatment | VKA monotherapy[a] |
| Intensity of OAC | Standard[b] |

*PCI* percutaneous coronary intervention, *VKA* vitamin K antagonist, *OAC* oral anticoagulation, *CAD* coronary artery disease, *INR* international normalized ratio

[a]Indefinite combination with either low-dose ASA (75–100 mg once daily) or clopidogrel 75 mg (depending on the individual risk of bleeding, especially gastrointestinal and stent thrombosis) may be considered in special situations (e.g., left main/last remaining vessel stenting, history of stent thrombosis/recurrent cardiac events, diffuse CAD), when bleeding risk is low

[b]That is, target INR 2.0–3.0

cardiac ischemia (which are indeed lowest in an elective setting), dual therapy (DT) of OAC and clopidogrel may be considered [1] (Table 1.8). These recommendations are mainly based on the results of the WOEST study that randomized 573 patients either to DT of OAC and clopidogrel or TT of OAC, clopidogrel, and aspirin [36]. The primary end point of any TIMI bleeding was significantly lower in the DT arm. The rates of myocardial infarction, stroke, target vessel revascularization, or stent thrombosis did not differ significantly, but all-cause mortality was significantly

lower in the DT group at 1 year. However, differences were driven by minor bleeding as major bleeding was not significantly lower, femoral access was used in the majority of patients (74 %), and TT was extended to 1 year. Because of the above limitations of the WOEST study, and the lack of a pathophysiological explanation for an antiplatelet potency of clopidogrel alone comparable to that of DAPT, at present DT is not routinely recommended [1, 2, 28].

No indication at present is accepted for DT of VKA and aspirin given the suboptimal efficacy reported in historical trials comparing such combination with DAPT for the prevention of stent thrombosis and adverse cardiac events [37].

### 1.4.1 Post-procedural Management

- Calculation of both stroke ($CHA_2DS_2$-VASc score 4) and bleeding (HAS-BLED score 2) risk was performed.
- TT of adjusted-dose warfarin (target INR 2.0–2.5), aspirin 100 mg once daily, and clopidogrel 75 mg once daily was selected.
- The next dose of warfarin was administered on the evening of the procedure.
- Gastric protection with pantoprazole was initiated at the dose of 20 mg once daily.
- The preexisting medical treatment with rosuvastatin 10 mg once daily, lisinopril 10 mg once daily, metoprolol 25 mg twice daily, and spironolactone 25 mg once daily was continued.

## 1.5 Medium- to Long-Term Issues

After an initial course of TT, one antiplatelet agent, generally aspirin, because of its gastric tolerability lower than clopidogrel, is withdrawn, and DT of VKA and clopidogrel continued up to 1 year from the index procedure (Table 1.9). Whereas aspirin only may be continued after 1 month of DAPT in elective patients implanted with a BMS, in similar OAC patients combination therapy of VKA and clopidogrel should better be continued up to 1 year owing to the uncertainty regarding the efficacy of VKA alone in preventing stent thrombosis during this time frame. Of note, guidelines issued by the American College of Cardiology Foundation (ACC)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Intervention (SCAI) recommend that even after BMS implantation in the elective setting, clopidogrel should ideally be continued in conjunction with aspirin up to 1 year, unless an increased risk of bleeding is present [38].

When TT is downgraded to DT of VKA and single antiplatelet agent (generally clopidogrel), the standard intensity of OAC, that is, target INR 2.0–3.0, should be

resumed [28] (Table 1.9). Gastric protection should be continued for as long as combination OAC and antiplatelet (either dual or single) therapy is maintained [28].

### 1.5.1 Medium- to Long-Term Management

- After an uneventful hospital course, the patient was discharged the day after the procedure.
- Recommendation to continue for 1 month TT of aspirin 100 mg once daily, clopidogrel 75 mg once daily, and warfarin with a target INR between 2.0 and 2.5 was given, followed by a combination of Coumadin (target INR 2.0–3.0) and clopidogrel up to 12 months from PCI.
- The ongoing remaining therapy was confirmed together with pantoprazole 20 mg once daily to be continued as long as combination therapy was ongoing (i.e., 12 months).

## 1.6 Long-Term Issues

Upon completion of the 12-month course of combination antithrombotic therapy, the remaining antiplatelet agent should be interrupted and VKA continued indefinitely (Table 1.9) [1, 28]. Historical data show that warfarin is at least as effective as aspirin for secondary prevention after an acute coronary syndrome [39, 40], at the price however, of a lower convenience of therapy. Long-term combination therapy of VKA and single antiplatelet agent, albeit in the different context of patients with no indication for OAC, appears associated with a relevant incidence of bleeding, without apparent benefit on adverse cardiovascular events [41], and therefore should not be considered routinely [1, 28]. Only in conditions where the atherothrombotic risk is high, such as in patients with history of stent thrombosis and/or recurrent cardiac events, especially with diabetes or diffuse coronary artery disease not amenable of revascularization, or when stent thrombosis may have catastrophic consequence, such as in left main or last remaining vessel stenting, combination of VKA and single antiplatelet therapy may be considered indefinitely [1, 28].

### 1.6.1 Long-Term Management

- After 1 year of combination therapy with TT for 1 month and DT for the remaining 11 months, clopidogrel was withdrawn, and adjusted-dose warfarin monotherapy (target INR 2.0–3.0) continued indefinitely.
- Pantoprazole 20 mg once daily was also interrupted, and the remaining therapy of rosuvastatin 10 mg once daily, lisinopril 10 mg once daily, metoprolol 25 mg twice daily, and spironolactone 25 mg once daily continued.

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# 2 Atrial Fibrillation on Non-vitamin K Antagonist Oral Anticoagulant Undergoing Elective Percutaneous Coronary Intervention for Stable Effort Angina

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## 2.1 Case Presentation

### 2.1.1 Baseline Characteristics

- Gender: male.
- Age: 68 years.
- Cardiovascular risk factors: type 2 diabetes mellitus (insulin treated), hypertension, hyperlipidemia, and current cigarette smoker (approximately 1 pack/day).
- Associated diseases: stage 3 chronic kidney disease (Table 2.1) (www.kdigo.org) (estimated glomerular filtration rate [eGFR] according to Cockroft-Gault formula 46 ml/min), peripheral neuropathy, hypothyroidism, and gastroesophageal reflux disease.

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- Previous history: approximately 2.5 years earlier, inferior ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI) with early-generation drug-eluting stent (DES) (TAXUS Express, Boston Scientific, 3.0×18 mm) in the midportion of the right coronary artery (RCA). Mild depression of left ventricular function (ejection fraction approximately 45%) subsequently developed. Atrial fibrillation (AF) subsequently developed, and a rate-control strategy (with a beta-blocker) was selected along with oral anticoagulation (OAC) with non-vitamin K-antagonist oral anticoagulant (NOAC) dabigatran 150 mg twice daily.
- Current history: after a prolonged period of clinical stability, with no cardiological symptoms during ordinary activity, dyspnea (NYHA class II) and angina on exertion (CCS II) developed over the previous 2 months, thereby prompting hospitalization for coronary angiography/intervention (CORO/PCI). Upon admission, the patient was asymptomatic, the electrocardiogram (ECG) was negative for ongoing myocardial ischemia (as well as for previous infarction) (Fig. 2.1), and cardiac-specific troponin levels were in the normal range. Blood pressure was 180/100 mmHg, whereas other vital signs and oxygen saturation were within normal limits. Ongoing medications included dabigatran 150 mg twice daily, aspirin 100 mg/day, carvedilol 6.25 mg twice daily, amlodipine 5 mg once daily, isosorbide mononitrate 20 mg three times daily, lisinopril 10 mg once daily, simvastatin 20 mg once daily, allopurinol 100 mg once daily, L-thyroxine 25 mcg once daily, metformin 850 mg twice daily, and insulin.
- Based on the history and clinical presentation, the probability of coronary artery disease was deemed high, and the patient was referred directly for CORO/PCI, with no preliminary noninvasive testing.

**Table 2.1** Stages of chronic kidney disease (www.kdigo.org)

| CKD stage | Description | GFR (ml/min per 1.73 $m^2$) |
|---|---|---|
| 1 | Kidney damage with normal or increased GFR | ≥90 |
| 2 | Kidney damage with mild decreased GFR | 60–89 |
| 3 | Moderate decreased GFR | 30–59 |
| 4 | Severe decreased GFR | 15–29 |
| 5 | Kidney failure | <15 (or dialysis) |

*CKD* chronic kidney disease, *GFR* glomerular filtration rate

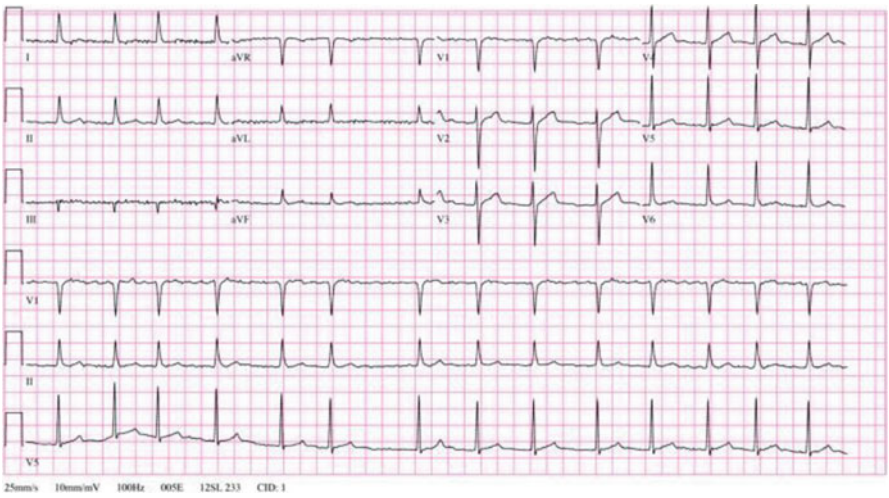


**Fig. 2.1** Electrocardiogram (ECG) on admission

## 2.2 Periprocedural Issues

Because of the increased risk of bleeding and/or vascular complications in patients undergoing elective CORO/PCI on aggressive antithrombotic therapy, including dabigatran (or other NOACs) and antiplatelet agents, measures aiming to minimize such risk, while not increasing at the same time the risk of thromboembolic/thrombotic complications, need to be implemented [1–3].

Regarding OAC, timely discontinuation of dabigatran (or other NOACs) is the preferable option [1–3] (Table 2.2). Owing to the rapid offset (as well as onset) of action of dabigatran (or other NOACs) (Table 2.3), withdrawing treatment 24–48 h in advance, depending on the patient's renal function, would generally be sufficient for performing CORO/PCI during low exposure to the drug (Table 2.4) [3]. Taking into account that the half-life of dabigatran (as well as of other NOACs) is approximately 12 h (Table 2.3), after 24 and 48 h from interruption, the drug concentration, and therefore the pharmacological effect, is expected to be 1/4 and 1/16, respectively, of the initial [3]. Conversely, continuation of dabigatran in elective patients has been shown not to provide sufficient suppression of coagulation activation during and after PCI, as indicated by a consistent increase in the levels of prothrombin fragment 1 + 2 and thrombin-antithrombin III complex plasma levels in comparison to standard unfractionated heparin (UFH) [4]. This might not be true for uninterrupted OAC with rivaroxaban, since the suppression of the above markers of thrombin generation and coagulation activity in a small group of patients undergoing elective PCI was reported comparable to standard UFH [5]. For now, however, pre-procedural NOAC interruption should be regarded as the standard

**Table 2.2** Periprocedural management recommendations

| Issue | Recommendations |
|---|---|
| Anticoagulation | Discontinuation[a] |
| Vascular access site | Radial/femoral |
| Antiplatelet therapy | Low-dose ASA[b, c] + clopidogrel PO[d] |

*NOAC* non-vitamin K-antagonist oral anticoagulant, *ASA* aspirin, *PO* orally
[a]24 to 48–72 h in advance (depending on the patient renal function and NOAC used), with no heparin bridging
[b]75–100 mg/day
[c]May be omitted in selected patients at high risk of bleeding and concomitant low risk of stent thrombosis
[d]600 (or 300 mg) front-loading

**Table 2.3** Main pharmacological properties of warfarin and non-vitamin K-antagonist oral anticoagulants

| | Warfarin | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|---|
| Target | Factors II, VII, IX, X | Factor IIa (thrombin) | Factor Xa | | |
| Prodrug | No | Yes | No | No | No |
| Bioavailability | 100 % | 6 % | 66[a]/100 %[b] | 50 % | 62 % |
| Plasma protein binding | 97 % | 35 % | 93 % | 87 % | 50 % |
| Time to peak | 4–5 days | 1.5–2 h | 2–3 h | 2–3 h | 1–2 h |
| Elimination half-life | 36–42 h | 12–17 h | 5–9[c]/11–13[d] hours | 12 h | 10–14 h |
| Route of clearance | Multiple | 80 % renal | 35 % renal | 27 % renal | 50 % renal |

[a]Without food
[b]With food
[c]In the young
[d]In the elderly

**Table 2.4** Recommended last drug intake before elective surgical/invasive procedure

| | Dabigatran | | Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) | |
|---|---|---|---|---|
| | Low risk[a] | High risk[b] | Low risk[a] | High risk[b] |
| CrCl ≥ 80 ml/min | ≥24 h | ≥48 h | ≥24 h | ≥48 h |
| CrCl 50–80 ml/min | ≥36 h | ≥72 h | ≥24 h | ≥48 h |
| CrCl 30–49 ml/min | ≥48 h | ≥96 h | ≥24 h | ≥48 h |
| CrCl 15–29 ml/min | Not indicated | Not indicated | ≥36 h | ≥48 h |
| CrCl < 15 ml/min | No official indication for use | | | |

From Heidbuchel et al. [3]
Note: when no important bleeding risk and/or adequate local hemostasis possible, perform procedure at trough level (i.e., ≥12 or 24 h after the last intake)
Note: there is no need for bridging with low-molecular-weight/unfractionated heparin
*CrCl* creatinine clearance
[a]With a low frequency of bleeding and/or minor impact of a bleeding
[b]With a high frequency of bleeding and/or important clinical impact

of treatment, regardless of the ongoing NOAC [1–3]. Effective ongoing anticoagulation with dabigatran (or other NOACs) would also preclude the use, if needed, of glycoprotein IIb/IIIa inhibitors, as they have been shown (in patients however on therapeutic OAC with warfarin) to largely increase the occurrence of major bleeding complications [6]. In addition, the lack of the possibility to reliably measure the intensity of OAC with dabigatran (as well as of other NOACs) would also make cumbersome the use of additional anticoagulants, such as unfractionated heparin (UFH), in the event that a thrombotic complication (e.g., acute stent/vessel occlusion) occurs. As an alternative to timely interruption of dabigatran (or other NOACs), consideration may be given to perform CORO/PCI at the drug trough level (i.e., ≥24–48 h from last intake), provided however that the bleeding risk is low and adequate hemostasis is possible (i.e., the procedure is performed by the radial approach) (Table 2.4) [3]. Given the short preprocedural interruption of OAC with dabigatran (or other NOACs) and therefore the associated low risk of thromboembolic events, bridging with other anticoagulants, generally represented by low-molecular-weight heparins (LMWHs), should be considered virtually in no case [3]. In patients on warfarin either because of AF or other indications, in whom perioperative interruption of anticoagulation is generally rather long (on average 5 days), forgoing bridging anticoagulation with LMWH has been recently shown to be as effective as and safer than perioperative bridging with LMWH [7–9].

Regarding oral antiplatelet therapy, front-loading with aspirin and clopidogrel (if not ongoing) is generally performed in patients referred for elective CORO/PCI. Because of the timely interruption of dabigatran before the procedure, effective OAC should be waning at the time of clopidogrel administration, which therefore can be performed with either 300 or 600 mg loading dose (Table 2.2) [2]. Of note, newer $P2Y_{12}$-receptor inhibitors, including prasugrel and ticagrelor, are not approved in this clinical setting [10], regardless of whether or not they are going to be combined with OAC and should therefore not be used [1, 2, 10].

Regarding the vascular access site, radial approach should generally be preferred because of the dramatic decrease in bleeding and/or vascular complications reported in general population [11], as well as in a small group of patients on OAC with warfarin [12] (Table 2.2). Given, however, that the effect of dabigatran (or other NOACs) should be minimal when timely interrupted, the choice of the radial as compared to femoral approach may not be as important as for patients undergoing PCI on ongoing therapeutic (i.e., international normalized ratio [INR] ≥2.0) OAC with warfarin.

### 2.2.1 Periprocedural Management

- Coronary angiography was scheduled 48 h after the last intake of dabigatran 150 mg.
- No periprocedural LMWH bridging anticoagulation was arranged after dabigatran interruption.

- Front-loading with 600 mg of clopidogrel orally was performed the evening before the procedure.
- Ongoing aspirin treatment was continued at the dose of 100 mg once daily.
- Right radial access site was selected.
- An intravenous (IV) bolus of 4.000 IU (about 50 IU/kg) of UFH was given through the arterial sheath at the beginning of procedure to prevent radial artery occlusion.
- CORO was carried with conventional JL and JR 6 F diagnostic catheters and showed a right dominant system with severe (>70%) stenosis proximal to the DES previously implanted in the mid-RCA, severe (>70%) ostial stenosis of posterior descending artery, and a proximal, severe (90%) stenosis of the right posterolateral branch (Fig. 2.2). No significant lesions were detected in the left coronary system.

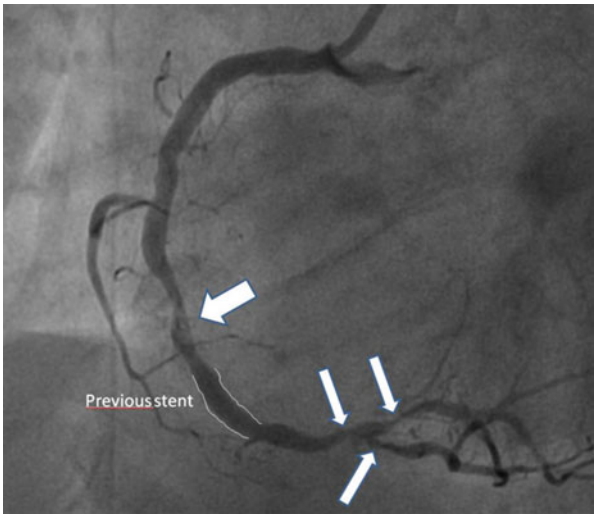


**Fig. 2.2** Diagnostic angiography of right coronary artery (RCA) (LAO view). *LAO* left anterior oblique

## 2.3 Procedural Issues

To prevent thrombosis at the PCI hardware and/or at the atherosclerotic plaque disrupted by balloon traumatism, effective anticoagulation is required throughout elective PCI. Once dabigatran (or other NOACs) has been timely interrupted, intra-procedural UFH administration should be carried out as per usual practice (Table 2.5) [1–3]. Therefore, a standard IV bolus of UFH at the dose of 70–100 IU/kg should be given upon the start of procedure [2]. Even though specific data are not available, also glycoprotein IIb/IIIa inhibitors might likely be used safely, should the indication arise (e.g., high thrombus burden or acute stent/vessel occlusion) [1–3].

**Table 2.5** Procedural management recommendations

| | |
|---|---|
| Additional intra-procedural IV UFH | Yes |
| Dose of additional intra-procedural IV UFH | Standard[a] |
| Type of stent | New-generation DES[b] |
| Adjunct IV GPI | Provisional[c] |

*IV* intravenous, *UFH* unfractionated heparin, *DES* drug elutin stent, *GPI* glycoprotein IIb/IIIa inhibit, *BMS* bare metal stent
[a]70–100 U/kg
[b]BMS may be considered in patients at high risk of bleeding or when unavoidable surgery is planned within 3–6 months
[c]In high-risk lesions, large thrombus burden, no reflow/slow flow, threatened vessel closure

**Table 2.6** Academic Research Consortium (ARC) definitions of stent thrombosis [13]

| | |
|---|---|
| Event certainty | (a) Definite: acute coronary syndrome with angiographic or autopsy confirmation of stent thrombosis |
| | (b) Probable: |
| | (i) Unexplained death within 30 days of stent implantation without autopsy |
| | (ii) Acute myocardial infarction in the territory of target vessel where stent was implanted without angiographic confirmation |
| Time frame | (a) Early: |
| | (i) Acute – within 24 h of stent implantation |
| | (ii) Subacute – between 24 h and 30 days of stent implantation |
| | (b) Late: between 30 days and 1 year of stent implantation |
| | (c) Very late: after 1 year of stent implantation |

Regarding the type of stent to be implanted, it has been extensively proven that DESs are more effective than bare-metal stents (BMSs) in preventing restenosis and associated clinical *sequelae*, at the price however of a possibly increased incidence of late/very late (i.e., >30 days from implantation) stent thrombosis (Table 2.6) [10, 13]. For this reason, dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$-receptor inhibitor, including clopidogrel, ticagrelor, and prasugrel (these latter two only in acute coronary syndromes), has been recommended for 1 month after BMS implantation and 6–12 months after DES implantation [10]. Based on several and increasing data showing that new-generation DESs, with both durable and bioabsorbable polymer coatings (Table 2.7), are associated with minimal, and likely not substantially different, incidence of stent thrombosis compared to BMSs, most recent recommendations reduce the suggested duration of DAPT to 6 months only [10]. Further, even durations as short as 1 month may possibly be considered after the implantation of zotarolimus and everolimus, durable polymer DES, as well as of a polymer-free, biolimus A9-DES, given the apparent lack of an increase in stent thrombosis with the interruption of one of the two antiplatelet agents after the first 4 weeks of treatment [14–16]. At present, however, standard prescription of 6-month DAPT may generally be preferable even with these stents, with the option however of more safely interrupt DAPT in the event that a need arises (e.g., bleeding complication) [1, 2]. Based on the above, the stent to be preferably implanted in an AF patient on dabigatran (or other NOACs) should generally be either a BMS or a new-generation DES, to be chosen taking into account the individual risk of restenosis, stent thrombosis, and bleeding

**Table 2.7** General classification of coronary stents/scaffolds

| | | |
|---|---|---|
| BMS | | (a) Stainless steel |
| | | (b) Non-stainless steel, cobalt- or platinum-chrome alloy |
| DES | Early generation | (a) Durable polymer: sirolimus, paclitaxel eluting |
| | New generation | (a) Durable polymer: zotarolimus, everolimus eluting |
| | | (b) Biodegradable polymer: biolimus A9 and everolimus eluting |
| | | (c) Polymer-free: biolimus A9, amphilimus eluting |
| BAS | | (a) Diamond-like carbon coated, titanium nitric oxide coated |
| | | (b) Endothelial progenitor cell capturing |
| BVS | | (a) Nondrug eluting |
| | | (b) Everolimus, myolimus, sirolimus eluting |

*BMS* bare-metal stent, *DES* drug-eluting stent, *BAS* bioactive stent, *BVS* bioresorbable vascular scaffold

(Table 2.5) [1–3]. The recently introduced bioresorbable vascular scaffolds (BVSs) appear at the moment not to have a specific role in AF patients on OAC given that DAPT is warranted at least until the start of BVS degradation, which occurs not earlier than 6 months from implantation [17]. Similarly, no specific role is currently apparent for drug-eluting balloons (DEBs). Given the indication for a short duration of DAPT (i.e., 1–3 months) [18], they may nonetheless represent a valuable option when treating conditions, like in-stent restenosis and small vessel disease, which represent commonly accepted indications for these devices are present.

### 2.3.1 Procedural Management

- An additional IV bolus of 2.000 IU of UFH was given upon the start of PCI to obtain a total dose of about 70 IU/kg.
- A new-generation, bioabsorbable polymer DES (BioMatrix Flex, Biosensors, 3.0 × 11 mm) was implanted in the mid-RCA proximal to the previous stent without overlap.
- Two additional new-generation, bioabsorbable polymer DESs were implanted (T-stenting technique) on distal RCA-proximal right posterolateral branch (BioMatrix Flex, Biosensors, 2.5 × 18 mm) and on posterior descending branch (BioMatrix Flex, Biosensors, 2.75 × 18 mm).

- An excellent angiographic result was obtained, with no residual stenosis (Fig. 2.3).
- The radial sheath was immediately removed upon completion of PCI and a local compression device applied (RadiStop, St. Jude Medical).
- Stratification of both the risk of stroke and bleeding was performed: $CHA_2DS_2$-VASc score 4 (Table 2.8) and HAS-BLED score 3 (Table 2.9).

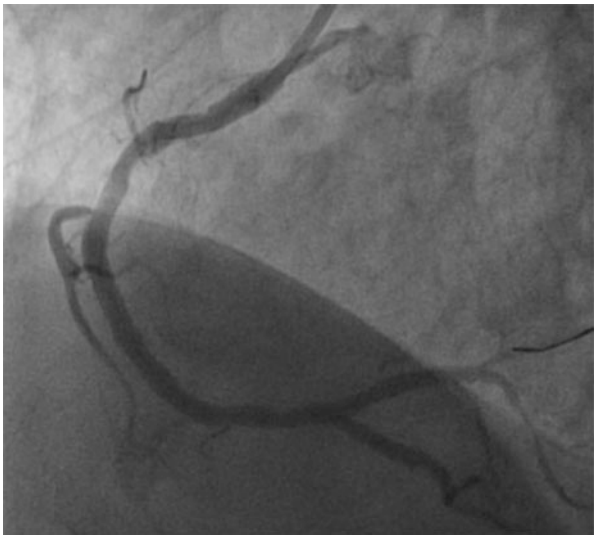

**Fig. 2.3** Final angiography after multiple stenting of RCA (LAO view). *LAO* left anterior oblique

**Table 2.8** $CHA_2DS_2$-VASc score and associated risk of stroke/year [19]

| | Condition | Points | Total score | Stroke risk/ year (%) |
|---|---|---|---|---|
| C | Congestive heart failure (or left ventricular ejection fraction ≤35 %) | 1 | 0 | 0 |
| H | Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication) | 1 | 2 | 1.3 |
| $A_2$ | Age ≥75 years | 2 | 2 | 2.2 |
| D | Diabetes mellitus | 1 | 3 | 3.2 |
| $S_2$ | Prior stroke or TIA or thromboembolism | 2 | 4 | 4.0 |
| V | Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque) | 1 | 5 | 6.7 |
| A | Age 65–74 years | 1 | 6 | 9.8 |
| Sc | Sex category (i.e., female sex) | 1 | 7 | 9.6 |
| | | | 8 | 6.7 |
| | | | 9 | 15.2 |

*TIA* transient ischemic attack

**Table 2.9** HAS-BLED score and associated risk of major bleeding/year [19]

| | Condition | Points | Total score | Risk of major bleeding/year (%) |
|---|---|---|---|---|
| H | Hypertension (uncontrolled blood pressure above 160/90 mmHg) | 1 | 0 | <1 |
| A | Renal (dialysis, transplant, creatinine >2.6 mg/dL or >200 μmol/L) and/or liver (cirrhosis, bilirubin >2× normal or AST/ALT/AP >3× normal) disease | 1 or 2 | 1–2 | 2–3 |
| S | Stroke | 1 | ≥3 | 4–12 |
| B | Bleeding (previous or predisposition to) | 1 | | |
| L | Labile INR (unstable/high or TTR <60 %) | 1 | | |
| E | Elderly (i.e., age >65 years) | 1 | | |
| D | Drug usage predisposing to bleeding (antiplatelet agents, NSAIDs) and/or alcohol (≥8 drinks a week) | 1 or 2 | | |

*INR* international normalized ratio, *TTR* time in therapeutic range, *NSAID* nonsteroidal anti-inflammatory drug *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *AP* alkaline phosphatase

## 2.4 Post-procedural Issues

Following PCI with stent implantation, combined OAC and antiplatelet therapy is warranted. DAPT with aspirin and clopidogrel is in fact inferior to OAC with warfarin for prevention of stroke in AF [20], and OAC with warfarin is inferior to DAPT for prevention of stent thrombosis and major adverse cardiac events (MACEs), including death, myocardial infarction, and repeat revascularization, after PCI with stent implantation [21]. Given, however, the lack of conclusive data on the optimal antithrombotic regimen and the general weakness of available evidence, some options should be considered, carefully taking into account the individual risk of stroke, stent thrombosis, MACEs, and bleeding (Fig. 2.4). In the presence of a high stroke risk, as expressed by a $CHA_2DS_2$-VASc score ≥2, OAC is warranted [22] (Table 2.8). In general, OAC should be given in conjunction with DAPT of aspirin and clopidogrel [1–3, 10, 23] (Fig. 2.4), as such so-called triple therapy (TT) has been generally shown to be the most effective antithrombotic regimen for the prevention of MACEs, stent thrombosis, and (especially) stroke. In patients at increased risk of bleeding, such as those with HAS-BLED score ≥3 (Table 2.9), and concomitant low risk of stent thrombosis and MACEs, such as those undergoing elective PCI with stent implantation in the context of stable coronary artery disease (CAD), dual therapy (DT) of OAC and clopidogrel may be considered [1–3, 10]. Available, yet suboptimal, data suggest in fact that DT may be significantly safer than TT, in terms of reduced incidence of (total) bleeding, while not being associated with reduced efficacy (i.e., incidence of MACEs, stent thrombosis, and stroke) [24, 25]. Based on historical data showing that DT of OAC and aspirin is largely insufficient to protect against MACEs and (especially) stent thrombosis, such combination has at present virtually no indication [1, 2, 23].

A relevant question is whether ongoing dabigatran (or other NOACs) should be confirmed or either another NOAC or warfarin should be preferred instead

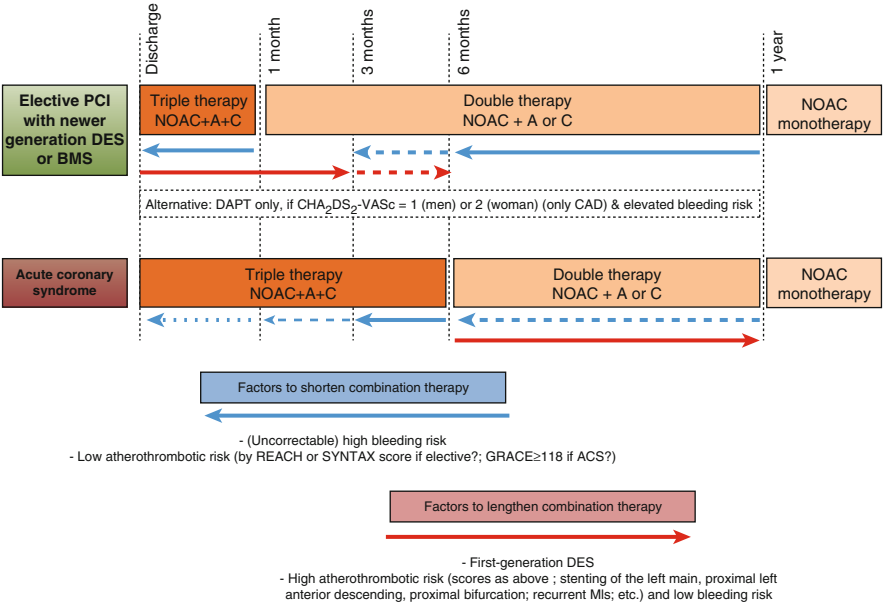


**Fig. 2.4** Management suggestions for antithrombotic therapy (Reproduced with permission from [3]). *PCI* percutaneous coronary intervention, *BMS* bare-metal stent, *DES* drug-eluting stent, *NOAC* non-vitamin K-antagonist oral anticoagulant, *A* aspirin, *C* clopidogrel, *ACS* acute coronary syndrome, *MI* myocardial infarction

following PCI with stent implantation. According to available, albeit limited, data, efficacy and safety of dabigatran when combined with (either single or dual) antiplatelet therapy appear comparable to that of warfarin [26]. Thus, there is apparently no reason to switch to warfarin, given also the superior convenience and safety on intracranial bleeding of dabigatran (and other NOACs) (Table 2.10) [2, 31]. The issue of anticoagulation reversal currently appears also to be overcome given the development of specific antidotes to NOACs, like idarucizumab for dabigatran [32] and andexanet alfa for factor Xa inhibitors [33] (Table 2.10). Their availability, together with nonspecific reversal agents, like prothrombin complex concentrates, recombinant factor VII and fresh frozen plasma, and short half-life of NOACs (i.e., approximately 12 h), is expected to allow safe management of relevant bleeding in the event it occurs [34]. Because of the lack of specific data with other NOACs and the apparent similar effect on the risk of bleeding compared to DAPT of the various NOACs [31], there is also no apparent reason to switch to a NOAC different from the one ongoing.

In patients at intermediate risk of stroke, as expressed by a $CHA_2DS_2$-VASc score 1 (Table 2.8) [22], while either TT or DT might indeed be considered (Fig. 2.4), temporary (i.e., 1–6 months, depending on whether a BMS or new-generation DES has been implanted) withdrawal of OAC appears the preferable option [1–3]. Given the low absolute risk of stroke in such category, especially in the short period, as well as some protection against stroke (i.e., approximately

**Table 2.10** Efficacy and safety of non-vitamin K-antagonist oral anticoagulants vs warfarin in clinical trials (hazard ratio, 95 % confidence intervals) [27–30]

| | Dabigatran 110 mg BID | Dabigatran 150 mg BID | Rivaroxaban 20 mg[a] OD | Apixaban 5 mg[b] BID | Edoxaban 30 mg BID | Edoxaban 60 mg BID |
|---|---|---|---|---|---|---|
| Stroke or systemic embolism | 0.91[c] (0.74–1.11) | 0.66[d] (0.53–0.82) | 0.88[c] (0.74–1.03) | 0.79[d] (0.66–0.95) | 1.07[c] (0.87–1.31) | 0.79[c] (0.63–0.99) |
| Major bleeding | 0.80[e] (0.69–0.93) | 0.93 (0.81–1.07) | 1.04 (0.90–1.20) | 0.69[e] (0.60.0.80) | 0.47[e] (0.41–0.55) | 0.80[e] (0.71–0.91) |
| Intracranial bleeding | 0.31[e] (0.20–0.47) | 0.40[e] (0.27–0.60) | 0.67[e] (0.47–0.93) | 0.42[e] (0.30–0.58) | 0.30[e] (0.21–0.43) | 0.47[e] (0.34–0.63) |
| Gastrointestinal bleeding | 1.10 (0.86–1.41) | 1.50[e] (1.19–1.89) | 1.60[e] (1.29–1.98) | 0.89 (0.70–1.15) | 0.67[e] (0.53–0.83) | 1.23[e] (1-02–1.50) |

*BID* twice daily, *OD* once daily
[a]15 mg OD in patients with creatinine clearance 30–50 ml/min
[b]2.5 mg BID in patients with two of the following three features: age ≥80 years, weight ≤60 kg, creatinine ≥1.5 ml/min
[c]Significant for non-inferiority
[d]Significant for superiority
[e]Statistically significant

30 % relative risk reduction compared to placebo) provided by DAPT [35], it appears more prudent to abstain from OAC in order to limit the incidence of bleeding, which, in turn, may offset the benefit in reducing the risk of stroke (Table 2.5) [1, 2].

Whatever combination of antithrombotic agents is chosen, that is, either TT or DT, dabigatran (or other NOACs) can be restarted soon after PCI with stent implantation has been completed, given the short time to the onset of the pharmacological effect (i.e., a few hours) of dabigatran (and other NOACs) (Table 2.3) [3]. The dose of dabigatran (and other NOACs) should generally be reduced to the lower tested in clinical trials [1–3]. Either when evaluated prospectively or adjusted according to the characteristics of the patients, the reduced NOAC doses appeared consistently safer than warfarin, with no substantial reduction in efficacy (Table 2.10) [27–30].

Regarding the antiplatelet therapy to be combined with dabigatran (or other NOACs), DAPT of aspirin and clopidogrel should generally be given (Table 2.2) [1–3]. Both data from clinical trials comparing clopidogrel to newer agents prasugrel and ticagrelor, albeit in the specific context of acute coronary syndrome [36, 37], and small data from a single-center cohort where prasugrel was used instead of clopidogrel in combination with OAC with VKA and aspirin show that the risk of bleeding may largely be increased. In patients also on VKA, such increase in bleeding appears not accompanied by any substantial advantage in preventing MACEs, stent thrombosis, and stroke [38]. Whether, on the other hand, combination with OAC and single antiplatelet therapy with prasugrel or ticagrelor may have a favorable efficacy and safety profile is being investigated in clinical trials, including PIONEER AF-PCI with rivaroxaban [39] and RE-DUAL PCI with dabigatran [40]. Initial, observational, and very limited data in patients with acute coronary syndrome suggest, however, that this might possibly be a safe and effective option [41].

### 2.4.1 Post-procedural Management

- Following the procedure, dabigatran was restarted, at the reduced dose of 110 mg twice daily, the evening (i.e., about 6 h after) of the day of the procedure.
- DAPT of aspirin at the dose of 100 mg once daily and clopidogrel 75 mg once daily was confirmed.
- Pantoprazole 20 mg once daily was added for gastric protection.
- Remaining therapies, including carvedilol 6.25 mg twice daily, amlodipine 5 mg once daily, isosorbide mononitrate 20 mg three times daily, lisinopril 10 mg once daily, simvastatin 20 mg once daily, allopurinol 100 mg once daily, L-thyroxine 25 mcg once daily, metformin 850 mg twice daily, and insulin, were confirmed.

## 2.5 Medium- to Long-Term Issues

While having consistently been shown that TT is the most effective antithrombotic combination for the prevention of MACEs, stent thrombosis, and (especially) stroke, this comes at the price of an increased incidence of total/major bleeding (approximately 2.5-fold that of either DAPT or OAC alone) [1, 2, 23, 31]. Even though such finding appears not to unbalance the favorable benefit-to-risk ratio of TT, the increased risk of bleeding requires nonetheless the careful implementation of measure aiming to reduce bleeding (Table 2.11). These should include the shortest possible duration of TT (given that the risk of bleeding apparently increases with the prolongation of the exposure), the reduction of the intensity of OAC (given the superior safety of both an international normalized ratio [INR] of 2.0–2.5 and of the lower dose of NOAC), and the extensive use of proton pump inhibitors (PPIs) [1–3, 23] (Table 2.11). All the above measures are of special importance in the presence of an increased risk of bleeding, as expressed by a HAS-BLED score ≥3 (Table 2.9) [22], which per se, however, should not be a reason to withhold TT [42]. The dose reduction might be especially appropriate for dabigatran and rivaroxaban, which at the higher dose may increase the risk of gastrointestinal bleeding (Table 2.11).

**Table 2.11** Medium- to long-term (i.e., up to 12 months after PCI) management recommendations

| Issue | Recommendations |
|---|---|
| Initial antithrombotic treatment | Triple therapy (NOAC + aspirin[a,b] + clopidogrel) |
| Duration of triple therapy | BMS in elective setting: 1 month<br>DES in elective setting: 3–6 months[c]<br>Either BMS or DES in ACS setting: 3–6 months[d] |
| Intensity of OAC throughout triple therapy | Reduced[e] |
| Special care throughout triple therapy | Frequent laboratory monitoring (CrCl, CBC, Hgb)[f]<br>Routine gastric protection[g] |
| Subsequent antithrombotic treatment[h] | NOAC[i] + clopidogrel (or ASA)[j] |

*PCI* percutaneous coronary intervention, *NOAC* non-vitamin K-antagonist oral anticoagulant, *BMS* bare-metal stent, *DES* drug-eluting stent, *ACS* acute coronary syndrome, *OAC* oral anticoagulation, *CrCl* creatinine clearance, *CBC* complete blood count, *Hgb* hemoglobin, *ASA* aspirin, *PPI* proton-pump inhibitors, *BID* twice daily, *OD* once daily, *TT* triple therapy

[a]75–100 mg once daily

[b]May be omitted in selected patients at high risk of bleeding and concomitant low risk of stent thrombosis

[c]One month only may be considered when the risk of bleeding is high, and new-generation DES has been implanted

[d]One month only may be considered when the risk of bleeding is high, and either a BMS or a new-generation DES has been implanted

[e]Lower dose of NOAC: dabigatran 110 mg BID, rivaroxaban 15 mg OD, and apixaban 2.5 mg BID (and, possibly, edoxaban 30 mg OD)

[f]Every two weeks

[g]Preferably with PPI not interfering with clopidogrel metabolism (e.g., pantoprazole, dexlansoprazole)

[h]After the initial course of 1 to 3–6 months of TT has been completed

[i]Low-dose NOAC (dabigatran 110 mg BID, rivaroxaban 15 mg OD, and apixaban 2.5 mg BID (and edoxaban 30 mg BID) should likely be maintained to keep minimizing the risk of bleeding)

[j]Depending on the individual risk of bleeding, especially gastrointestinal, and stent thrombosis

The duration of TT, namely, clopidogrel, after PCI with stent implantation in the context of stable CAD is driven by the type of stent (i.e., BMS or DES) implanted [3, 10] (Table 2.11) (Fig. 2.4). Thus, either after 1 or 6 months, respectively, clopidogrel or aspirin (preferably) should be interrupted, and a single antiplatelet agent only continued in conjunction with OAC (Table 2.11) [1–3, 23].

Throughout such combination therapy, the ongoing reduced-dose dabigatran (or other NOACs) should generally be maintained in order to minimize the risk of bleeding (which is approximately 1.6-fold higher compared to OAC alone). In the absence of conditions increasing the risk of bleeding, such as moderate renal insufficiency (i.e., creatinine clearance 30–50 ml/min), low body weight (i.e., <60 kg), and advanced age (i.e., >80 years) alone or in combination, the full dose of rivaroxaban and apixaban should be reinstituted instead, given the uncertain efficacy of the lower dose in patients without the above characteristics [2]. Renal function should be periodically (i.e., every 1–3 months) checked during combined therapy with dabigatran (or other NOACs) and antiplatelet agents [1–3].

Because most of bleeding events in patients on TT occur from the gastrointestinal tract, extensive use of gastric protection, preferably with PPIs not interfering with the metabolism of clopidogrel (e.g., pantoprazole), is generally warranted during combined OAC and antiplatelet therapy [1–3]. This is especially true when TT includes a NOAC as the anticoagulant, given the consistent increase in gastrointestinal bleeding compared to warfarin reported with these agents [43].

### 2.5.1 Medium- to Long-Term Management

- The patient was discharged with the recommendations to (a) continue TT of dabigatran 110 mg twice daily and DAPT for 1 month and then withdraw aspirin while continuing clopidogrel 75 mg once daily up to 12 months in combination with dabigatran 110 mg twice daily; (b) continue gastric protection with pantoprazole 20 mg once daily for 12 months (as long as combination therapy of dabigatran and DAPT or single antiplatelet therapy was ongoing); and (c) check renal function (i.e., creatinine clearance) periodically, the first time after 2 weeks from discharge.

## 2.6 Long-Term Issues

After 1 year from the index procedure and in the absence of further cardiac events, ongoing single antiplatelet therapy should generally be interrupted, and dabigatran (or other NOACs) only continued lifelong (Table 2.12) [1–3] (Fig. 2.4). Although data on effective secondary prevention after an acute coronary syndrome were reported with VKAs [44, 45] and specific evidence with NOACs is currently lacking, there appears no reason why these agents would not be effective in such regard.

**Table 2.12** Long-term (i.e., >12 months after PCI, in the absence of recurrent events) management recommendations

| Issue | Recommendation |
|---|---|
| Antithrombotic treatment | NOAC monotherapy[a] |
| Intensity of OAC | Standard[b] |

*PCI* percutaneous coronary intervention, *NOAC* non-vitamin K-antagonist oral anticoagulant, *ASA* aspirin, *BID* twice daily, *OD* once daily *OAC* oral anticoagulation

[a]Indefinite combination with either low-dose ASA (75–100 mg once daily) or clopidogrel 75 mg (depending on the individual risk of bleeding, especially gastrointestinal, and stent thrombosis) may be considered in special situations (e.g., left main/last remaining vessel stenting, history of stent thrombosis/recurrent cardiac events, diffuse CAD), when bleeding risk is low

[b]That is, dabigatran 150 mg BID, rivaroxaban 20 mg OD, apixaban 5 mg BID, and edoxaban 60 mg BID, unless other indications for reduced dose are present *CAD* coronary artery disease

In the presence, however, of high risk of recurrent cardiac events, such as in patients with a history of stent thrombosis or with diffuse coronary artery disease, especially if not amenable of revascularization and associated with diabetes, or in conditions where stent thrombosis might have catastrophic consequence, such as in left main or last remaining vessel stenting, combination of dabigatran (or other NOACs) and single antiplatelet therapy may be continued long term [1–3]. Albeit in the different contexts of patients with no indication for OAC, long-term combination therapy of OAC and single antiplatelet appears, however, associated with a relevant incidence of bleeding, without apparent benefit on MACEs [46] and therefore should not be considered routinely [1–3].

Unless reasons for keeping the lower dose of dabigatran (or other NOACs) are present, initial full dose of the drug should be resumed and the management of OAC carried out as per usual recommendations (Table 2.12) [1–3].

### 2.6.1 Long-Term Management

- Upon completion of the 1-year combined therapy of OAC and DAPT or single antiplatelet therapy, ongoing clopidogrel 75 m once daily was discontinued and dabigatran, after increasing of the dose to the initial 150 mg twice daily (given that conditions mandating the use of low dose, including age ≥80 years and/or concomitant use of P-glycoprotein inhibitors, like verapamil, amiodarone, or quinidine, were not present), prescribed lifelong.

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# 3 Atrial Fibrillation on Vitamin K Antagonist Undergoing Urgent Percutaneous Coronary Intervention for Non-ST-Elevation Acute Coronary Syndrome

Kurt Huber

## 3.1 Case Presentation

### 3.1.1 Baseline Characteristics

- Gender: male.
- Age: 79 years.
- CV risk factors: hypertension.
- Associated diseases: chronic gastritis.
- Previous history: approximately 10 years earlier, transient ischemic attack (TIA) with no permanent sequelae during a first episode of paroxysmal atrial fibrillation (AF). Oral anticoagulation (OAC) with the vitamin K antagonist (VKA) warfarin with an international normalized ratio (INR) target between 2.0 and 3.0 was initiated. Since then, occasional, brief episodes of paroxysmal AF recurred for which however no antiarrhythmic therapy was prescribed.
- Current history: in the absence of previous symptoms, precordial chest pain, with radiation to the jaw, developed at rest and lasted approximately 30 min. Despite spontaneous cessation of chest pain, advice was given by the family physician to seek medical attention. Upon arrival at the emergency department at 3:15 PM, the patient was asymptomatic, and the electrocardiogram (ECG) was normal except for the detection of AF (Fig. 3.1). Blood pressure was 160/95 mmHg and other vital signs and $O_2$ saturation

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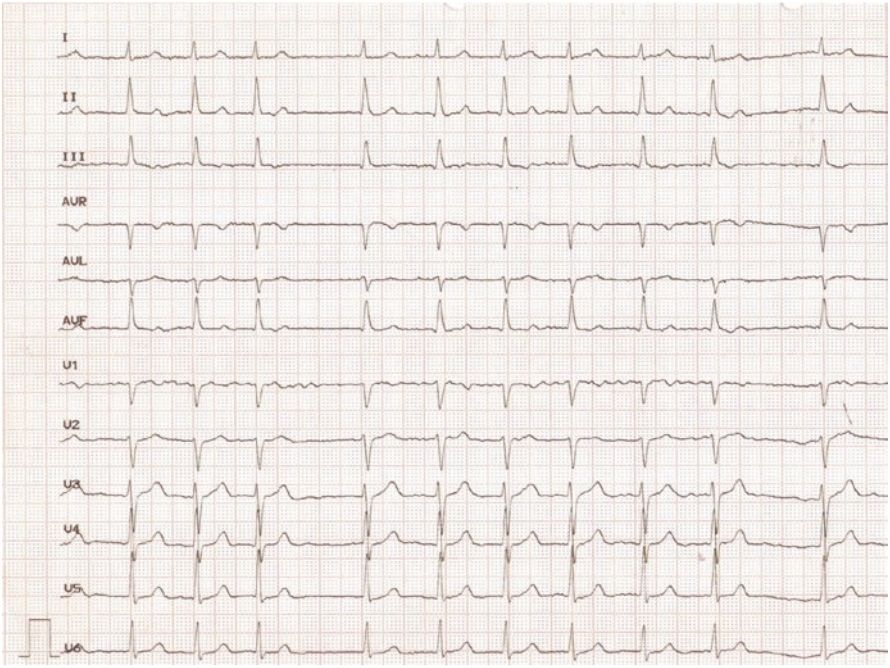


**Fig. 3.1** Electrocardiogram (ECG) on admission

were within normal limits. First sampling of high sensitive troponin I (hs-TnI) was in the normal range, but a significant increase above the normal limit was detected at the second measurement performed 3 h later, thereby leading to the diagnosis of non-ST-elevation myocardial infarction (NSTEMI). Because of that, the patient was referred to the cardiology department and coronary angiography/percutaneous coronary intervention (CORO/PCI) scheduled. Ongoing treatment upon admission included nebivolol 5 mg once daily, lisinopril 10 mg once daily, and warfarin according to INR (value at admission: 2.2).

## 3.2 Periprocedural Issues

Indication for and timing of CORO/PCI in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) are driven by the risk of adverse prognosis, as estimated by clinical, instrumental, and laboratory findings and/or by the application of the GRACE score [1] (Tables 3.1 and 3.2). With the exception of patients at low risk, in whom a noninvasive stress test (preferably with imaging) for inducible ischemia is recommended before deciding on an invasive strategy, all other

**Table 3.1** Risk criteria mandating for, and recommended timing of, invasive strategy in NSTE-ACS [1]

| |
|---|
| *Very high-risk criteria* (*within 2 h when at least one is present*) |
| Hemodynamic instability or cardiogenic shock |
| Recurrent or ongoing chest pain refractory to medical treatment |
| Life-threatening arrhythmias or cardiac arrest |
| Mechanical complications of myocardial infarction |
| Acute heart failure |
| Recurrent dynamic ST-T wave changes, particularly with intermittent ST-elevation |
| *High-risk criteria* (*within 24 h when at least one is present*) |
| Rise or fall in cardiac troponin compatible with myocardial infarction |
| Dynamic ST- or T-wave changes (symptomatic or silent) |
| GRACE score >140 |
| *Intermediate-risk criteria* (*within 72 h when at least one is present*) |
| Diabetes mellitus |
| Renal insufficiency (eGFR < 60 ml/min/1.73 $m^2$) |
| LVEF <40 % or congestive heart failure |
| Early postinfarction angina |
| Prior PCI |
| Prior CABG |
| GRACE risk score >109 and <140 |
| *Low-risk criteria* |
| Any characteristics not mentioned above |

*NSTE-ACS* non-ST-elevation acute coronary syndrome, *eGFR* estimated glomerular filtration rate, *LVEF* left ventricular ejection fraction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting

NSTE-ACS patients should undergo CORO/PCI because of the superiority of a routine compared to a selective invasive strategy on clinical outcomes and recurrent ACS episodes, subsequent rehospitalization, and revascularization [1]. Whereas all NSTE-ACS patients should undergo invasive evaluation/treatment within 72 h of admission, those at higher risk should undergo CORO/PCI within 24 h [1] (Table 3.1). NSTE-ACS patients at highest risk should enter a fast-track management program allowing for emergency CORO/PCI as in ST-elevation myocardial infarction (STEMI), i.e., within 2 h [1] (Table 3.1). Therefore, the periprocedural management of both anticoagulation and antiplatelet therapy is an issue of relevance in patients who are on chronic OAC. Such condition, in fact, likely increases the risk of in-hospital bleeding complications, which in turn are associated with increased mortality, especially in the event that invasive evaluation/treatment is carried out. The CRUSADE score currently recommended for stratification of in-hospital risk of bleeding in NSTE-ACS patients has not been validated in the subset on OAC, and therefore its predictive value in these patients has not been established (Table 3.3) [1]. Nonetheless, application of the CRUSADE score may be of value also in patients on OAC to identify, and potentially correct, established factors for increased

**Table 3.2** GRACE score calculation [1]

| Background | | Findings at the time of admission | | Findings during hospital stay | |
|---|---|---|---|---|---|
| *1. Age (years)* | *Points* | *4. Heart rate at admission (bpm)* | *Points* | *7. Serum creatinine at admission (ml/min)* | *Points* |
| ≤29 | 0 | ≤49.9 | 0 | 0.0–0.39 | 1 |
| 30–39 | 0 | 50–69.9 | 3 | 0.4–0.79 | 3 |
| 40–49 | 18 | 70–89.9 | 9 | 0.8–1.19 | 5 |
| 50–59 | 36 | 90–109.9 | 14 | 1.2–1.59 | 7 |
| 60–69 | 55 | 110–149.9 | 23 | 1.6–1.99 | 9 |
| 70–79 | 73 | 150–199.9 | 35 | 2.0–3.99 | 15 |
| 80–89 | 91 | ≥200 | 43 | ≥4.0 | 20 |
| ≥90 | 100 | | | | |
| | | *5. SAP at admission (mmHg)* | | *8. Elevated enzymes or markers* | 15 |
| *2. History of heart failure* | 24 | ≤79.9 | 24 | | |
| | | 80–99.9 | 22 | *9. No percutaneous revascularization* | 14 |
| *3. History of myocardial infarction* | 12 | 100–119.9 | 18 | | |
| | | 120–139.9 | 14 | | |
| | | 140–159.9 | 10 | | |
| | | 160–199.9 | 4 | | |
| | | ≥200 | 0 | | |
| | | | | | |
| | | *6. Depressed ST-segment* | 11 | | |

*SAP* systolic arterial pressure

risk of bleeding and to estimate, if not the absolute, at least the relative risk of bleeding.

In the acute phase of an NSTE-ACS, effective anticoagulation is required to inhibit thrombin generation and/or activity, thereby reducing thrombus-related events [1]. Effective anticoagulation is also required throughout PCI to avoid thrombus formation, both at the PCI hardware and the vessel plaque injured by the balloon or stent trauma. Several anticoagulant strategies are currently approved for NSTE-ACS patients (Table 3.4).

In patients on OAC with warfarin (or other VKAs) undergoing CORO/PCI in the context of an NSTE-ACS, the periprocedural anticoagulation strategies may include (1) continuation of ongoing OAC or (2) interruption of ongoing OAC, associated or not with heparin bridging, and perform CORO/PCI after the INR has reached < 1.8–2.0. While this latter option would delay performance of CORO/PCI of several days, therefore hampering the benefits of early revascularization, as recommended in most recent guidelines [1], available data suggest that uninterrupted OAC with warfarin is an option as safe and effective [2, 3] and should therefore generally selected (Table 3.5) [1, 4–6].

**Table 3.3** CRUSADE bleeding risk score [1]

| | Points | Bleeding risk category | In-hospital bleeding rate (%) |
|---|---|---|---|
| *Baseline hematocrit, %* | | Very low, ≤ 20 | 3.0 |
| <31 | 9 | Low, 21–30 | 5.5 |
| 31–33.9 | 7 | Moderate, 31–40 | 9.0 |
| 34–36.9 | 3 | High, 41–50 | 12.0 |
| 37–39.9 | 2 | Very high, > 50 | 19.0 |
| ≥40 | 0 | | |
| *Creatinine clearance,* [a] *mL/min* | | | |
| ≤15 | 39 | | |
| >15–30 | 35 | | |
| >30–60 | 28 | | |
| >60–90 | 17 | | |
| >90–120 | 7 | | |
| >120 | 0 | | |
| *Heart rate (bpm)* | | | |
| ≤70 | 0 | | |
| 71–80 | 1 | | |
| 81–90 | 3 | | |
| 91–100 | 6 | | |
| 101–110 | 8 | | |
| 111–120 | 10 | | |
| ≥121 | 11 | | |
| *Sex* | | | |
| Male | 0 | | |
| Female | 8 | | |
| *Signs of CHF at presentation* | | | |
| No | 0 | | |
| Yes | 7 | | |
| *Prior vascular disease†* | | | |
| No | 0 | | |
| Yes | 6 | | |
| *Diabetes mellitus* | | | |
| No | 0 | | |
| Yes | 6 | | |
| *Systolic pressure, mmHg* | | | |
| ≤90 | 10 | | |
| 91–100 | 8 | | |
| 101–120 | 5 | | |
| 121–180 | 1 | | |
| 181–200 | 3 | | |
| ≥201 | 5 | | |

*CHF* congestive heart failure
[a]According to Cockroft-Gault formula
† history of peripheral artery disease or prior stroke

Besides allowing to provide the optimal invasive management within the recommended time frame, this strategy would also avoid the common INR fluctuations associated with warfarin interruption, and subsequent re-initiation, and the prothrombotic state

**Table 3.4** Anticoagulant regimens for NSTE-ACS patients [1]

| | | Normal renal function or stage 1–3 CKD (eGFR ≥ 30 ml/min/1–73 $m^2$) | Stage 4 CKD (eGFR 15–29 ml/min/1.73 $m^2$) | Stage 5 CKD (eGFR < 15 ml/min/1.73 $m^2$) |
|---|---|---|---|---|
| UFH | Prior to CORO | Bolus 60–70 IU/kg IV (max 5000 IU) + infusion 12–15 IU/kg/h (max 1000 IU/h), target aPTT 1-5-2.5 × control | No dose adjustment | No dose adjustment |
| | During PCI | According to ACT or bolus 70–100 IU/kg (50–70 IU/kg if concomitant GP IIb/IIIa inhibitors) IV | | |
| Enoxaparin | | 1 mg/kg SC BID | 1 mg/kg SC OD | Not recommended |
| Fondaparinux | | 2.5 mg SC OD | Not recommended if eGFR < 20 ml/min/1.73 $m^2$ | Not recommended |
| Bivalirudin | | Bolus 0.75 mg/kg IV + infusion 1.75 mg/kg/h | Not recommended | Not recommended |

*NSTE-ACS* non-ST-elevation acute coronary syndrome, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *UFH* unfractionated heparin, *CORO* coronary angiography, *PCI* percutaneous coronary intervention, *IU* international units, *h* hour, *IV* intravenous, *aPTT* activated thromboplastin time, *ACT* activate coagulation time, *SC* subcutaneously, *BID* twice daily, *OD* once daily

**Table 3.5** Recommended peri- and intra-procedural anticoagulation

| Periprocedural anticoagulation | Uninterrupted warfarin (preprocedural INR ideally between 2.0 and 2.5) |
|---|---|
| Intra-procedural anticoagulation[a] | UFH IV bolus 50–70 IU/kg (when INR > 2.0) |
| | UFH IV bolus 70–100 IU/kg (when INR < 2.0) |

*INR* international normalized ratio, *UFH* unfractionated heparin, *IV* intravenous, *IU* international units

[a]No or very limited data are available for enoxaparin and bivalirudin, and therefore these anticoagulants are generally not recommended

induced by inhibition of the anticoagulant proteins C and S occurring upon initiation of warfarin, which are in turn associated with increased incidence of bleeding and risk of thromboembolic complications, respectively. Finally, the uninterrupted OAC strategy would reduce the duration of hospitalization. Concern regarding the reversal of OAC with warfarin in the event that the need arises (e.g., severe periprocedural bleeding and/or procedural complication, such as coronary perforation) should not represent a barrier for the adoption of the uninterrupted strategy given that administration of nonspecific (e.g., prothrombin complex concentrates, fresh frozen plasma, recombinant factor VII) and/or specific (i.e., vitamin K) reversal agents are generally, and rather rapidly, effective in antagonizing the anticoagulant effect [7]. To further increase the safety of

COR/PCI during uninterrupted OAC with warfarin, however, targeting the preprocedural INR between 2.0 and 2.5 may be preferable.

Provided that OAC with warfarin with an INR > 2.0 has been continued throughout CORO/PCI, the next issue is whether or not additional anticoagulation should be given at the time of procedure. Whereas heparin administration is required upon initiation of PCI to avoid thrombus formation at the angioplasty hardware and/or at the coronary lesion site traumatized by balloon inflation and/or stent implantation in non-OAC patients, whether such strategy is necessary also in patients on effective OAC with warfarin is uncertain. On the one hand, warfarin has been shown to prolong the activated coagulation time (ACT), which is commonly used to monitor the degree of intra-procedural anticoagulation with heparin, in a predictable manner [8], thereby suggesting that no additional anticoagulation is needed. On the other hand, the need for operating in a highly prothrombotic milieu, such as that of an NSTE-ACS, as well as the mechanism of anticoagulation exerted by warfarin (which does not directly inhibit the coagulation factors that have been activated, like heparins and bivalirudin do, but rather leads to the presence in the circulation of inactive coagulation factors) may suggest that additional intra-procedural anticoagulation is advisable [4, 6]. Also, recent data suggest that additional UFH in patients on effective OAC with VKAs may benefit of additional UFH for the prevention of radial artery occlusion, when such access is used for CORO/PCI [10]. Therefore, it appears prudent to provide further anticoagulation, irrespective of the current INR level: a reduced dose of 50–70 IU/kg of intravenous (IV) unfractionated heparin (UFH) should be given in the presence of an INR > 2.0, whereas a standard 70–100 IU/kg dose should be administered for an INR < 2.0 [6]. Whereas enoxaparin may be used for intra-procedural anticoagulation in non-OAC patients, it should preferably be avoided in those on effective OAC with warfarin undergoing CORO/PCI, given the lack of data and the uncertainty regarding the optimal dose and timing of administration. Regarding bivalirudin, which has been shown to be associated to a reduced incidence of both bleeding and adverse ischemic events, both in general ACS populations [10] and a small dataset of AF patients on OAC [11], again there is uncertainty regarding the optimal dose and the infusion scheme, therefore making this option of uncertain value.

Regarding the type, dose, and timing of antiplatelet therapy to be given to patients on OAC with warfarin undergoing CORO/PCI because of NSTE-ACS, again there is no specific evidence. As in non-OAC patients [1], dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$-receptor inhibitor is generally recommended [4–6]. Therefore, the patient should be loaded upon presentation with 150–300 mg of aspirin orally or IV [4, 6] (Table 3.6). Whereas newer $P2Y_{12}$-receptor inhibitors ticagrelor and prasugrel should not be used in association with warfarin and aspirin because of the reported increase in bleeding with prasugrel in combination [12, 13], as well as because of the significant increase in bleeding compared to clopidogrel reported in non-OAC populations of NSTE-ACS patients [14, 15], loading with clopidogrel may either be considered at presentation or after CORO has been performed and indication for PCI has emerged [4]. Withholding triple therapy (TT) until performance PCI may, in fact, reduce the risk of bleeding associated with an

**Table 3.6** Recommended peri- and intra-procedural oral antiplatelet therapy

| | |
|---|---|
| Upon presentation | Aspirin 150–300 mg orally or IV + clopidogrel 600 mg orally[a] |
| | or |
| | Clopidogrel 600 mg orally[a] (+ aspirin 150–300 mg orally or IV to be given upon start of PCI) |
| | or |
| | Aspirin 150–300 mg orally or IV (+ clopidogrel 600 mg to be given upon start of PCI) |

Note: no indication for newer $P2Y_{12}$-receptor inhibitors ticagrelor and prasugrel
*IV* intravenous, *PCI* percutaneous coronary intervention
[a]At least 2 h before procedure

invasive procedure performed during aggressive antithrombotic therapy. With the same intent, it may be considered an alternative strategy, recently proposed but not properly validated, consisting of withholding aspirin (which has almost an immediate antiplatelet effect) until performance of PCI, and pretreat the patient with clopidogrel instead [16]. Given, in fact, the need for several hours (approximately 6 and 2, respectively, depending on whether 600 or 300 mg of clopidogrel are given) before effective inhibition of platelet aggregation is reached [17], as opposed to the nearly immediate antiplatelet effect of aspirin, such strategy may be preferable [16]. The higher loading dose of 600 mg of clopidogrel, however, should generally be preferred [5, 6]. The strategy of pretreating patients on warfarin with clopidogrel may also be valuable in the selected cases at high hemorrhagic risk and concomitant low risk of atherothrombotic and thromboembolic events in whom dual therapy (DT) with warfarin and clopidogrel may be considered [4–6]. Even in these cases, however, it needs to be remarked that additional intra-procedural aspirin at the standard dose of 150–300 mg is warranted, because of the likely insufficient protection against periprocedural ischemic complications of the antiplatelet effect of clopidogrel only.

As, and even more than, in non-OAC patients referred for CORO/PCI because of NSTE-ACS, there is currently no indication for preprocedural initiation of glycoprotein IIb/IIIa inhibitors given the lack of significant clinical benefit [4–6].

Finally, as an additional strategy to limit the risk of periprocedural bleeding in patients undergoing CORO/PCI while on effective OAC with warfarin, the radial vascular access site should routinely be preferred, when expertise is available [4–6]. Both in large populations not on OAC [18] and in a small observational experience of warfarin patients [19], the radial approach has been shown to dramatically decrease the incidence of access-site complications. Should the radial access not be feasible, the conventional femoral approach may nonetheless be used also when the INR is > 2.0, provided, however, that is meticulously carried out according to optimal technique (i.e., puncture below the inguinal ligament and of anterior wall only) and possibly with the support of ultrasonographic guidance.

### 3.2.1 Periprocedural Management

- Upon admission to the cardiology department, oral loading with aspirin 300 mg and clopidogrel 600 was performed.
- CORO was performed the next morning at 10:00 by the right radial approach.
- The morning of procedure, the INR value was 2.3.
- Following radial artery cannulation, an intravenous bolus of 4,000 IU, corresponding to approximately 50 IU/kg, of UFH was given to prevent radial artery occlusion.
- CORO was performed with conventional JL and JR 5 French diagnostic catheters and disclosed a 75–80 % narrowed proximal left anterior descendent artery (LAD) with only minimal wall irregularities in the right and circumflex coronary arteries (Fig. 3.2).

## 3.3 Procedural Issues

Apart from the management of antithrombotic therapy, the main procedural issue in patients on OAC with VKA undergoing CORO/PCI in the context of an NSTE-ACS is the choice of the stent to implant (Table 3.7). While, in fact, drug-eluting stents (DESs) have been undoubtedly shown to reduce restenosis and associated cardiac events, an increased tendency toward stent thrombosis, especially late or very late,

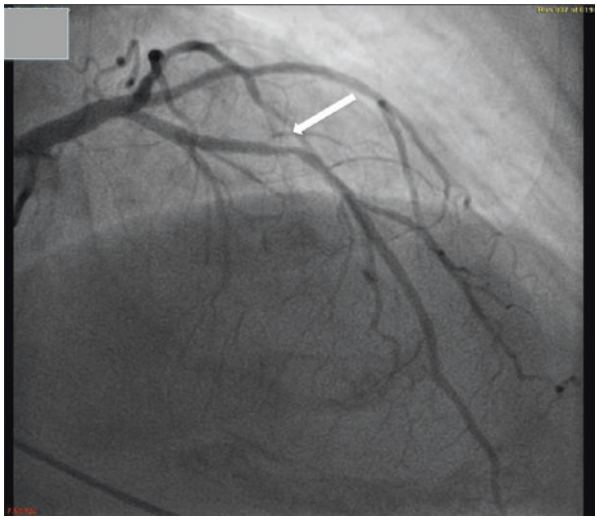

**Fig. 3.2** Coronary angiography (RAO view cranial) showing critical stenosis of mid-LAD (*arrow*). *RAO* right anterior oblique, *LAD* left anterior descending

**Table 3.7** General classification of coronary stents/scaffolds

| | | |
|---|---|---|
| BMS | | (a) Stainless steel<br>(b) Non-stainless steel, cobalt- or platinum-chrome alloy |
| DES | Early generation | (a) Durable polymer: sirolimus, paclitaxel eluting |
| | New generation | (a) Durable polymer: zotarolimus, everolimus eluting<br>(b) Biodegradable polymer: biolimus A9, and everolimus eluting<br>(c) Polymer free: amphilimus, biolimus A9 eluting |
| BAS | | (a) Diamond-like carbon coated, titanium nitric oxide coated<br>(b) Endothelial progenitor cells capturing |
| BVS | | (a) Non-drug eluting<br>(b) Everolimus, myolimus, sirolimus eluting |

*BMS* bare-metal stent, *DES* drug-eluting stent, *BAS* bioactive stent, *BVS* bioresorbable vascular scaffold

**Table 3.8** Academic Research Consortium (ARC) definitions of stent thrombosis [20]

| | |
|---|---|
| Event Certainty | (a) Definite: acute coronary syndrome with angiographic or autopsy confirmation of stent thrombosis |
| | (b) Probable: |
| | (i) Unexplained death within 30 days of stent implantation without autopsy |
| | (ii) Acute myocardial infarction in the territory of target vessel where stent was implanted without angiographic confirmation |
| Time frame | (a) Early: |
| | (i) Acute – within 24 h of stent implantation |
| | (ii) Subacute – between 24 h and 30 days of stent implantation |
| | (b) Late: between 30 days and 1 year of stent implantation |
| | (c) Very late: after 1 year of stent implantation |

compared to bare-metal stents (BMS) has equally been established (Table 3.8). As a consequence, a longer duration of DAPT compared to BMS (i.e., 6–12 months vs. 1 month) is recommended [5]. Of note, such durations are related to the prevention of stent thrombosis inherently associated with the implantation of a foreign body in the coronary artery and not to the prevention of recurrent coronary events inherently associated with the existence of coronary artery disease. And since it is established that the risk of recurrences is much higher in patients experiencing an NSTE-ACS, this clinical context mandates a 12-month course of DAPT, regardless of the type of stent implanted (and even regardless of whether or not CORO/PCI has been performed and a stent has been implanted) [1, 5]. Given that combination therapy of OAC and antiplatelet agents is warranted in these patients, having the possibility to limit its duration by choosing a stent requiring a shorter duration of DAPT is highly advised both to prescribe a limited period of combination therapy since discharge and to more safely interrupt prematurely such therapy in the event that the need arises (e.g., because of a bleeding event or unplanned surgery). New-generation DESs, including everolimus-, zotarolimus- and biolimus-eluting stents, with either durable or resorbable polymer coating, or even without any polymer coating, have been generally shown to be associated to a very low incidence of thrombosis, thereby requiring DAPT for not longer than 6 months in stable patients and elective PCI. Additional data also suggest that a

duration of DAPT as short as 3 months, or even 1 month, may be sufficient with new-generation DESs [21–24], thereby almost eliminating differences in this regard with BMSs. These latter, therefore, should be reserved at present to those patients at very high bleeding risk in whom even a course of DAPT as short as 3–6 months appears not feasible. Such short duration of DAPT appears also reasonable to optimize the risk-to-benefit ratio in the context of an NSTE-ACS treated with PCI in an OAC patient, given the reported highest incidence of adverse events early after (i.e., first 3 months) the index event [25].

Should the indication for PCI not emerge after CORO, either because of absence of critical coronary lesions or at opposite because of coronary disease not amenable of PCI, dual therapy (DT) of OAC and single antiplatelet agent (either aspirin 75–100 mg once daily or clopidogrel 75 mg once daily, depending on the estimated individual risk of bleeding, especially at the gastrointestinal site) rather than TT should be continued. Indirect data suggest indeed that after an ACS, the efficacy on major adverse cardiovascular events, including death, myocardial infarction, and stroke, of DAPT with aspirin and clopidogrel is comparable to that of warfarin and aspirin, at the price however of an increased risk of major bleeding [26].

### 3.3.1 Procedural Management

- Ad hoc PCI with a new-generation drug-eluting stent (DES) polymer-free, biolimus A9-eluting stent (Biofreedom, 5.0×18 mm, Biomatrix) was performed immediately after CORO with an optimal angiographic result (Fig. 3.3).
- Stratification of the risk of both stroke ($CHA_2DS_2$-VASc score 6) (Table 3.9) and bleeding (HAS-BLED score 4) (Table 3.10) risk was performed.

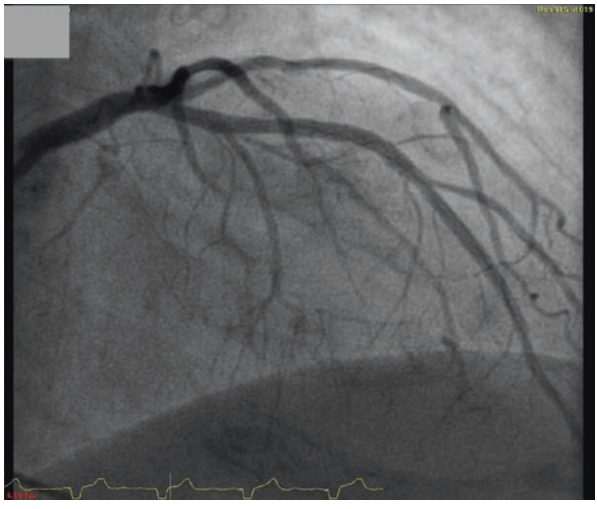

**Fig. 3.3** Coronary angiography (RAO view cranial) showing final result after stent implantation in mid-LAD. *RAO* right anterior oblique, *LAD* left anterior descending

**Table 3.9** $CHA_2DS_2$-VASc score and associated risk of stroke/year [27]

| | Condition | Points | Total score | Stroke risk/ year (%) |
|---|---|---|---|---|
| C | Congestive heart failure (or left ventricular ejection fraction ≤ 35 %) | 1 | 0 | 0 |
| H | Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication) | 1 | 2 | 1.3 |
| $A_2$ | Age ≥ 75 years | 2 | 2 | 2.2 |
| D | Diabetes mellitus | 1 | 3 | 3.2 |
| $S_2$ | Prior Stroke or TIA or thromboembolism | 2 | 4 | 4.0 |
| V | Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque) | 1 | 5 | 6.7 |
| A | Age 65–74 years | 1 | 6 | 9.8 |
| Sc | Sex category (i.e., female sex) | 1 | 7 | 9.6 |
| | | | 8 | 6.7 |
| | | | 9 | 15.2 |

*TIA* transient ischemic attack

**Table 3.10** HAS-BLED score and associated risk of major bleeding/year [27]

| | Condition | Points | Total score | Risk of major bleeding/year (%) |
|---|---|---|---|---|
| H | Hypertension (uncontrolled blood pressure above 160/90 mmHg) | 1 | 0 | <1 |
| A | Renal (dialysis, transplant, creatinine > 2.6 mg/dL or >200 μmol/L) and/or liver (cirrhosis, bilirubin > 2× normal or AST/ALT/AP > 3× normal) disease | 1 or 2 | 1–2 | 2–3 |
| S | Stroke | 1 | ≥3 | 4–12 |
| B | Bleeding (previous or predisposition to) | 1 | | |
| L | Labile INR (unstable/high or TTR < 60 %) | 1 | | |
| E | Elderly (i.e., age > 65 years) | 1 | | |
| D | Drug usage predisposing to bleeding (antiplatelet agents, NSAIDs) and/or alcohol (≥8 drinks a week) | 1 or 2 | | |

*INR* international normalized ratio, *TTR* time in therapeutic range, *NSAID* nonsteroidal anti-inflammatory drugs, *AST* aspartate aminotranspherase, *ALT* alanine aminotranspherase, *AP* alkaline phosphatase

## 3.4 Post-procedural Issues

Given that OAC anticoagulation with VKA has been shown significantly more effective than DAPT for stroke prevention in AF [28] and that DAPT is capable to reduce the incidence of subacute stent thrombosis significantly more than OAC after PCI [29], combination therapy of OAC and antiplatelet agents is warranted when indication for both treatments exists. Albeit suboptimal, as it mostly derives from observational, not randomized, single-center data or administrative databases, available evidence supports TT of OAC with warfarin, aspirin, and clopidogrel as the preferable antithrombotic combination [1, 4–6]. In general, TT appears more effective than any other combination on the occurrence of major

**Table 3.11** Relative efficacy and safety of medium-term TT after PCI with stent in OAC patients

| Outcomes | Vs. DAPT [36] | Vs. DT[a] [36] | Vs. non-TTs (2010) [31] |
|---|---|---|---|
| MACE + stroke | 0.76 (0.70–0.83)<br>$p < 0.00001$ | 0.67 (0.59–0.75)<br>$p < 0.00001$ | – |
| Stroke | – | – | 0.29 (0.15–0.58)<br>$p = 0.0004$ |
| All-cause death | 0.64 (0.56–0.73)<br>$p < 0.00001$ | 0.48 (0.39–0.58)<br>$p < 0.00001$ | 1.20 (0.63–2.27)<br>$p =$ NS |
| Major bleeding | 1.36 (1.17–1.58)<br>$p < 0.0001$ | 0.96 (0.75–1.21)<br>$p =$ NS | 2.00 (1.42–2.83)<br>$p < 0.0001$ |

*MACE* major adverse cardiac events, *DAPT* dual antiplatelet therapy, *DT* dual therapy, *NS* nonsignificant

[a]Either OAC + aspirin or OAC + clopidogrel

adverse cardiovascular events, including death, myocardial infarction, repeat revascularization, stent thrombosis, and stroke, at the price however of an increased incidence of bleeding (Table 3.11). Because of that, while representing the antithrombotic strategy generally to be prescribed, implementation of bleeding-avoiding strategies, including duration for as short as possible, reduced intensity of OAC (i.e., target INR 2.0–2.5), and extensive use of gastric protection with proton pump inhibitors (PPIs), is recommended [4, 6] (Table 3.12). Concurrent use of warfarin and single or dual antiplatelet therapy in NSTE-ACS patients is indeed an established indication for the use of PPIs [32]. The preference should generally be given to PPIs not interfering with clopidogrel metabolism (e.g., pantoprazole) because of the possible association between use of PPI gastric protection and adverse outcome in patients on clopidogrel therapy [33]. Whether, however, these measures really work is currently insufficiently proven, with the possible exception of the lower target INR which in an observational series has indeed been shown to be associated with an incidence of bleeding comparable to that of DAPT [29]. In the same experience, an INR of 2.6 has been identified as the cutoff value above which the risk of bleeding of TT is substantially increased [34].

Among the bleeding-avoiding strategies, omission of aspirin and prescription of dual therapy (DT) with OAC and clopidogrel only have recently emerged. In the randomized, prospective, multicenter WOEST study, DT has been proven significantly safer (incidence of total bleeding) and more effective (incidence of death, myocardial infarction, re-revascularization, stent thrombosis, and stroke) than conventional TT [30]. The several limitations in study design and size, however, are currently considered to make the results not conclusive, especially regarding the efficacy side [31, 32]. At present, DT may be therefore considered as an option essentially for patients at very high bleeding risk and associated low risk of atherothrombotic and thromboembolic events [1, 4–6]. Of note, the use of DT appears of even more uncertain applicability in OAC patients undergoing PCI in the context of an NSTE-ACS, where the risk of atherothrombotic events, namely, recurrent cardiac ischemia and stent thrombosis, is higher than in stable patients, because of the minority of unstable patients who were included in the WOEST study [30]. Of note,

**Table 3.12** Short-, medium- to long-term (i.e., up to 12 months after PCI) management recommendations

| Issue | Recommendations |
|---|---|
| Initial antithrombotic treatment | Triple therapy (OAC + aspirin[a, b] + clopidogrel) |
| Duration of triple therapy | BMS in elective setting: 1 month<br>DES in elective setting: 3–6 months[c]<br>Either BMS or DES in ACS setting: 3–6 months[d] |
| Intensity of OAC throughout triple therapy | Reduced[e] |
| Special care throughout triple therapy | Frequent INR monitoring[f]<br>Attention to high-quality OAC[g]<br>Routine gastric protection[h] |
| Subsequent antithrombotic treatment[i] | OAC[j] + either clopidogrel[k] or aspirin |

*PCI* percutaneous coronary intervention, *BMS* bare-metal stent, *DES* drug-eluting stent, *ACS* acute coronary syndrome, *OAC* oral anticoagulation, *INR* international normalized ratio

[a]75–100 mg once daily

[b]May be omitted in selected patients at high risk of bleeding and concomitant low risk of stent thrombosis

[c]One month only may be considered when the risk of bleeding is high, and new-generation DES has been implanted

[d]One month only may be considered when the risk of bleeding is high, and either a BMS or a new-generation DES has been implanted

[e]Target INR 2.0–2.5

[f]Every 2 weeks

[g]Aiming at an average INR > 70 %

[h]Preferably with PPI not interfering with clopidogrel metabolism (e.g., pantoprazole, dexlansoprazole)

[i]After the initial course of 1 to 3–6 months of TT has been completed

[j]Standard intensity of OAC, that is, INR 2.0–3.0, should be resumed

[k]Preferred due to its superior gastric tolerability

the findings of the WOEST study [35] have not been observed in subsequent, large, observational datasets and/or meta-analyses, where nonetheless a comparable efficacy and safety of DT and TT has been repeatedly reported [30, 36–40].

Once TT of OAC, aspirin, and clopidogrel has been selected, a question may be whether ongoing VKA should be confirmed or a non-vitamin K antagonist oral anticoagulant (NOAC), such as dabigatran, rivaroxaban, apixaban, or edoxaban, might be better used instead. In clinical trials of stroke and systemic embolism prevention in AF, all NOACs have been shown at least as effective and safe as conventional, dose-adjusted warfarin therapy [41–44]. Also, in a secondary analysis of the RE-LY trial [45], concomitant use of single or dual antiplatelet therapy appears to have no interaction with respect to the overall efficacy results. While being the absolute incidence of major bleeding the lowest with dabigatran 110 mg twice daily compared to both dabigatran 150 mg twice daily and warfarin both in triple and dual combination, the relative risk is approximately the same irrespective of the OAC used (i.e., 1.6 and 2.3 with one and two antiplatelet agents, respectively) [45]. Because of that, switching from VKA to a NOAC only because antiplatelet therapy needs to be added (for a definite period of time) requires thoughtful consideration. On the one hand in fact, nearly all the evidence on TT has been obtained with warfarin being the OAC, and it may therefore be questionable to switch from a more proven therapy to another where the evidence is lacking or extremely limited. Also, the superior confidence in managing

warfarin therapy, in the cumbersome perioperative setting, and its complications, including thromboembolism and bleeding, may be a further point in maintaining warfarin as the OAC to be combined with DAPT. On the other hand, all NOACs compared to warfarin have been associated to comparable occurrence of major bleeding and dramatically lesser incidence of intracranial bleeding (which is the most feared and devastating complication of OAC) making therefore switching from VKA to a NOAC an attractive option. This is also taking into account the much higher convenience of use, also considering the likely difficulty in keeping the INR during warfarin therapy within the recommended, narrow range of 2.0–2.5. The fear of a major bleeding during OAC with a NOAC which cannot be properly managed is nowadays likely outdated given the recent reporting of an effective antidote to both dabigatran [46] and factor Xa inhibitors, including rivaroxaban, apixaban, and edoxaban [47]. Given that dabigatran is the NOAC so far best tested in combination with antiplatelet agents, the availability of an antidote is a further argument possibly speaking for a preferred use of this NOAC in combination with antiplatelet agents. Should switching from warfarin to a NOAC be selected, the use of the lower tested dose of NOAC, that is, dabigatran 110 mg twice daily, rivaroxaban 15 mg once daily, apixaban 2.5 mg twice daily, and likely edoxaban 30 mg once daily, appears preferable. All other recommendations regarding intensity, duration, and monitoring of patients on TT with warfarin as the OAC should also be followed for NOACs [4, 6, 48].

### 3.4.1 Post-procedural Management

- TT of OAC with warfarin (targeted to an INR of 2.0–2.5), aspirin 75 mg once daily, and clopidogrel 75 mg once daily was selected.
- Gastric protection with pantoprazole 20 mg once daily was added together with atorvastatin 40 mg once daily, while the remaining therapy of nebivolol 5 mg once daily and lisinopril 10 mg once daily was confirmed.

## 3.5 Medium- to Long-Term Issues

Upon discharge, an initial period of TT should generally be prescribed and its duration and intensity carefully individualized as previously mentioned, aiming to keep an optimal balance between effective prevention of recurrent cardiac events, stent thrombosis, and stroke on the one hand and minimization of the risk of bleeding on the other hand. Together with the above recommendations, tight and frequent control of the INR should be carried out, aiming at obtaining a time in therapeutic range (TTR) > 70 % (Table 3.12) [6].

After the mandatory initial course of 3–6 months of TT has been completed, DT of OAC and single antiplatelet agent should be continued up to 12 months. The question at this stage is whether to interrupt aspirin or clopidogrel. On the one hand, aspirin has been more extensively studied for secondary prevention after an

**Table 3.13** Long-term (i.e., > 12 months after PCI, in the absence of recurrent events) management recommendations

| Issue | Recommendation |
|---|---|
| Antithrombotic treatment | OAC monotherapy[a] |
| Intensity of OAC | Standard[b] |

*PCI* percutaneous coronary intervention, *OAC* oral anticoagulation
[a]Indefinite combination with either low-dose ASA (75–100 mg once daily) or clopidogrel 75 mg (depending on the individual risk of bleeding, especially gastrointestinal and stent thrombosis) may be considered in special situations (e.g., left main/last remaining vessel stenting, history of stent thrombosis/recurrent cardiac events, diffuse CAD), when bleeding risk is low or when the NOAC used is dabigatran
[b]That is, target INR 2.0–3.0

NSTE-ACS and might therefore be preferred in patients at not increased risk of gastrointestinal bleeding (to which aspirin treatment is associated), whereas on the other clopidogrel may (preferably) be selected because of its superior safety on gastrointestinal bleeding and likely higher efficacy on recurrent cardiac events [4, 49].

Upon completion of 12-month combined OAC and (initially dual and subsequently single) antiplatelet therapy, the question is whether or not to withdraw antiplatelet therapy. Given the reported efficacy in secondary prevention of warfarin [50, 51] and the increased risk of bleeding with long-term combined OAC and single antiplatelet agent (without apparent additional benefit on ischemic events) [52], warfarin monotherapy should generally be prescribed after the first 12 months of combined OAC and antiplatelet therapy (Table 3.13) [4–6]. Possible exceptions are conditions where stent thrombosis might have catastrophic consequences, such as after PCI in the left main, proximal bifurcations, or last remaining vessel, or when the patient appears at particularly high risk of recurrences, such in the presence of diffuse coronary disease, especially if not amenable of revascularization, diabetes, and history of recurrent events [4–6] (Table 3.13).

Standard intensity of OAC with warfarin, that is, a target INR between 2.0 and 3.0, should be resumed when all antiplatelet agents have been withdrawn and also possibly after DAPT has been interrupted and single antiplatelet therapy is carried out together with OAC [6]. Standard monitoring and follow-up of the OAC patient should also be resumed.

### 3.5.1 Medium- to Long-Term Management

- The patient was discharged after 4 days from admission, with TT planned for 3 months and confirmation of remaining therapy including nebivolol 5 mg once daily, lisinopril 10 mg once daily, atorvastatin 40 mg once daily, and pantoprazole 20 mg once daily.
- After 3 months of TT, aspirin was withdrawn and DT with warfarin and clopidogrel 75 mg once daily continued up to 12 months.

- At this time, target INR was resumed to 2.0–3.0, while continuing however gastric protection therapy with pantoprazole 20 mg once daily.
- Upon completion of 12-month antithrombotic treatment, clopidogrel was withdrawn, and pantoprazole as well, and warfarin monotherapy prescribed lifelong (target INR between 2.0 and 3.0).

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# 4 Atrial Fibrillation on Vitamin K Antagonist Oral Anticoagulant Undergoing Urgent Percutaneous Coronary Intervention for Non-ST-Elevation Acute Coronary Syndrome

Uwe Zeymer

## 4.1 Case Presentation

### 4.1.1 Baseline Characteristics

- Gender: female.
- Age: 76 years.
- Cardiovascular risk factors: type 2 diabetes mellitus on diet and metformin therapy, hypertension.
- Associated diseases: stage 3 chronic kidney disease (estimated glomerular filtration rate [eGFR] according to Cockroft-Gault formula 70 ml/min) [1] (Table 4.1), polyarthritis.
- Previous history: approximately 2 years before, a recent history of dyspnea and palpitations prompted diagnostic workup which revealed atrial fibrillation (AF). An echocardiogram showed no significant valvular disease, and no ischemia was detected at resting electrocardiogram (ECG) nor at bicycle stress test. A rate-control strategy was selected, and a therapy including a beta-blocker and an ACE inhibitor oral anticoagulation (OAC) with the non-vitamin K antagonist oral anticoagulant (NOAC) rivaroxaban at the dose of 20 mg once daily was prescribed.
- Current history: over the previous 4 weeks, lowering of the threshold for chest pain, occurring during moderate exercise, was noted with a first episode at rest lasting about 30 min 6 h before referral to the chest pain unit. Upon presentation in the late afternoon, the patient was asymptomatic,

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while the ECG showed AF with an average heart rate of 100 bpm and ST segment depression over the anterolateral leads (Fig. 4.1). Blood pressure was 185/95 mmHg, whereas other vital signs and $O_2$ saturation were within normal limits. Ongoing medications included rivaroxaban 20 mg once daily, bisoprolol 5 mg once daily, lisinopril 5 mg once daily, and metformin 850 mg twice daily. The troponin I at baseline was already above normal limit and it further increased at subsequent measurement performed 3 h later. Calculations of relevant risk scores, including GRACE for ischemic risk, $CHA_2DS_2$-VASc for stroke risk, CRUSADE for short-term bleeding risk, and HAS-BLED for long-term bleeding risk (Tables 4.2, 4.3, 4.4, and 4.5), allowed classification of the patient at high risk for ischemic events, stroke, and long-term bleeding and at very high risk for short-term bleeding (Table 4.6).

- Based on the patient's history, the acute clinical presentation, and the significant change in troponin I, the patient was diagnosed a non-ST-elevation myocardial infarction (NSTEMI) and therefore transferred to the catheterization laboratory for urgent coronary angiography/percutaneous coronary intervention (CORO/PCI) with no previous noninvasive testing [2].

**Table 4.1** Stages of chronic kidney disease (www.kdigo.org)

| CKD stage | Description | GFR (ml/min per 1.73 $m^2$) |
|---|---|---|
| 1 | Kidney damage with normal or increased GFR | ≥90 |
| 2 | Kidney damage with mild decreased GFR | 60–89 |
| 3 | Moderate decreased GFR | 30–59 |
| 4 | Severe decreased GFR | 15–29 |
| 5 | Kidney failure | <15 (or dialysis) |

*GFR* glomerular filtration rate

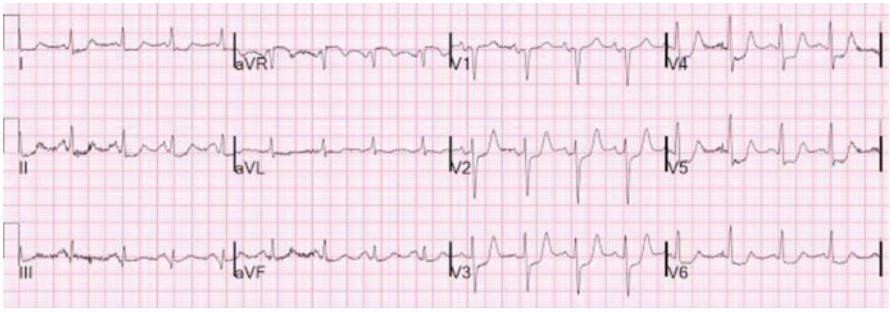


**Fig. 4.1** Electrocardiogram (ECG) on admission

**Table 4.2** GRACE score calculation [2]

| Background | | Findings at the time of admission | | Findings during hospital stay | |
|---|---|---|---|---|---|
| *1. Age (years)* | *Points* | *4. Heart rate at Admission (bpm)* | *Points* | *7. Serum creatinine At admission (ml/min)* | *Points* |
| ≤ 29 | 0 | ≤ 49.9 | 0 | 0.0–0.39 | 1 |
| 30–39 | 0 | 50–69.9 | 3 | 0.4–0.79 | 3 |
| 40–49 | 18 | 70–89.9 | 9 | 0.8–1.19 | 5 |
| 50–59 | 36 | 90–109.9 | 14 | 1.2–1.59 | 7 |
| 60–69 | 55 | 110–149.9 | 23 | 1.6–1.99 | 9 |
| 70–79 | 73 | 150–199.9 | 35 | 2.0–3.99 | 15 |
| 80–89 | 91 | ≥ 200 | 43 | ≥ 4.0 | 20 |
| ≥ 90 | 100 | | | | |
| | | *5. SAP at admission (mmHg)* | | *8. Elevated enzymes or markers* | 15 |
| *2. History of heart failure* | 24 | ≤ 79.9 | 24 | | |
| | | 80–99.9 | 22 | *9. No percutaneous revascularization* | 14 |
| *3. History of myocardial infarction* | 12 | 100–119.9 | 18 | | |
| | | 120–139.9 | 14 | | |
| | | 140–159.9 | 10 | | |
| | | 160–199.9 | 4 | | |
| | | ≥ 200 | 0 | | |
| | | | | | |
| | | *6. Depressed ST-segment* | 11 | | |

*SAP* systolic arterial pressure

**Table 4.3** $CHA_2DS_2$-VASc score and associated risk of stroke/year [3]

| | Condition | Points | Total score | Stroke risk/ year (%) |
|---|---|---|---|---|
| C | Congestive heart failure (or left ventricular ejection fraction ≤ 35 %) | 1 | 0 | 0 |
| H | Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication) | 1 | 2 | 1.3 |
| $A_2$ | Age ≥ 75 years | 2 | 2 | 2.2 |
| D | Diabetes mellitus | 1 | 3 | 3.2 |
| $S_2$ | Prior stroke or TIA or thromboembolism | 2 | 4 | 4.0 |
| V | Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque) | 1 | 5 | 6.7 |
| A | Age 65–74 years | 1 | 6 | 9.8 |
| Sc | Sex category (i.e., female sex) | 1 | 7 | 9.6 |
| | | | 8 | 6.7 |
| | | | 9 | 15.2 |

*TIA* transient ischemic attack

**Table 4.4** CRUSADE bleeding risk score [2]

| | Points | Bleeding risk category | In-hospital bleeding rate (%) |
|---|---|---|---|
| *Baseline hematocrit, %* | | Very low, ≤20 | 3.0 |
| <31 | 9 | Low, 21–30 | 5.5 |
| 31–33.9 | 7 | Moderate, 31–40 | 9.0 |
| 34–36.9 | 3 | High, 41–50 | 12.0 |
| 37–39.9 | 2 | Very high, >50 | 19.0 |
| ≥40 | 0 | | |
| *Creatinine clearance, amL/min* | | | |
| ≤15 | 39 | | |
| >15–30 | 35 | | |
| >30–60 | 28 | | |
| >60–90 | 17 | | |
| >90–120 | 7 | | |
| >120 | 0 | | |
| *Heart rate (bpm)* | | | |
| ≤70 | 0 | | |
| 71–80 | 1 | | |
| 81–90 | 3 | | |
| 91–100 | 6 | | |
| 101–110 | 8 | | |
| 111–120 | 10 | | |
| ≥121 | 11 | | |
| *Sex* | | | |
| Male | 0 | | |
| Female | 8 | | |
| *Signs of CHF at presentation* | | | |
| No | 0 | | |
| Yes | 7 | | |
| *Prior vascular disease†* | | | |
| No | 0 | | |
| Yes | 6 | | |
| *Diabetes mellitus* | | | |
| No | 0 | | |
| Yes | 6 | | |
| *Systolic pressure, mmHg* | | | |
| ≤90 | 10 | | |
| 91–100 | 8 | | |
| 101–120 | 5 | | |
| 121–180 | 1 | | |
| 181–200 | 3 | | |
| ≥201 | 5 | | |

*CHF* congestive heart failure
[a]According to Cockroft-Gault formula
†History of peripheral artery disease or prior stroke

**Table 4.5** HAS-BLED score and associated risk of major bleeding/year [3]

| | Condition | Points | Total score | Risk of major bleeding/year (%) |
|---|---|---|---|---|
| H | Hypertension (uncontrolled blood pressure above 160/90 mmHg) | 1 | 0 | <1 |
| A | Renal (dialysis, transplant, creatinine > 2.6 mg/dL or >200 μmol/L) and/or liver (cirrhosis, bilirubin > 2× normal or AST/ALT/AP > 3× normal) disease | 1 or 2 | 1–2 | 2–3 |
| S | Stroke | 1 | ≥3 | 4–12 |
| B | Bleeding (previous or predisposition to) | 1 | | |
| L | Labile INR (unstable/high or TTR < 60 %) | 1 | | |
| E | Elderly (i.e., age > 65 years) | 1 | | |
| D | Drug usage predisposing to bleeding (antiplatelet agents, NSAIDs) and/or alcohol (≥8 drinks a week) | 1 or 2 | | |

*INR* international normalized ratio, *TTR* time in therapeutic range, *NSAID* nonsteroidal anti-inflammatory drugs, *AST* aspartate aminotranspherase, *ALT* alanine aminotranspherase, *AP* alkaline phosphatase

**Table 4.6** Patient's risk profile

| $CHA_2DS_2$-VASc | GRACE | HAS-BLED | CRUSADE |
|---|---|---|---|
| Congestive heart failure<br>0 | Age | Hypertension<br>1 | Baseline hematocrit<br>3 |
| Hypertension<br>1 | Heart rate | Abnormal liver or renal function<br>1 | Creatinine clearance<br>28 |
| Age > 75 years<br>2 | Systolic blood pressure | Stroke<br>0 | Heart rate<br>3 |
| Diabetes mellitus<br>1 | Creatinine | Bleeding<br>0 | Sex<br>8 |
| Previous stroke/TIA<br>0 | Congestive heart failure | Labile INR<br>0 | Signs of congestive heart failure<br>0 |
| Vascular disease<br>1 | Cardiac arrest on admission | Elderly > 65 years<br>1 | Prior vascular disease<br>0 |
| Age 65–75<br>0 | ST segment deviation | Drugs or alcohol<br>0 | Diabetes mellitus<br>6 |
| Sex (female gender)<br>1 | Elevated cardiac enzymes | | Systolic blood pressure<br>3 |
| Total score | | | |
| 6 = high risk | 145 = high risk | 3 = high risk | 51 = very high risk |

## 4.2 Periprocedural Issues

There are a number of considerations on timing of CORO/PCI, vascular access site, and management of antithrombotic therapy in a patient undergoing CORO/PCI on aggressive antithrombotic therapy, including OAC and concomitant administration

**Table 4.7** Risk criteria mandating for, and recommended timing of, invasive strategy in NSTE-ACS [2]

| |
|---|
| *Very high-risk criteria* (*within 2 h when at least one is present*) |
| Hemodynamic instability or cardiogenic shock |
| Recurrent or ongoing chest pain refractory to medical treatment |
| Life-threatening arrhythmias or cardiac arrest |
| Mechanical complications of myocardial infarction |
| Acute heart failure |
| Recurrent dynamic ST- or T-wave changes, particularly with intermittent ST-elevation |
| *High-risk criteria* (*within 24 h when at least one is present*) |
| Rise or fall in cardiac troponin compatible with myocardial infarction |
| Dynamic ST- or T-wave changes (symptomatic or silent) |
| GRACE score >140 |
| *Intermediate-risk criteria* (*within 72 h when at least one is present*) |
| Diabetes mellitus |
| Renal insufficiency (eGFR < 60 ml/min/1.73 $m^2$) |
| LVEF <40 % or congestive heart failure |
| Early postinfarction angina |
| Prior PCI |
| Prior CABG |
| GRACE risk score >109 and <140 |
| *Low-risk criteria* |
| Any characteristics not mentioned above |

*NSTE-ACS* non-ST-elevation acute coronary syndrome, *eGFR* estimated glomerular filtration rate, *LVEF* left ventricular ejection fraction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting

of antiplatelet agents, because of the increased risk of bleeding and/or vascular complications.

The current European Society of Cardiology (ESC) guidelines on the management of non-ST-elevation acute coronary syndromes (NSTE-ACS) [2] recommend early angiography within 24 h after admission in patients with at least one of the following high-risk criteria (Table 4.7): a) rise or fall in cardiac troponin, compatible with myocardial infarction (MI), b) dynamic ST- or T-wave changes (symptomatic or silent), and c) GRACE score > 140.

Regarding periprocedural anticoagulation, it should be noted that rivaroxaban (and all other NOACs on average) has a half-life of 5–9 h and 7–13 h in elderly patients (Table 4.8) [4]. Whereas mild impairment of renal function is not expected to substantially prolong the elimination of (and the exposure to) rivaroxaban (and other NOACs), moderate renal impairment (i.e., creatinine clearance 30-50 ml/min) has been shown to prolong half-life (Table 4.8). In this latter situation, the recommended dose of rivaroxaban is 15 mg once daily. Periprocedural recommendations on the management of rivaroxaban should therefore be considered the same for both the settings above (Table 4.9) [5].

**Table 4.8** Main pharmacological properties of warfarin and non-vitamin K antagonist oral anticoagulants

| | Warfarin | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|---|
| Target | Factors II, VII, IX, X | Factor IIa (thrombin) | Factor Xa | | |
| Prodrug | No | Yes | No | No | No |
| Bioavailability | 100 % | 6 % | 66[a]/100 %[b] | 50 % | 62 % |
| Plasma protein binding | 97 % | 35 % | 93 % | 87 % | 50 % |
| Time to peak | 4–5 days | 1.5–2 h | 2–3 h | 2–3 h | 1–2 h |
| Elimination half-life | 36–42 h | 12–17 h | 5–9[c]/11–13[d] h | 12 h | 10–14 h |
| Route of clearance | Multiple | 80 % renal | 35 % renal | 27 % renal | 50 % renal |

[a]Without food
[b]With food
[c]In the young
[d]In the elderly

**Table 4.9** Recommended last drug intake before elective surgical/invasive procedure [5]

| | Dabigatran | | Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) | |
|---|---|---|---|---|
| | Low risk[a] | High risk[b] | Low risk[a] | High risk[b] |
| CrCl ≥ 80 ml/min | ≥ 24 h | ≥ 48 h | ≥ 24 h | ≥ 48 h |
| CrCl 50–80 ml/min | ≥ 36 h | ≥ 72 h | ≥ 24 h | ≥ 48 h |
| CrCl 30–49 ml/min | ≥ 48 h | ≥ 96 h | ≥ 24 h | ≥ 48 h |
| CrCl 15–29 ml/min | Not indicated | Not indicated | ≥ 36 h | ≥ 48 h |
| CrCl < 15 ml/min | No official indication for use | | | |

Note: When no important bleeding risk and/or adequate local hemostasis is possible, perform procedure at trough level (i.e., ≥12 or 24 h after last intake)
Note: There is no need for bridging with low-molecular-weight/unfractionated heparin
*CrCl* creatinine clearance
[a]With a low frequency of bleeding and/or minor impact of a bleeding
[b]With a high frequency of bleeding and/or important clinical impact

Also, such consideration likely applies to other NOACs, including the other factor Xa inhibitors apixaban and edoxaban, as well as the thrombin inhibitor dabigatran. Controversial, but apparently limited, is the value of laboratory tests to determine the level of anticoagulation in patients treated with NOACs [4]. A specific anti-Xa level can be determined for factor Xa inhibitors, whereas specific tests may be used for the thrombin inhibitor, but the clinical consequence for the given patient (i.e., that for adjusting the dose of an intravenous anticoagulant during PCI) is currently undefined. So far, no strong correlations have been shown between the anti-Xa level and the risk for embolic, ischemic, or bleeding complications [5].

The question if anticoagulation with rivaroxaban alone would be sufficient for the prevention of thrombotic complications during PCI cannot be finally answered

yet. In a small pilot trial in patients pretreated with aspirin and clopidogrel undergoing elective PCI rivaroxaban given 2–4 h before the procedure was as effective and safe as unfractionated heparin [6]. If anything, rivaroxaban was more effective in suppressing coagulation activation. There was no increase of thrombotic or bleeding events with rivaroxaban compared to heparin. Conversely, such effect was not shown with dabigatran in the similar context of stable patients where suppression of thrombin generation and coagulation activation was shown significantly lower with dabigatran than with UFH [7]. However, if these results can be extrapolated to patients with ACS, who have a higher activation of the coagulation system and a higher risk of thrombotic complications, is unclear. At present, therefore, it is suggested to timely interrupt ongoing rivaroxaban, or other NOAC, before PCI (Table 4.10).

In randomized trials comparing the femoral and radial approach in patients with ACS, a reduction in access site bleeding complications has been observed [8]. This reduction seems to be of special importance in patients on OAC. Therefore, as stated in the current ESC NSTE-ACS guidelines, the radial approach should be preferred in such patients in order to reduce bleeding complications.

Regarding the antiplatelet therapy before angiography, the current ESC NSTE-ACS guidelines recommend the administration of aspirin intravenously or orally at first medical contact [2]. This recommendation holds true even for patients on chronic OAC. However, pretreatment with $P2Y_{12}$ receptor inhibitors may be withheld until CORO has been carried out in case of an early invasive strategy (i.e., within 24 h), with the aim to reduce periprocedural bleeding and/or vascular complications. The question about the optimal timepoint of administration of clopidogrel, ticagrelor, or prasugrel is not finally answered yet [9]. While acknowledging that prasugrel and ticagrelor are not recommended for NSTE-ACS patients on OAC [4, 10–12], it is of note that pretreatment with prasugrel 30 mg in patients with NSTEMI at intermediate risk, a median of 4 h before angiography, did not reduce ischemic complications but increased bleeding complications [13], whereas no randomized data are available on pretreatment with ticagrelor in NSTE-ACS patients, since in the PLATO trial all patients were pretreated with ticagrelor before angiography [14]. A meta-analysis performed on trials with pretreatment with clopidogrel suggested a reduction in ischemic events in NSTE-ACS patients [15]. Given the mixed results on pretreatment, it seems reasonable to defer $P2Y_{12}$ inhibitor

**Table 4.10** Periprocedural management recommendations

| Issue | Recommendations |
|---|---|
| Anticoagulation | Discontinuation[a] |
| Vascular access site | Radial/femoral |
| Antiplatelet therapy | Low-dose ASA[b,c] + clopidogrel PO[d] |

*ASA* aspirin, *PO* orally, *NOAC* Non-vitamin K-antagonist oral anticoagulant

[a]24 to 48–72 h in advance (depending on the patient renal function and NOAC used), with no heparin bridging

[b]75–100 mg/day

[c]May be omitted in selected patients at high risk of bleeding and concomitant low risk of stent thrombosis

[d]600 (or 300 mg) front loading

administration in a patient on chronic OAC after the diagnostic CORO and the decision to proceed to PCI. Alternatively, it has been proposed to pretreat OAC patients with a loading dose of clopidogrel, either 600 or 300 mg depending on the time scheduled for CORO/PCI, while withholding aspirin until, and whether, PCI is performed [16]. Given the prolonged time (i.e., at least 2 and 6 h when 600 and 300 mg, respectively, are given) required for clopidogrel to induce effective platelet inhibition [17], as opposed to aspirin which, after either oral or intravenous administration, has nearly immediate effect [18], such strategy might be useful to reduce bleeding on the one hand and not to load with aggressive antithrombotic treatment patients who may end up with no indication for PCI on the other [16].

### 4.2.1 Periprocedural Management

- Intravenous 500 mg aspirin was given on admission and the next scheduled dose of rivaroxaban withheld.
- CORO was scheduled the next morning, corresponding approximately to 14 h after the last NOAC intake.
- Left radial access was selected for coronary angiography and no additional anticoagulation was given at this point of time.
- CORO was carried with conventional Judkins left and right 4 French diagnostic catheters and showed a left dominant system with high-grade stenosis (90%) of the proximal left anterior descending (Fig. 4.2) and no significant lesions in the right coronary artery (Fig. 4.3). Left ventricular angiography revealed normal function (60%).
- It was decided to perform PCI of culprit lesion of the LAD.

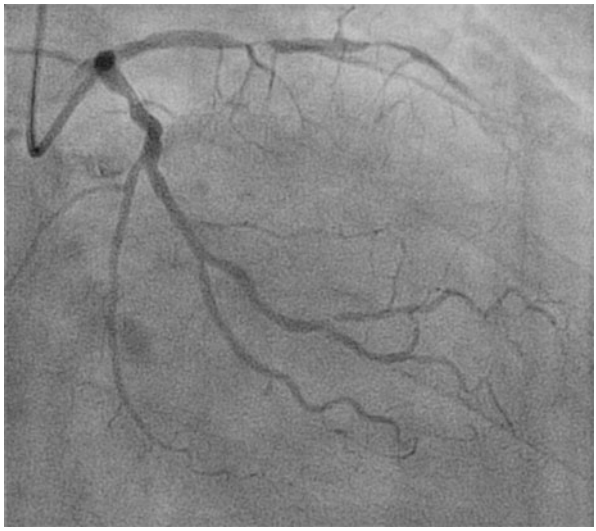

**Fig. 4.2** Baseline left coronary angiography (RAO view). *RAO* right anterior oblique

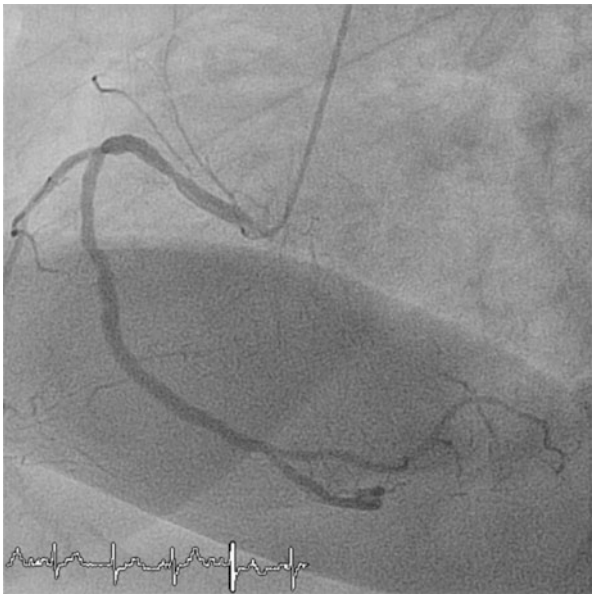

**Fig. 4.3** Baseline right coronary angiography (LAO view). *LAO* left anterior oblique

## 4.3 Procedural Issues

There is a need for effective anticoagulation during coronary intervention to limit the occurrence of thrombosis at the angioplasty catheters and wires, as well as at the plaque disrupted by the trauma of the PCI procedure or at the stent itself [12]. In a patient on rivaroxaban, or other NOAC, there are three options for intra-procedural anticoagulation: bivalirudin, enoxaparin, or unfractionated heparin (UFH) (Table 4.11). Bivalirudin has the advantage of its short half-life and predictable level of anticoagulation. In the ACUITY, ISAR-REACT 4, and MATRIX trials in patients with NSTE-ACS undergoing PCI, bivalirudin was as effective as UFH plus a glycoprotein IIb/IIIa inhibitor but associated with a significant reduction in bleeding complications [19–21]. Enoxaparin has a greater Xa action than UFH and has been shown to be at least as effective as UFH in PCI for NSTE-ACS in the SYNERGY trial [12]. Although there are no prospective data available comparing enoxaparin, bivalirudin, and UFH in patients with chronic rivaroxaban therapy undergoing PCI, at least, theoretically, enoxaparin would be of advantage to avoid crossover from a factor Xa to a factor IIa inhibition. In contrast, in patients treated with dabigatran, bivalirudin might be preferred, as both are factor IIa inhibitors. The specific factor Xa inhibitor fondaparinux has been shown to be associated with an increased rate of catheter thrombosis and thrombotic complications during PCI in the OASIS-5 trial [22] and appears therefore to be no valuable alternative.

Regarding the choice of stent, there is a large body of evidence that drug-eluting stents (DESs) are more effective than bare-metal stents (BMSs) (Table 4.12) in preventing restenosis and target lesion revascularizations [12]. However, since DESs

**Table 4.11** Periprocedural management recommendations

| Issue | Recommendation |
|---|---|
| Additional intra-procedural anticoagulation | Yes |
| Recommended anticoagulants and doses | (a) UFH 50–70 IU/kg[a] IV bolus or<br>(b) Bivalirudin[b] 0.75 mg/kg IV bolus followed by 1.75 mg/kg/h infusion for up to 4 h post-PCI[c] or<br>(c) Enoxaparin 0.3 mg/kg IV bolus (where approved) |
| Antiplatelet therapy | (a) Aspirin 150–300 mg orally (or 80–150 mg IV if oral ingestion not possible), followed by 75–100 mg once daily maintenance dose<br>(b) A $P2Y_{12}$-receptor inhibitor:<br>Clopidogrel 600 mg oral loading dose followed by 75 mg once daily maintenance dose<br>Prasugrel not indicated<br>Ticagrelor not indicated |
| Vascular access site | Radial |

*UFH* unfractionated heparin, *IU* international unit, *IV* intravenous

[a]Depending on whether < 24 vs. > 24–48 h (depending on ongoing NOAC and renal function) have been elapsed since last drug intake

[b]Especially in patients deemed at high risk of bleeding

[c]After cessation of the 1.75 mg/kg/h infusion, 0.25 mg/kg/h infusion may be continued for 4–12 h

**Table 4.12** General classification of coronary stents/scaffolds

| | | |
|---|---|---|
| BMS | | (a) Stainless steel<br>(b) Non-stainless steel, cobalt- or platinum-chrome alloy |
| DES | Early generation | (a) Durable polymer: sirolimus, paclitaxel eluting |
| | New generation | (a) Durable polymer: zotarolimus-, everolimus-eluting<br>(b) Biodegradable polymer: biolimus A9 and everolimus-eluting<br>(c) Polymer-free: amphilimus-, biolimus A9 eluting |
| BAS | | (a) Diamond-like carbon coated, titanium nitric oxide coated<br>(b) Endothelial progenitor cells capturing |
| BVS | | (a) Nondrug eluting<br>(b) Everolimus, myolimus, sirolimus eluting |

*BMS* bare-metal stent, *DES* drug-eluting stent, *BAS* bioactive stent, *BVS* bioresorbable vascular scaffold

are associated with a prolonged healing process, longer-term (i.e., ≥ 6 months) dual antiplatelet therapy (DAPT) is necessary to avoid stent thrombosis (Table 4.13), while after BMS implantation 4 weeks of DAPT is usually sufficient. Recent data from new-generation DES (Table 4.10) suggest that DAPT can be shortened to 6 months or even 3 months [12]. Therefore current ESC revascularization guidelines recommend 6 months DAPT [12]. Further, even durations as short as 1 month may possibly be considered after zotarolimus- and everolimus-eluting DES given the apparent lack of an increase in stent thrombosis with the interruption of one of the two antiplatelet agents after the first 4 weeks of treatment [12]. While in patients with NSTE-ACS 12 months DAPT is advised, regardless of the type of stent used, and even regardless of whether or not a stent has been implanted, in OAC patients,

**Table 4.13** Academic Research Consortium (ARC) definitions of stent thrombosis [23]

| | |
|---|---|
| Event Certainty | (a) Definite: acute coronary syndrome with angiographic or autopsy confirmation of stent thrombosis<br>(b) Probable:<br>(i) Unexplained death within 30 days of stent implantation without autopsy<br>(ii) Acute myocardial infarction in the territory of target vessel where stent was<br>implanted without angiographic confirmation |
| Time frame | (a) Early:<br>(i) Acute – within 24 h of stent implantation<br>(ii) Subacute – between 24 h and 30 days of stent implantation<br>(b) Late: between 30 days and 1 year of stent implantation<br>(c) Very late: after 1 year of stent implantation |

a duration generally not longer than 6 months is currently recommended [4]. Should specific circumstances increasing the risk of bleeding be present, a duration as short as 3 months only may be considered, also given the fact that the risk of adverse outcome in NSTE-ACS appears highest during this time frame [24].

### 4.3.1 Procedural Management

- After discussion with the patient, the decision to proceed to PCI was taken, and, after insertion of a 5 French sheath, a 5 French EBU 4 guiding catheter was advanced to the left coronary artery.
- An intravenous bolus of 0.5 mg/kg enoxaparin (total dose 40 mg) and a loading dose of 600 mg clopidogrel orally were given before starting PCI.
- A new-generation DES (Resolute Integrity 3.5×12 mm, Medtronic) was implanted in the LAD with excellent angiographic result without any residual stenosis and with normal antegrade flow (TIMI grade 3) (Fig. 4.4).
- The radial sheath was removed immediately after the procedure and a local compression assist device applied (TR-Band, Terumo).

## 4.4 Post-procedural Issues (Table 4.14)

In patients with AF, long-term OAC is necessary, even after ACS and stent implantation [3]. An exception may be male patients with $CHA_2DS_2$-VASc score of 1, that is, with coronary heart disease as the only risk factor [10]. Here the low stroke risk does not justify the risk of combination therapy, and DAPT seems enough to protect from embolic and ischemic events [25]. Given the rapid onset of action of rivaroxaban and the low risk of bleeding associated with a valid procedure, OAC should be restarted

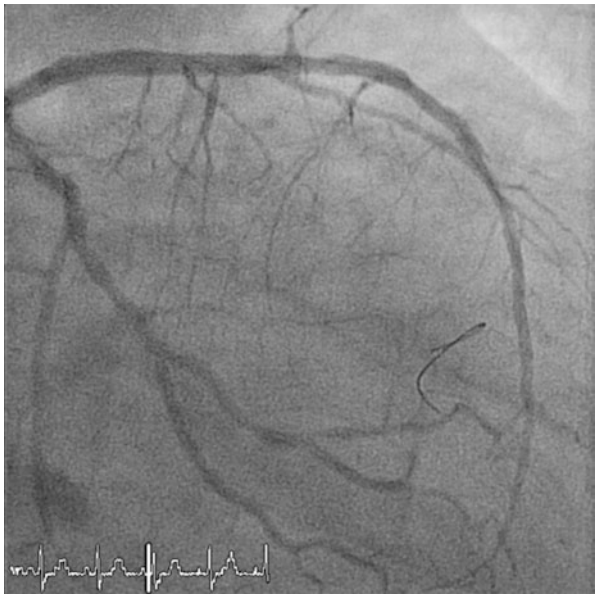

**Fig. 4.4** Left coronary angiography (RAO view) after stent implantation. *RAO* right anterior oblique

**Table 4.14** Medium- to long-term (i.e., up to 12 months after PCI) management recommendations

| Issue | Recommendations |
|---|---|
| Initial antithrombotic treatment | Triple therapy (NOAC + aspirin[a,b] + clopidogrel) |
| Duration of triple therapy | BMS in elective setting: 1 month<br>DES in elective setting: 3–6 months[c]<br>Either BMS or DES in ACS setting: 3–6 months[d] |
| Intensity of OAC throughout triple therapy | Reduced[e] |
| Special care throughout triple therapy | Frequent monitoring[f]<br>Routine gastric protection[g] |
| Subsequent antithrombotic treatment[h] | NOAC[i] + either clopidogrel[j] or aspirin |

*PCI* percutaneous coronary intervention, *BMS* bare-metal stent, *DES* drug-eluting stent, *ACS* acute coronary syndrome, *OAC* oral anticoagulation, *INR* international normalized ratio

[a]75–100 mg once daily

[b]May be omitted in selected patients at high risk of bleeding and concomitant low risk of stent thrombosis

[c]One month only may be considered when the risk of bleeding is high and new-generation DES has been implanted

[d]One month only may be considered when the risk of bleeding is high and either a BMS or a new-generation DES has been implanted

[e]Low-dose of NOAC: dabigatran 110 mg twice daily, rivaroxaban 15 mg once daily, apixaban 2.5 mg twice daily (and likely edoxaban 30 mg once daily)

[f]Creatinine clearance and complete blood count every month

[g]Preferably with PPI not interfering with clopidogrel metabolism (e.g., pantoprazole, dexlansoprazole)

[h]After the initial course of 1 to 3–6 months of TT has been completed

[i]Standard dose of dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, apixaban 5 mg twice daily, and edoxaban 60 mg once daily (if taken before and if no subsequent indication for reduced dose developed) should be resumed

[j]Preferred due to its superior gastric tolerability

soon after the procedure itself. However, since the half-lives of enoxaparin and rivaroxaban are comparable (Table 4.8), reinitiating of rivaroxaban can be deferred to the next morning after PCI.

A question might be whether after PCI rivaroxaban should be continued or another NOAC or even a vitamin K antagonist (VKA) should be preferred instead. In the ASPECT and WARIS trials, vitamin K antagonists have been more effective than aspirin in patients after myocardial infarction, treated however without PCI [26, 27]. According to available, albeit limited, data, efficacy and safety of rivaroxaban appears comparable to that of warfarin in patients with prior myocardial infarction in the ROCKET AF trial [28]. Thus, there is apparently no special reason to switch to a VKA, especially given the superiority in convenience and safety regarding intracranial bleeding of NOACs [28]. The ongoing PIONEER AF-PCI [29] and RE-Dual PCI [30] trials will investigate the comparative efficacy and safety of rivaroxaban and dabigatran respectively, versus warfarin in patients with AF and coronary stent implantation.

The issue of the lack of an antidote has been widely discussed. However, it is also of limited relevance, as the short half-life of NOACs is expected to allow quite safe management of relevant bleeding events if it occurs. Indeed, outcome after bleeding, as observed in the ROCKET AF trial with rivaroxaban, as well in patients treated with dabigatran in several clinical trials [31], appears not inferior after NOAC compared to that after warfarin [32]. While noting that nonspecific reversal agents, including prothrombin complex concentrates and fresh frozen plasma, may be of value in treating bleeding complications of NOACs, specific antidotes to dabigatran, namely, idarucizumab [33], and factor Xa inhibitors, namely, andexanet alfa [34], have been recently made available.

When the triple therapy (TT) antithrombotic regimen, including NOAC, aspirin, and clopidogrel, has been selected after PCI in a patent with AF, the lower dose of NOAC should be used to minimize bleeding complications [4, 10, 11]. Albeit nonspecific data on this issue are available, this makes sense since numerous trials have shown that combination therapy with OAC and antiplatelets is associated with an increase in bleeding complications. Also, reducing the intensity of OAC with vitamin K antagonist, that is, targeting an INR of 2.0–2.5, appears to be associated to an incidence of major bleeding not much different from that of DAPT [35]. The concern that low doses of rivaroxaban and apixaban, as well as of edoxaban, may not confer enough protection against stroke and thromboembolism when given to patients not qualifying for such dose reduction (i.e., creatinine clearance 30–49 ml/min for rivaroxaban and two out of the following criteria: age $\geq$ 80 years, body weight $\leq$ 60 kg, and serum creatinine $\geq$ 1.5 ml/min for apixaban) should be mitigated by the approximately 30% reduction in the risk of thromboembolism reported with DAPT which is given in conjunction [36].

Since there are no direct comparisons between the NOACs available, current knowledge does not suggest to switch to a NOAC different from the one ongoing at the time of procedure. Rivaroxaban, albeit in a much lower dose, has been even shown to improve prognosis after an ACS in the ATLAS-ACS 2 trial [37] in combination with antiplatelet therapy and seems therefore a valuable option in such setting.

The optimal intensity and duration of antiplatelet therapy in patients with AF who have undergone PCI with stent is still a matter of debate [10]. From the limited

data available, the newer $P2Y_{12}$ inhibitors prasugrel and ticagrelor should not be used in TT because of an increased risk of bleeding [38, 39]. If prasugrel or ticagrelor in combination with OAC alone, by omitting aspirin, will be safe and effective, it will be investigated in the ongoing PIONEER AF-PCI [28] and RE-DUAL PCI [29] trials. Before these results are available, this combination therapy, although of theoretical advantage over TT, cannot be recommended [4, 10–12]. TT is considered still standard of care, especially after ACS. In the WOEST trial, only 25 % of patients had an ACS; therefore the finding that leaving out aspirin is effective and reduces the rate of total bleeding complications cannot be generalized [40]. In the ISAR-TRIPLE trial comparing a 6-week versus a 6-month triple therapy after DES implantation, no differences were found regarding ischemic or bleeding complications [41]. From these data the current ESC guidelines recommend 4 weeks triple therapy in a patient with high bleeding risk and another 11 months combination therapy with OAC and one antiplatelet agent [2, 4, 10–12].

Gastric protection with proton pump inhibitors (PPIs), especially those not interfering with the metabolism of clopidogrel, such as pantoprazole, should routinely be administered for as long as TT is ongoing [4, 10–11]. Available data consistently show that most bleeding events in patients on TT (generally with warfarin as OAC) arise from the gastrointestinal tract [10–14]. Given the reported increase in overall gastrointestinal bleeding with NOACs as compared with warfarin [42], routine gastric protection when these latter agents are part of TT may be of even more importance.

### 4.4.1 Post-procedural Management

- $CHA_2DS_2$-VASc and HAS-BLED scores were calculated (6 and 3 respectively).
- In the evening of the day of the procedure, rivaroxaban at the reduced dose of 15 mg was restarted.
- DAPT of aspirin 100 mg once daily and clopidogrel 75 mg once daily was maintained.
- Gastric protection with pantoprazole 20 mg once daily was added.
- Additional therapy included lisinopril 5 mg once daily, bisoprolol 10 mg once daily, and atorvastatin 20 mg once daily.
- The patient was discharged the next day with the advice to continue TT for 3 months and then drop aspirin while continuing clopidogrel up to 12 months in combination with rivaroxaban to be increased to the standard dose of 20 mg once daily upon discontinuation of aspirin.

## 4.5 Medium- to Long-Term Issues (Table 4.15)

After 1 year from the ACS and PCI procedure and in the absence recurrent ischemic events, antiplatelet therapy should generally be interrupted and OAC, in this case rivaroxaban, only continued lifelong [2, 4, 10–12].

**Table 4.15** Long-term (i.e., > 12 months after PCI, in the absence of recurrent events) management recommendations

| Issue | Recommendation |
|---|---|
| Antithrombotic treatment | NOAC monotherapy[a] |
| Intensity of OAC | Standard[b] |

*PCI* percutaneous coronary intervention, *OAC* oral anticoagulation, *CAD* coronary artery disease, *NOAC* Non-vitamin K-antagonist oral anticoagulant

[a]Indefinite combination with either low-dose ASA (75–100 mg once daily) or clopidogrel 75 mg (depending on the individual risk of bleeding, especially gastrointestinal and stent thrombosis) may be considered in special situations (e.g., left main/last remaining vessel stenting, history of stent thrombosis/recurrent cardiac events, diffuse CAD), when bleeding risk is low or when the NOAC used is dabigatran

[b]That is, standard dose of dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, apixaban 5 mg twice daily, and edoxaban 60 mg once daily (if taken before and if no subsequent indication for reduced dose developed) should be resumed

The issue if very high-risk patients, e.g., such as those with multiple stents or left main PCI, should be continued on combination therapy is not answered yet. Data from a Danish registry do not suggest any benefit from combination therapy over anticoagulation alone but an increase in bleeding complications [43]. This registry, however, did not evaluate high-risk patients separately [43].

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# 5 Atrial Fibrillation on Vitamin K Antagonist Undergoing Primary Percutaneous Coronary Intervention for Acute ST-Elevation Myocardial Infarction

Giuseppe Gargiulo and Davide Capodanno

## 5.1 Case Presentation

### 5.1.1 Baseline Characteristics

- Gender: male.
- Age: 68 years.
- Cardiovascular risk factors: hypertension, former smoker.
- Previous history: ischemic stroke 2 years earlier with documentation of atrial fibrillation (AF) for which a rate-control strategy was chosen and oral anticoagulation (OAC) with warfarin was started.
- Current history: the patient called the emergency medical system after 30 min from the onset of typical chest pain. Upon arrival at the emergency room, the electrocardiogram (ECG) showed AF and 1.5 mm ST-segment elevation in the inferior leads (Fig. 5.1). The local ST-elevation myocardial infarction (STEMI) network for primary percutaneous coronary intervention (PCI) was then immediately activated. Ongoing treatment upon admission included ramipril 2.5 mg/hydrochlorothiazide 12.5 mg once daily and OAC with warfarin since the time of stroke (international normalized ratio [INR] values reported to range regularly between 2.0 and 3.0).

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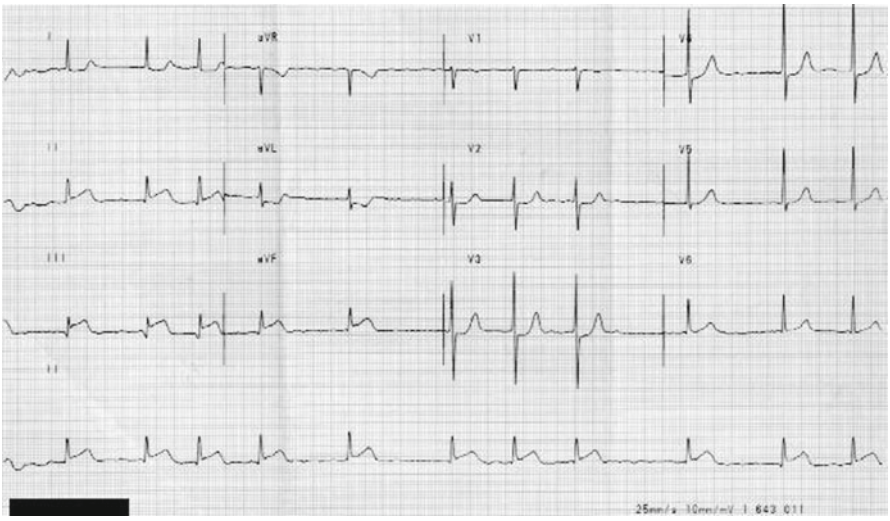


**Fig. 5.1** Twelve-lead electrocardiogram (ECG) at presentation

## 5.2 Periprocedural Issues

Primary PCI coupled with adjuvant antithrombotic therapy is the current standard of care for patients presenting with STEMI (Fig. 5.2) (Table 5.1) [1]. However, managing antithrombotic therapy in patients presenting with both STEMI and AF is a challenge due to the increased risk of bleeding when antiplatelet therapy is combined with OAC [2]. Many trials are available to guide antithrombotic management of patients with either AF or those with STEMI undergoing primary PCI, but there is a limited amount of randomized data focusing on patients with both conditions.

When a patient on warfarin, or other vitamin K antagonist (VKA), is admitted to the cardiac catheterization laboratory for emergency primary PCI, the question arises on how to manage periprocedural anticoagulation and antiplatelet therapy.

Regarding anticoagulation, additional intravenous (IV) unfractionated heparin (UFH), bivalirudin, or, where approved, enoxaparin should generally be administered, regardless of whether or not current INR is known (Table 5.2) [3, 4]. Albeit available, and of possible clinical value in selected emergency patients [5], point-of-care determination of the INR has not an established role in OAC patients undergoing emergency PCI for STEMI. Given that a thrombus has formed in a coronary artery despite ongoing OAC, it can be assumed that either the anticoagulation effect was suboptimal or that the *stimulus* to thrombus formation was so strong to overcome even effective anticoagulation. Therefore, additional IV UFH should be given, albeit at a reduced dose (i.e., 30–50 IU/kg) in order to limit the risk of bleeding [4] (Table 5.2). The value of monitoring intra-procedural anticoagulation by means of the activated clotting time (ACT), as commonly performed in non-OAC patients, is currently undetermined, as it is also its value in guiding additional intra-procedural

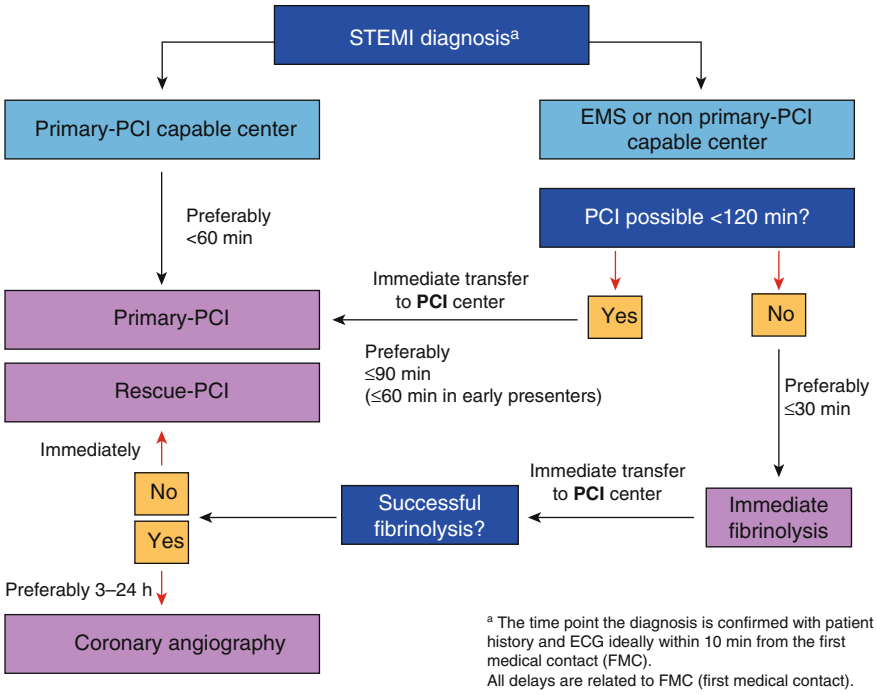


**Fig. 5.2** Prehospital and in-hospital management, and reperfusion strategies within 24 h of first medical contact Reproduced with permission from Steg et al. [1]

administration of UFH. No data are available regarding enoxaparin in this setting. When used, however, an IV bolus dose of 0.3 mg/kg at the beginning of the procedure appears reasonable. IV bivalirudin at the standard dose of 0.75 mg/kg bolus + 1.75 mg/kg/h infusion may be given in alternative (especially when the bleeding risk is deemed particularly high) (Table 5.2), given both the decrease in bleeding complications and mortality reported in large studies on general populations undergoing PCI in the setting of an acute coronary syndrome (ACS), either with or without ST-elevation [6–8], as well as in a small experience in AF patients receiving a VKA [9].

Regarding antiplatelet therapy, aspirin should be given as soon as possible at the standard dose of 150–300 mg orally (or 80–150 mg IV, when ingestion is not possible) as in standard, non-OAC patients [3, 4]. (Table 5.2). At variance, it seems reasonable not to pretreat with $P2Y_{12}$-receptor inhibitors patients on warfarin or other VKAs [3]. Although current guidelines recommend administration of $P2Y_{12}$-receptor inhibitors at the first medical contact (1, 10), the evidence supporting pretreatment in STEMI is not conclusive, particularly in the current era of shorter door-to-balloon times, and no pretreatment data exist in patients on warfarin (or other VKAs) [11]. While the newer,

**Table 5.1** Recommended periprocedural antithrombotic therapy in primary PCI

| |
|---|
| *Antiplatelet therapy:* |
| Aspirin 150–300 mg orally (or 80–150 mg IV if oral ingestion not possible), followed by 75–100 mg once daily maintenance dose |
| A $P2Y_{12}$-receptor inhibitor:<br>(a) Prasugrel[a] 60 mg oral loading dose followed by 10 mg once daily maintenance dose[b] or<br>(b) Ticagrelor 180 mg oral loading dose followed by 90 mg twice daily maintenance dose or<br>(c) Clopidogrel 300–600 mg oral loading dose followed by 75 mg once daily maintenance dose |
| Glycoprotein IIb/IIIa inhibitor for bailout therapy when massive thrombus and/or no- or slow-flow and/or thrombotic complications:<br>(a) Abciximab 0.25 mg/kg IV bolus followed by 0.125 mcg/kg/min infusion for 12 h<br>(b) Eptifibatide IV double bolus 180 mcg/kg (10 min apart) followed by 2.0 mcg/kg/min infusion for 18 h<br>(c) Tirofiban 25 mcg/kg over 3 min IV followed by 0.15 mcg/kg/min infusion for 18 h |
| *Anticoagulant therapy*:<br>(a) UFH 70–100 IU/kg IV bolus (50–60 IU/kg in conjunction with glycoprotein IIb/IIIa inhibitors)<br>(b) Enoxaparin 0.5 mg IV bolus (where approved)<br>(c) Bivalirudin 0.75 mg/kg IV bolus followed by 1.75 mg/kg/h infusion for up to 4 h post-PCI[c] |

Steg et al. [1]
*PCI* percutaneous coronary intervention, *IV* intravenous, *UFH* unfractionated heparin, *IU* international unit
[a]Clopidogrel naïve and no history of previous stroke/transient ischemic attack
[b]Maintenance dose of 5 mg once daily is recommended for patients with body weight < 60 mg and/or age > 75 years
[c]After cessation of the 1.75 mg/kg/h infusion, 0.25 mg/kg/h infusion may be continued for 4–12 h

**Table 5.2** Periprocedural management recommendations

| Issue | Recommendation |
|---|---|
| Additional intra-procedural anticoagulation | Yes |
| Recommended anticoagulants and doses | (a) UFH 50 IU/kg IV bolus (regardless of the INR value, if known) or<br>(b) Bivalirudin[a] 0.75 mg/kg IV bolus followed by 1.75 mg/kg/h infusion for up to 4 h post-PCI[b] or<br>(c) Enoxaparin 0.3 mg/kg IV bolus (where approved) |
| Antiplatelet therapy | (a) Aspirin 150–300 mg orally (or 80–150 mg IV if oral ingestion not possible), followed by 75–100 mg once daily maintenance dose<br>(b) A $P2Y_{12}$-receptor inhibitor:<br>Clopidogrel 600 mg oral loading dose followed by 75 mg once daily maintenance dose<br>Prasugrel not indicated<br>Ticagrelor not indicated |
| Vascular access site | Radial |

*UFH* unfractionated heparin, *IU* international unit, *IV* intravenous stent
[a]Especially in patients deemed at high risk of bleeding
[b]After cessation of the 1.75 mg/kg/h infusion, 0.25 mg/kg/h infusion may be continued for 4–12 h

more potent, and less safe $P2Y_{12}$-receptor inhibitors prasugrel and ticagrelor are not recommended in OAC patients [3, 4, 10], and the delayed onset of effect of clopidogrel even at the higher loading dose of 600 mg may be an issue of concern for acute stent thrombosis, waiting until coronary angiography has been performed and indication for PCI has arisen before administering a $P2Y_{12}$-receptor inhibitor is preferable. Whereas prasugrel and ticagrelor should be preferred to clopidogrel, owing to the superior efficacy observed in their respective TRITON [12] and PLATO [13] trials, the addition of prasugrel and aspirin to VKA has been shown to come at the price of unacceptable bleeding both in a small, single-center experience [14] and a large population of myocardial infarction patients undergoing PCI [15]. Until reassuring data on the safety of combining prasugrel and ticagrelor to warfarin, or other VKAs (with or without aspirin) will be available, it seems more prudent to prefer clopidogrel as the $P2Y_{12}$-receptor inhibitor to be added on top of warfarin, or other VKAs, even though the delayed onset of effect of clopidogrel (i.e., approximately 2–4 to 6–8 h for 600 and 300 mg, respectively [16]), remains a limitation [3, 4]. Regarding whether a loading dose of 300 or 600 mg of clopidogrel should be given, no specific data comparing the safety and efficacy of the two doses are available for patients on warfarin or other VKAs. The 600 mg dose, however, is associated with a more rapid and intense platelet inhibition and should therefore generally be preferred [4].

On top of the considerations above, the radial vascular access should generally be preferred over femoral access in STEMI patients on warfarin (or other VKAs) due to the established reduction in bleeding and vascular complications reported both in large datasets of ordinary patients, as well as in small groups of patients on warfarin [3, 17–19]. Whenever the radial approach is not feasible, ongoing therapeutic (i.e., with $INR \geq 2.0$) OAC should not exclude the femoral approach, provided that the puncture is carefully carried out according to the proper technique (common femoral artery, anterior artery wall only). Fluoroscopic, and likely even more, ultrasonographic guidance may be of value in further enhancing the safety of the femoral approach. Although a clear superiority of vascular closure devices to manual compression has not been established [20, 21], and data on patients on OAC with warfarin (or other VKAs) are lacking, their use is generally recommended after PCI to shorten time to hemostasis.

### 5.2.1 Periprocedural Management

- Aspirin loading dose of 325 mg orally was given.
- In the absence of recent coagulation tests and despite warfarin being on board, an intravenous bolus of 4000 UI UFH, corresponding to approximately 50 IU/kg, was administered, with ACT being measured at regular intervals during the procedure.
- Right radial vascular access was obtained as first-line bleeding avoiding strategy, and standard 6-French diagnostic catheters were selected.
- The coronary angiography revealed a proximal thrombotic occlusion of the right coronary artery (RCA) (Fig. 5.3a), while the left circumflex and left anterior descending arteries did not show significant obstructions.

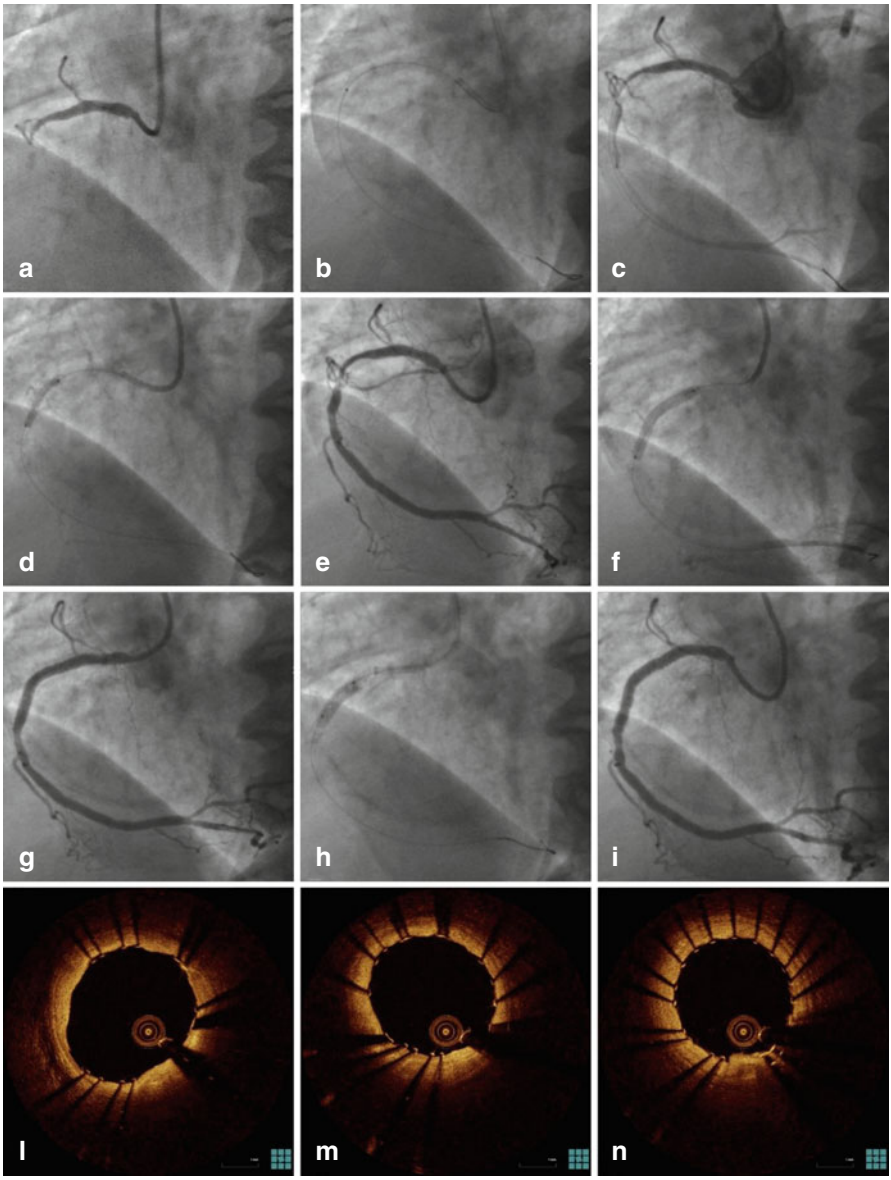


**Fig. 5.3** Coronary angiograms during primary PCI of an occluded RCA (**a**–**i**) and optical coherence tomography cross-sections post-stent implantation (**l**–**n**) (see text for details)

## 5.3 Procedural Issues

Manual thrombus aspiration has not been shown to impact significantly on hard cardiac outcomes of patients undergoing primary PCI [22, 23]. However, it remains a valuable tool to clear the vessel from large thrombi, reduce the likelihood of slow flow/no reflow, and take appropriate decisions about balloon and stent sizes [10].

**Table 5.3** Procedural management recommendations

| Issue | Recommendations |
|---|---|
| Manual thrombus aspiration | Yes |
| Adjunct IV glycoprotein IIb/IIIa inhibitors | Not recommended[a] |
| Type of stent | New-generation DES[b] |

*BMS* bare-metal stent, *DES* drug-eluting stent, *IV* intravenous
[a]May be considered when international normalized ratio (INR), is < 2.0 and/or as bailout therapy (even with INR > 2.0) in the presence of large thrombus burden, threatened vessel closure, or thrombotic complications
[b]BMS may be considered in patients at high risk of bleeding

**Table 5.4** General classification of coronary stents/scaffolds

| | | |
|---|---|---|
| BMS | | (a) stainless steel<br>(b) Non-stainless steel, cobalt- or platinum-chrome alloy |
| DES | Early generation | (a) Durable polymer: sirolimus, paclitaxel eluting |
| | New generation | (a) Durable polymer: zotarolimus , everolimus eluting<br>(b) Biodegradable polymer: biolimus A9 And everolimus eluting<br>(c) Polymer-free: biolimus A9, amphilimus, umirolimus eluting |
| BAS | | (a) Diamond-like carbon coated, titanium nitric oxide coated<br>(b) Endothelial progenitor cells capturing |
| BRS | | (a) Nondrug eluting<br>(b) Everolimus, myolimus, sirolimus eluting |

*BMS* bare-metal stent, *DES* drug-eluting stent, *BAS* bio-active stent, *BRS* bioresorbable scaffold

This technique may therefore be of special value in a setting like that of STEMI in a patient on warfarin, or other VKAs, where the thrombus burden is generally large, and aggressive antithrombotic therapy with additional anticoagulants, and antiplatelet agents, namely, IV glycoprotein IIb/IIIa inhibitors (GPIs), is hindered by the increased risk of bleeding (Table 5.3). To minimize the risk of stroke, special care should be devoted to ensure that the guiding catheter is engaged in the coronary while retrieving the thrombus aspiration device. Except for patients on warfarin, or other VKAs, with known INR < 2.0, IV GPIs may generally be considered only as a bailout therapy in patients with large thrombus burden [10] (Table 5.3), but their use increases bleeding in patients on warfarin [24]. In the different scenario of patients with no AF, the presence of a large thrombotic burden and the lack of preloading with any $P2Y_{12}$-receptor inhibitor would suggest a lower threshold for the use of GPIs at this stage, with the goal of addressing the expected gap in platelet inhibition. However, the impact of this "blocking and bridging" strategy (with intracoronary 0.25 mg/kg bolus-only administration of abciximab plus oral loading with a $P2Y_{12}$-receptor inhibitor) [25] is uncertain and potentially harmful in patients on warfarin, or other VKAs, and should therefore not be used.

Regarding the choice of the stent to be implanted (Table 5.4), the consideration made for the general patient not on OAC should at present be generally made also for patients on warfarin or other VKAs. Whereas bare-metal stents (BMSs) allow for a duration of dual antiplatelet therapy (DAPT) of only 1 month, current new-generation drug-eluting stents (DESs) are associated with similar or even lower rates of stent thrombosis compared with BMSs which adds to their established benefit in reducing restenosis [26]. In elective PCI, the package insert of

everolimus- and zotarolimus-eluting stents demands for a minimum of 1-month DAPT, but whether this is also valid for STEMI remains hypothetical and unproven. Of note, a polymer-free umirolimus-coated DES versus BMSs (with 1 month of DAPT in each group) has been recently shown significantly more effective and safer in patients at high bleeding risk (including patients on VKAs) undergoing PCI [27]. The limited proportion of ACS patients evaluated needs to be acknowledged as a possible limitation of the study [27]. Indeed, in patients with ACS, the benefit of extended duration of DAPT goes beyond the reduction of stent thrombosis [28]. Patients on warfarin, or other VKAs, who receive stents will generally necessitate a period of triple therapy (TT), including OAC plus DAPT, whose duration essentially depends on the bleeding risk [3, 4]. For this reason, the choice of the stent should take the bleeding issue into consideration: whereas new-generation DESs should generally be preferred over BMSs in patients who according to clinical judgment cannot safely tolerate more than 4 weeks, either polymer-free umirolimus-coated DESs or BMSs should generally be prioritized.

### 5.3.1 Procedural Management

- After cannulation of the RCA with a Judkins right guiding catheter, a workhorse guide-wire was rapidly passed through the thrombotic lesion reaching the distal posterior descending artery, with resulting TIMI (Thrombolysis In Myocardial Infarction) flow grade 1. Due to the uncertain anticoagulation status, the idea of administering bailout GPIs was rejected and manual thrombus aspiration was performed (Fig. 5.3b) with restoration of TIMI flow grade 3 (Fig. 5.3c).
- The culprit lesion located at the mid-proximal portion of the RCA was sequentially dilated with 2.5×20 and a 3.0×20 mm balloons (Fig. 5.3d) with suboptimal angiographic result (Fig. 5.3e). Then, a new-generation zotarolimus-eluting stent (Resolute 3.5×28 mm, Medtronic) was implanted (Figs 5.3f, g) at 12 atm and post-dilated with a 4.0×15 mm non-compliant balloon (NC Trek, Abbott Vascular) at 16 atm (Fig. 5.3h) with final TIMI flow and myocardial blush grade 3 (Fig. 5.3i). Intracoronary imaging with optical coherence tomography (OCT) showed a good apposition and expansion of the stent with no visible edge dissections (Figs. 5.3l–n).
- Radial hemostasis was achieved with a radial band.

## 5.4 Post-procedural Issues

Prescribing the correct antithrombotic regimen in patients undergoing primary PCI in the context of STEMI and AF requires a clear definition of the individual stroke and bleeding risk. While this assessment is difficult before and during primary PCI, it can be easily accomplished in the hours after a successful and uncomplicated

**Table 5.5** $CHA_2DS_2$-VASc score and associated risk of stroke/year [25]

| | Condition | Points | Total score | Stroke risk/ year (%) |
|---|---|---|---|---|
| C | Congestive heart failure (or left ventricular ejection fraction ≤ 35 %) | 1 | 0 | 0 |
| H | Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication) | 1 | 2 | 1.3 |
| $A_2$ | Age ≥ 75 years | 2 | 2 | 2.2 |
| D | Diabetes mellitus | 1 | 3 | 3.2 |
| $S_2$ | Prior stroke or TIA or thromboembolism | 2 | 4 | 4.0 |
| V | Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque) | 1 | 5 | 6.7 |
| A | Age 65–74 years | 1 | 6 | 9.8 |
| Sc | Sex category (i.e., female sex) | 1 | 7 | 9.6 |
| | | | 8 | 6.7 |
| | | | 9 | 15.2 |

*TIA* transient ischemic attack

**Table 5.6** HAS-BLED score and associated risk of major bleeding/year [25]

| | Condition | Points | Total score | Risk of major bleeding/year (%) |
|---|---|---|---|---|
| H | Hypertension (uncontrolled blood pressure above 160/90 mmHg) | 1 | 0 | <1 |
| A | Renal (dialysis, transplant, creatinine > 2.6 mg/dL or >200 μmol/L) and/or liver (cirrhosis, bilirubin > 2x normal or AST/ALT/AP > 3x normal) disease | 1 or 2 | 1–2 | 2–3 |
| S | Stroke | 1 | ≥3 | 4–12 |
| B | Bleeding (previous or predisposition to) | 1 | | |
| L | Labile INR (unstable/high or TTR < 60 %) | 1 | | |
| E | Elderly (i.e., age > 65 years) | 1 | | |
| D | Drug usage predisposing to bleeding (antiplatelet agents, NSAIDs) and/or alcohol (≥8 drinks a week) | 1 or 2 | | |

*INR* international normalized ratio, *TTR* time in therapeutic range, *NSAIDs* nonsteroidal anti-inflammatory drugs, *AST* aspartate aspartate aminotranspherase, *ALT* alanine aminotranspherase, *AP* alkaline phosphatase

procedure. Defining the stroke and bleeding risks in a patient with AF requires the calculation of the $CHA_2DS2_2$-VASc (Table 5.5) and the HAS-BLED (Table 5.6) scores, respectively [29]. In STEMI patients at high stroke risk (i.e., $CHA_2DS_2$-VASc score ≥ 2), the duration of TT should be guided by the individual risk of bleeding, namely, up to 12 months, and for a minimum duration of 6 months, when the risk of bleeding is low (i.e., HAS-BLED score 0–2), as opposed to 1–3 months only when the risk of bleeding is high (i.e., HAS-BLED score ≥ 3) [3, 10] (Table 5.7). In these latter patients, considerations on the drop of aspirin could be even cautiously taken into account and dual therapy (DT) of OAC with warfarin (or other VKAs) and clopidogrel therefore prescribed, based on the results of a small, randomized, prospective trial [30] where, however, ACS were poorly represented and efficacy data were not conclusive [11, 31, 32] (Table 5.7). When the risk of stroke is low (i.e., $CHA_2DS_2$-VASc score 1, because of coronary artery disease as the only

**Table 5.7** Medium- to long-term (i.e., up to 12 months after PCI) management recommendations

| Issue | Recommendations |
|---|---|
| Initial antithrombotic treatment | Triple therapy (VKA + aspirin[a, b] + clopidogrel) |
| Duration of triple therapy | 1–3 months[c] to 6–12 months[d] |
| Intensity of OAC throughout triple therapy | Reduced[e] |
| Special care throughout triple therapy | Frequent INR monitoring[f]<br>Attention to high-quality OAC[g]<br>Routine gastric protection[h] |

*PCI* percutaneous coronary intervention, *BMS* bare-metal stent, *DES* drug-eluting stent, *ACS* acute coronary syndrome, *OAC* oral anticoagulation, *INR* international normalized ratio, *VKA* vitamin K antagonist

[a]75–100 mg once daily

[b]May be omitted in selected patients at high risk of bleeding and concomitant low risk of stent thrombosis

[c]With high bleeding risk (i.e., HAS-BLED score ≥ 3)

[d]With low bleeding risk (i.e., HAS-BLED score 0–2)

[e]Target INR 2.0–2.5

[f]Every 2 weeks

[g]Aiming at an average INR > 70 %

[h]Preferably with proton pump inhibitors not interfering with clopidogrel metabolism (e.g., pantoprazole, dexlansoprazole)

**Table 5.8** Relative risk of stroke of the individual components of $CHA_2DS_2$-VASc score

| | Hazard ratio (95 % confidence intervals) |
|---|---|
| Age (years) | 1.0 (Reference) |
| <65 | 2.97 (2.54–3.48) |
| 65–74 | 5.28 (4.57–6.09) |
| ≥75 | |
| Female gender | 1.17 (1.11–1.22) |
| Previous stroke | 2.81 (2.68–2.85) |
| Vascular disease | 1.14 (1.06–1.23) |
| Previous myocardial infarction | 1.09 (1.03–1.15) |
| Previous coronary artery bypass | 1.19 (1.06–1.33) |
| Peripheral artery disease | 1.22 (1.12–1.32) |
| Hypertension | 1.17 (1.11–1.22) |
| Congestive heart failure | 0.98 (0.93–1.03) |
| Diabetes | 1.19 (1.13–1.26) |

From [29]

risk factor) (Table 5.8), especially in association with high bleeding risk (i.e., HAS-BLED ≥ 3), temporary withdrawal (i.e., 3–6 months) of OAC and prescription of DAPT only (in this case also possible with prasugrel or ticagrelor as $P2Y_{12}$-receptor inhibitor) may be considered [3]. Given the low risk of stroke associated to a $CHA_2DS_2$-VASc score of 1, in fact, the potential benefit on stroke reduction of adding OAC to DAPT may be easily offset by the increase in bleeding associated with TT.

Together with the short possible duration of TT, another recommended bleeding avoiding strategy is to reduce the intensity of OAC and therefore targeting the INR

to 2-0–2.5 [3, 4] (Table 5.7). Also, in such circumstances great attention should be given to ensure high-quality OAC, and therefore frequent (e.g., every 2 weeks) controls of the INR should be performed, also aiming at obtaining a time in therapeutic range (TTR) > 70 % [3, 4] (Table 5.7). Percutaneous left atrial appendage closure remains a viable option in patients with a high stroke risk and unacceptably high bleeding risk with long-term OAC [33].

Notwithstanding the increased risk of bleeding with TT of warfarin (or other VKAs), aspirin, and clopidogrel, temporary withdrawal of warfarin and bridging with low-molecular-weight heparin appears not feasible because such strategy has been reported to be associated to an increase in bleeding complications [34].

The use of proton pump inhibitors should be encouraged in patients on DAPT to reduce the risk of gastrointestinal bleeding, particularly in case of combination therapy with warfarin [35] (Table 5.7). However, pharmacokinetic and pharmacodynamic studies suggest that concomitant use of clopidogrel and omeprazole reduces the antiplatelet effects of clopidogrel, possibly through competitive metabolic effects of cytochrome CYP2C19 or reduced biological action of clopidogrel related to genetic polymorphisms, leading to a box warning from drug-regulating agencies in the United States and Europe. Although this issue remains still debated, non-CYP2C19 interfering proton pump inhibitors (i.e., pantoprazole or dexlansoprazole) should generally be preferred.

### 5.4.1 Post-procedural Management

- At the end of the procedure, a 600 mg loading dose of clopidogrel was administered.
- During hospitalization, the daily antithrombotic therapy consisted of a TT of aspirin 100 mg, clopidogrel 75 mg, and warfarin (targeting an INR between 2.0 and 2.5), and the antihypertensive therapy was optimized by increasing ongoing therapy to ramipril 5 mg/hydrochlorothiazide 12.5 mg once daily and adding bisoprolol 5 mg once daily in order to obtain a more adequate control of blood pressure thus reducing the bleeding risk.
- Stratification of both the risk of stroke and bleeding was performed: $CHA_2DS_2$-VASc score 5 and HAS-BLED score 3.
- Therapy at discharge was ramipril 5 mg/hydrochlorothiazide 5 mg/12.5 mg once daily, bisoprolol 5 mg once daily, rosuvastatin 20 mg once daily, pantoprazole 40 mg once daily, warfarin to keep INR between 2.0 and 2.5, aspirin 100 mg, and clopidogrel 75 mg once daily. Because the bleeding risk was also judged to be high based on a calculated HAS-BLED score of 3, TT was mandated for 3 months only.

## 5.5 Medium- to Long-Term Issues

After the initial period with TT chosen based on the individual stroke and bleeding risk, transition to safer antithrombotic regimens can be considered. As previously mentioned, the duration of the initial period depends on the balance between the clinical circumstances (i.e., STEMI patients necessitates prolonged DAPT regardless of the type of stent implanted and even whether or not a stent has been implanted) and the risk of bleeding with combination therapy. In patients at increased risk of bleeding and low atherothrombotic risk (i.e., of stent thrombosis and recurrence of ischemic cardiac events), DT with warfarin and a single antiplatelet agent should be considered after at least 6 months of TT and maintained up to 12 months (Table 5.9) [3, 4, 36]. In patients at high risk of bleeding, this transition should occur sooner, namely, at 4 weeks and being maintained up to 12 months (Table 5.8). Which of the two antiplatelet agents (i.e., aspirin or clopidogrel) should be dropped after the initial period of TT has not been established. Whereas combination therapy of warfarin and aspirin has been more extensively studied in patients with ischemic heart disease, that of warfarin and clopidogrel likely shows a better efficacy to safety (especially at the gastrointestinal level) profile but carries the unknown of clopidogrel-resistance in a proportion of patients. [3].

After 1 year from primary PCI and in the absence of further events, it is recommended to stop ongoing (single) antiplatelet therapy and continue warfarin, or other VKAs, only [3, 4, 36] (Table 5.9). Compared to prolongation of combined OAC and (single) antiplatelet therapy, in fact, OAC monotherapy has been shown comparably effective but largely safer [37–39]. However, if the risk of adverse events without any antiplatelet on board, namely, of stent thrombosis (e.g., multiple stents in the setting of primary PCI or left main/bifurcation stenting), as well as of recurrent cardiac events (e.g., diffuse coronary artery disease, especially if not amenable of revascularization and/or associated with diabetes), is perceived as high as the risk of bleeding by the clinician, then aspirin may be continued long term.

**Table 5.9** Medium (i.e., up to 12 months)- to long (i.e., > 12 months)-term management recommendations

| Issue | Recommendation |
|---|---|
| Antithrombotic treatment | (a) Up to 12 months: VKA + either clopidogrel or aspirin<br>(b) >12 months: VKA monotherapy[a] |
| Intensity of OAC | Standard[b] |

*PCI* percutaneous coronary intervention, *VKA* vitamin K antagonist, *OAC* oral anticoagulation,
[a]Indefinite combination with either low-dose aspirin (ASA) (75–100 mg once daily) or clopidogrel 75 mg (depending on the individual risk of bleeding, especially gastrointestinal and stent thrombosis) may be considered in special situations (e.g., left main/last remaining vessel stenting, history of stent thrombosis/recurrent cardiac events, diffuse coronary artery disease (CAD), when bleeding risk is low
[b]That is, target International Normalized Ratio (INR) 2.0–3.0

### 5.5.1 Medium- to Long-Term Management

- At 3 months, aspirin was interrupted and clopidogrel only continued together with warfarin up to 12 months.
- At 12 months, the patient was event free so that clopidogrel was withdrawn and warfarin only continued, targeting the conventional INR range (between 2.0 and 3.0). Pantoprazole was also withdrawn, whereas rosuvastatin 20 mg once daily, ramipril/hydrochlorothiazide 5/12.5 mg once daily, and bisoprolol 5 mg once daily were continued.

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# 6 Atrial Fibrillation on Vitamin K Antagonist Oral Anticoagulant Undergoing Primary Percutaneous Coronary Intervention for ST-Elevation Acute Myocardial Infarction

Tuomas O. Kiviniemi and K.E. Juhani Airaksinen

## 6.1 Case Presentation

### 6.1.1 Baseline Characteristics

- Gender: female
- Age: 75 years
- Associated diseases: stage 3 chronic kidney disease [1] (Table 6.1) (estimated glomerular filtration rate [eGFR] according to Cockroft-Gault formula 57 ml/min), type 2 diabetes mellitus, hypertension, asthma.
- Previous history: since 10 years before, recurrent paroxysmal atrial fibrillation (AF) with prior transient ischemic attack (TIA), initially on warfarin then switched to apixaban 5 mg twice daily because of labile international normalized ratio (INR) levels; since 5 years before, stable effort angina Canadian Cardiovascular Society (CCS) II [2] (Table 6.2), with documentation at computed tomography of coronary arteries of mild stenosis in the left anterior descending (LAD) and significant stenosis at the crux of right coronary artery (RCA), for which, however, a conservative treatment was chosen because of mild symptoms, distal and bifurcation lesion, and relatively small estimated ischemic territory.
- Current history: worsening of chest pain over the last 2 days until a persistent angina at rest (CCS IV) class angina [2] (Table 6.2) urged her to call the emergency medical service. The on-site electrocardiogram (ECG) showed sinus rhythm and ST elevation in the inferior leads (Fig. 6.1),

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therefore qualifying the event as acute ST-elevation myocardial infarction (STEMI) and prompting immediate transfer of the patient to the cardiac catheterization laboratory for emergency primary coronary angiography/intervention (CORO/PCI). Upon admission, the patient was still symptomatic, blood pressure was 135/85, and other vital signs and $O_2$ saturation were within normal limits. Ongoing medications included: apixaban 5 mg twice daily, losartan 50 mg twice daily, long-acting isosorbide mononitrate 60 mg once daily, bisoprolol 5 mg twice daily, pantoprazole 40 mg once daily, lercanidipine 20 mg once daily, simvastatin 40 mg once daily, salmeterol/fluticasone 50/500 mg twice daily, and salbutamol 4 mg twice daily.

**Table 6.1** Stages of chronic kidney disease (www.kdigo.org)

| CKD stage | Description | GFR (ml/min per 1.73 $m^2$) |
|---|---|---|
| 1 | Kidney damage with normal or increased GFR | ≥90 |
| 2 | Kidney damage with mild decreased GFR | 60–89 |
| 3 | Moderate decreased GFR | 30–59 |
| 4 | Severe decreased GFR | 15–29 |
| 5 | Kidney failure | <15 (or dialysis) |

*GFR* glomerular filtration rate

**Table 6.2** Canadian Cardiovascular Society (CCS) grading of angina pectoris [2]

| | |
|---|---|
| Class I | Angina only during strenuous or prolonged physical activity |
| Class II | Slight limitation, with angina only during vigorous physical activity |
| Class III | Symptoms with everyday living activities, i.e., moderate limitation |
| Class IV | Inability to perform any activity without angina or angina at rest, i.e., severe limitation |

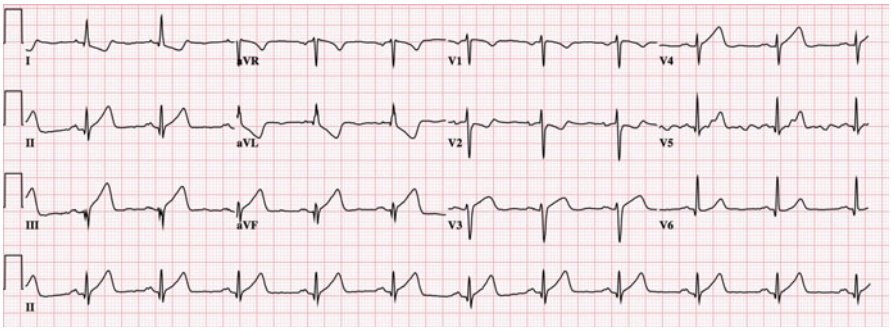


**Fig. 6.1** Electrocardiogram (ECG) on admission

**Table 6.3** Recommended periprocedural antithrombotic therapy in primary PCI [3]

| |
|---|
| *Antiplatelet therapy*: |
| Aspirin 150–300 mg orally (or 80–150 mg IV if oral ingestion not possible), followed by 75–100 mg once daily maintenance dose |
| A $P2Y_{12}$-receptor inhibitor: |
| (a) Prasugrel[a] 60 mg oral loading dose followed by 10 mg once daily maintenance dose[b] OR |
| (b) Ticagrelor 180 mg oral loading dose followed by 90 mg twice daily maintenance dose OR |
| (c) Clopidogrel 300–600 mg oral loading dose followed by 75 mg once daily maintenance dose |
| Glycoprotein IIb/IIIa inhibitor for bailout therapy when massive thrombus and/or no or slow flow and/or thrombotic complications: |
| (a) Abciximab 0.25 mg/kg IV bolus followed by 0.125 mcg/kg/min infusion for 12 h |
| (b) Eptifibatide IV double bolus 180 mcg/kg (10 min apart) followed by 2.0 mcg/kg/min infusion for 18 h |
| (c) Tirofiban 25 mcg/kg over 3 min IV followed by 0.15 mcg/kg/min infusion for 18 h |
| *Anticoagulant therapy*: |
| (a) UFH 70–100 IU/kg IV bolus (50–60 IU/kg in conjunction with glycoprotein IIb/IIIa inhibitors) OR |
| (b) Enoxaparin 0.5 mg IV bolus (where approved) OR |
| (c) Bivalirudin 0.75 mg/kg IV bolus followed by 1.75 mg/kg/h infusion for up to 4 h post-PCI[c] |

*PCI* percutaneous coronary intervention, *IV* intravenous, *UFH* unfractionated heparin, *IU* international unit

[a]Clopidogrel naïve and no history of previous stroke/TIA

[b]Maintenance dose of 5 mg once daily is recommended for patients with body weight < 60 mg and/or age > 75 years

[c]After cessation of the 1.75 mg/kg/h infusion, 0.25 mg/kg/h infusion may be continued for 4–12 h

## 6.2 Periprocedural Issues

When dealing with a patient on oral anticoagulation (OAC) with a non-vitamin K-antagonist oral anticoagulant (NOAC) referred for emergency primary CORO/PCI, the immediate challenge is how to manage anticoagulant therapy. In accordance with most recent guidelines on the management of STEMI patients, parenteral anticoagulation with either bivalirudin or unfractionated heparin (UFH) must be routinely used during primary PCI [3] (Table 6.3). In alternative, intravenous (IV) enoxaparin may also be considered [3] (Table 6.3). Whether and how a patient on chronic NOAC therapy should be further anticoagulated when undergoing emergency primary CORO/PCI is currently incompletely defined. While directly inhibiting thrombin (dabigatran) or factor Xa (rivaroxaban apixaban, edoxaban) and effectively preventing clinical events associated with spontaneous thrombosis (and thromboembolism) both at the arterial and venous site [4–11], NOACs have yielded equivocal results when evaluated regarding the activation of coagulation induced by PCI. In stable patients undergoing elective PCI, dabigatran as compared to standard UFH has been shown ineffective in inhibiting the generation and activation of

**Table 6.4** Periprocedural management recommendations

| Issue | Recommendation |
|---|---|
| Additional intraprocedural anticoagulation | Yes |
| Recommended anticoagulants and doses | (a) UFH 50–70 IU/kg[a] IV bolus OR<br>(b) Bivalirudin[b] 0.75 mg/kg IV bolus followed by 1.75 mg/kg/h infusion for up to 4 h post-PCI[c] OR<br>(c) Enoxaparin 0.3 mg/kg IV bolus (where approved) |
| Antiplatelet therapy | (a) Aspirin 150–300 mg orally (or 80–150 mg IV if oral ingestion not possible), followed by 75–100 mg once daily maintenance dose<br>(b) A $P2Y_{12}$-receptor inhibitor:<br>Clopidogrel 600 mg oral loading dose followed by 75 mg once daily maintenance dose<br>Prasugrel not indicated<br>Ticagrelor not indicated |
| Vascular access site | Radial |

*UFH* unfractionated heparin, *IU* international unit, *IV* intravenous

[a]Depending on whether < 24 vs. > 24–48 h (depending on ongoing NOAC and renal function) have been elapsed since last drug intake

[b]Especially in patients deemed at high risk of bleeding

[c]After cessation of the 1.75 mg/kg/h infusion, 0.25 mg/kg/h infusion may be continued for 4–12 h

thrombin [12], which in contrast appears to be effectively antagonized by rivaroxaban in the same setting [13]. Given this disparity, for which a clear explanation is lacking, and in the absence of a laboratory test allowing for rapid and reliable information on the presence and magnitude of the anticoagulant effect of ongoing NOAC [14], it is currently suggested to further anticoagulate a patient on chronic NOAC treatment undergoing PCI [15] (Table 6.4). This appears even more applicable in patients submitted to PCI in the context of an acute coronary syndrome (ACS) because of the highly thrombogenic milieu and the evident inability of ongoing anticoagulation with NOAC to prevent coronary thrombosis responsible for the current coronary event. Based on previous observations of preserved efficacy [16] and aiming at increasing the overall safety, a reduced dose of IV UFH, however, should preferably be given [15] (Table 6.4). When deciding, however, on the dose of additional IV UFH, the time of last NOAC intake, as well as the renal function (if known), should be taken into account: in the presence of normal renal function, the elimination half-life of NOACs is approximately 12 h [17] (Table 6.5), and therefore the exposure to the drug (and to its pharmacological effect) will be reducing by approximately 50 % every 12 h passing by (Fig. 6.2). Given that after 24 h from last administration the drug concentration (and pharmacological effect) is expected to be about 25 % of initial, full-dose UFH (i.e., 70–100 IU/kg) should be added upon start of PCI [15]. A reduced dose of UFH (i.e., 50 IU/kg) should on the contrary be administered when the last NOAC intake has occurred within the previous 12–24 h [15]. Adjustments of the above doses should be carried out based on the presence and degree of renal insufficiency, with reduced UFH dose to be given for creatinine clearance < 50 ml/min [15].

**Table 6.5** Procedural management recommendations

| Issue | Recommendations |
|---|---|
| Manual thrombus aspiration | Yes[a] |
| Adjunct IV glycoprotein IIb/IIIa inhibitors | Not recommended[b] |
| Type of stent | New-generation DES[c] |

*BMS* bare-metal stent, *DES* drug-eluting stent, *IV* intra venous

[a]If large thrombus burden

[b]May be considered when 24–48 h (depending on ongoing NOAC and renal function) have been elapsed since last drug intake and/or as bailout therapy in the presence of large thrombus burden, threatened vessel closure, or thrombotic complications

[c]BMS may be considered in patients at high risk of bleeding

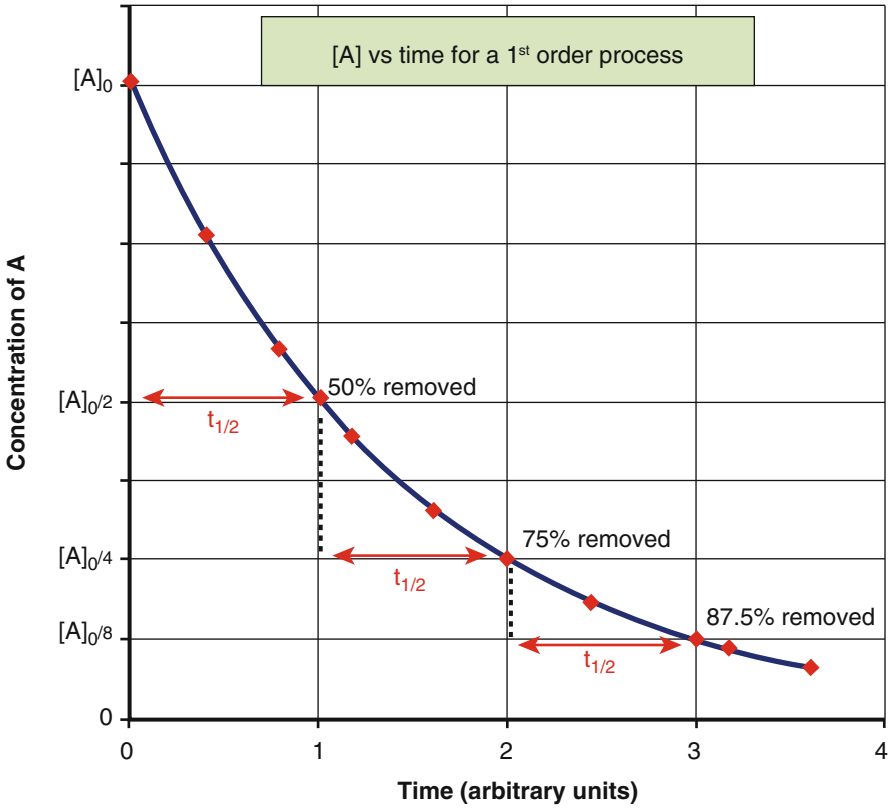


**Fig. 6.2** Plasma concentration as a function of time after drug withdrawal (note: with first-order kinetics)

Whether additional UFH may be of value to prevent radial artery occlusion (when this approach is used for CORO/PCI), as it has been shown for patients on warfarin [18], is currently unknown. Given that NOACs have a direct inhibitory effect on activated coagulation factors, similarly to UFH and differently from warfarin (which acts by promoting the hepatic synthesis of inactive coagulation factors), further anticoagulation to prevent radial artery occlusion might not be needed.

As an alternative to UFH, IV bivalirudin may be considered, especially when the bleeding risk is deemed particularly high [14, 15, 19] (Table 6.4). In large studies on general populations undergoing primary PCI [20], as well as in a small experience in patients with AF on warfarin [21], bivalirudin at the standard dose of 0.75 mg/kg bolus followed by 1.75 mg/kg/h infusion has been shown significantly more effective and safer than standard IV UFH. The very limited evidence in this regard, as well the lack of information regarding the optimal dose (standard vs. reduced) and administration scheme (standard vs. shorter infusion duration), does not strongly support at present the routine use of bivalirudin in place of standard IV UFH in NOAC patients undergoing emergency primary PCI.

The other main challenge in dealing with patients on NOAC undergoing emergency primary CORO/PCI for STEMI is the management of antiplatelet therapy. In accordance with the most recent guidelines on the management of STEMI patients, dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$-receptor inhibitor should be given as early as possible [3] (Table 6.3). The newer, more potent, and more effective $P2Y_{12}$-receptor inhibitors ticagrelor and prasugrel (this latter when not contraindicated, i.e., in patients with previous stroke or transient ischemic attack) should generally be preferred over clopidogrel [3]. In patients with ACS, however, both ticagrelor and prasugrel are associated with increased noncoronary bypass-related major bleeding events compared to clopidogrel [22, 23]. Accordingly, the use of the newer, more potent, $P2Y_{12}$-receptor inhibitors ticagrelor and prasugrel should generally be avoided in patients who are at increased risk of bleeding at baseline, such as those on chronic OAC who also receive aspirin [14, 15, 19, 24]. Initial experiences on both mixed and myocardial infarction populations undergoing PCI [25, 26] indeed show the significantly increased risk of bleeding when prasugrel is added to OAC (with vitamin K antagonist) and aspirin in triple combination. Together with aspirin (at the standard recommended doses), which has a nearly immediate antiplatelet effect [27], clopidogrel only should then be considered for patients on NOAC undergoing emergency PCI for STEMI [14, 15, 19, 24] (Table 6.4). A loading dose of 600 mg should be given as early as possible, taking however into account that effective antiplatelet inhibition may not be reached before at least 2 h [28]. Clopidogrel loading dose of 300 mg should generally not be considered, given the required time of at least 9 h for effective platelet inhibition [28]. Similarly to non-OAC patients, prasugrel and ticagrelor may likely be considered when STEMI is related to stent thrombosis during ongoing clopidogrel therapy, provided that technical problems (e.g., incomplete stent expansion and/or lesion coverage) have been excluded (possibly also based on intracoronary imaging) and/or nonresponsiveness to clopidogrel has been documented (by using platelet reactivity testing) [19].

As a final periprocedural issue, selection of the vascular approach associated with the lowest incidence of bleeding is of great importance. Both in large, general populations not on OAC [29] and in a small experience in OAC patients on warfarin [30], the radial access has been shown to decrease the rate of bleeding and/or vascular complications compared to the femoral approach and should therefore be considered routinely [19]. In the event that the radial approach has failed or is not feasible, ongoing therapeutic OAC (i.e., last NOAC intake within 12–24 h) should not exclude the femoral approach, provided that the puncture is carefully carried out according to the proper technique (i.e., puncture of common femoral artery and of the anterior artery wall only) and possibly guided by fluoroscopy or, even better, by ultrasonography. Whereas no specific data are available regarding hemostasis in patients on NOAC undergoing emergency primary PCI via the femoral route in STEMI, it appears reasonable to routinely consider the use of hemostatic devices in this setting. In general populations, they have been consistently shown comparably effective and safe to manual compression, while allowing for more rapid ambulation (and discharge) [31, 32].

### 6.2.1 Periprocedural Management

- A loading dose of aspirin 250 mg orally was given prior to the procedure.
- Pretreatment with $P2Y_{12}$-receptor inhibitor was withheld.
- The radial access site was attempted but it was not accessible due to weak pulse and vessel tortuosity. Therefore, femoral approach was chosen and a 6-French sheath inserted.
- A dose of 5.000 IU of IV UFH, corresponding to approximately 70 IU/kg, was given.
- Coronary angiography showed borderline stable stenosis in the small and tortuous left anterior descending (LAD) and mild atherosclerotic disease in the left circumflex (LCX) and some collaterals to right coronary artery (RCA) periphery (Fig. 6.3). Culprit lesion was the total occlusion of the proximal RCA (Fig. 6.4).

## 6.3 Procedural Issues

A first issue to be considered in the presence of acute thrombotic occlusion of a coronary artery in the context of STEMI is whether thrombus aspiration may be of value. While having shown not to impact significantly on hard cardiac outcomes of patients undergoing emergency primary PCI [33, 34], manual thrombus aspiration may nonetheless be considered (Table 6.5). Given the proven ability to remove thrombus, thereby reducing the risk of slow flow/no reflow, manual thrombus aspiration might be especially helpful in the context of STEMI in a patient on NOAC where aggressive antithrombotic therapy with additional anticoagulant and

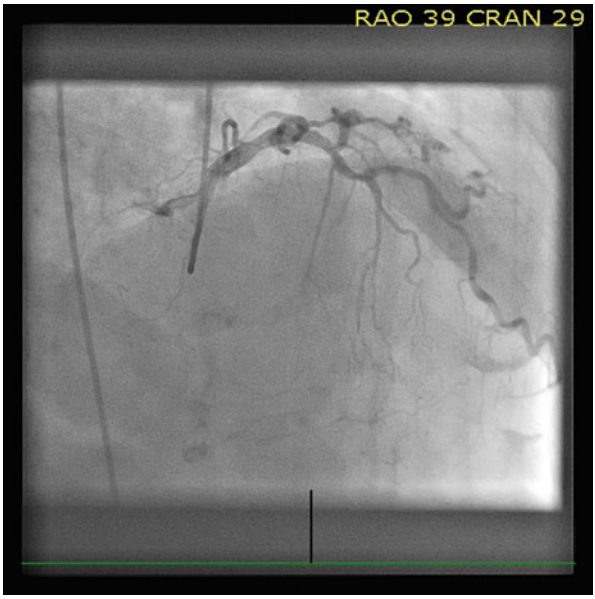


**Fig. 6.3** Baseline coronary angiography (*RAO view cranial*) of left coronary artery. *RAO* right anterior oblique

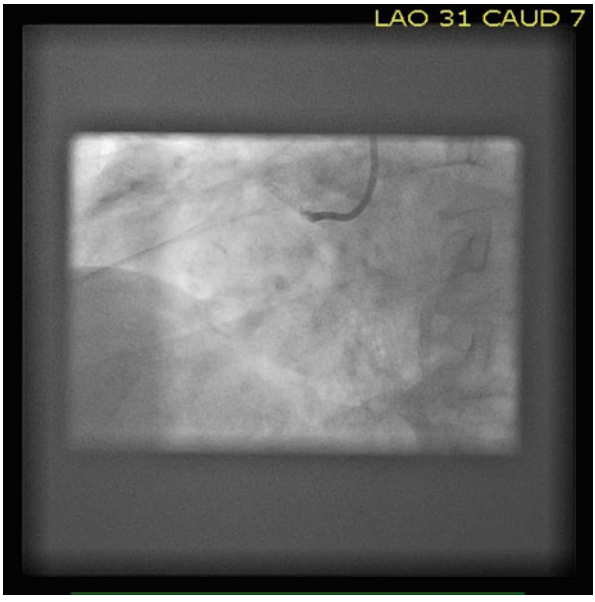


**Fig. 6.4** Baseline coronary angiography (*LAO view*) of right coronary artery. *LAO* left anterior oblique

**Table 6.6** Suggested time from last drug intake before IV glycoprotein IIb/IIIa inhibitors may be considered

| | Dabigatran | Factor Xa inhibitors (Rivaroxaban, apixaban edoxaban) |
|---|---|---|
| CrCl ≥ 80 ml/min | ≥24 h | ≥24 h |
| CrCl 50–80 ml/min | ≥36 h | ≥24 h |
| CrCl 30–49 ml/min | ≥48 h | ≥24 h |
| CrCl 15–29 ml/min | Not indicated | ≥36 h |

*CrCl* creatinine clearance, *IV* introvenous

antiplatelet agents, namely, IV glycoprotein IIb/IIIa inhibitors (GPIs), is hindered by the increased risk of bleeding.

Regarding the use of parenteral platelet inhibition, glycoprotein IIb/IIIa inhibitors (GPIs) should generally be avoided when ongoing anticoagulation is presumed effective, that is, within 24 h from last drug intake (or longer in the presence of renal dysfunction) (Table 6.6), or may be considered only as a bailout therapy in patients with large thrombus burden [24]. Data from patients on effective OAC with warfarin (i.e., INR > 2.0) show, in fact, a substantial increase in the risk of bleeding with apparent no benefit on the occurrence of major adverse cardiac and cerebrovascular events [35]. Owing to the reported lack of differences in terms of major bleeding, as well as of clinical benefits, with the intracoronary administration of abciximab as a bolus compared to standard IV infusion [36], the limitations in the use of GPIs should be confirmed regardless of the route of administration.

Whether the potent, rapid-acting, reversible, parenteral $P2Y_{12}$-receptor inhibitor cangrelor, which on top of standard antithrombotic therapy has been shown effective in reducing ischemic events without increasing bleeding in elective or ACS patients undergoing PCI [37–39], may be of value in OAC patients remains to be determined. As yet therefore, cangrelor has no specific indication in patients on NOAC undergoing emergency PCI in STEMI.

A key decision during the procedure is the choice between drug-eluting stents (DESs) and bare-metal stents (BMSs). Even though the main determinant of the duration of dual antiplatelet therapy (DAPT) is the clinical syndrome in which the stent has been implanted (i.e., ACS as compared to elective) and not the type of stent implanted (as is on the contrary the case for PCI performed in elective patients) [24], the type of device implanted may nonetheless have an impact in the management of subsequent antithrombotic therapy. This is particularly true in OAC patients in whom the increased risk of bleeding associated with the unavoidable combination of OAC and antiplatelet therapy after stenting may induce to tailor the duration of DAPT more on the time required for prevention of stent thrombosis (i.e., between 1 month for BMSs and 1–6 months for new-generation DESs) rather than on that required for prevention of recurrent cardiac events after an ACS (i.e., 12 or more months). Currently available new-generation DESs, either with durable or resorbable polymer coating or polymer-free (Table 6.7), are associated with similar or even lower rates of thrombosis than BMSs, thereby generally allowing for a duration of DAPT not longer than 6 months, and possibly as short as 1 month only. Because of that, as well

**Table 6.7** General classification of coronary stents/scaffolds

| | | |
|---|---|---|
| BMS | | (a) Stainless steel<br>(b) Non-stainless steel, cobalt- or platinum-chrome alloy |
| DES | Early generation | (a) Durable polymer: sirolimus and paclitaxel eluting |
| | New generation | (a) Durable polymer: zotarolimus and everolimus eluting<br>(b) Biodegradable polymer: biolimus A9 and everolimus eluting<br>(c) Polymer-free: biolimus A9 and amphilimus eluting |
| BAS | | (a) Diamond-like carbon coated, titanium nitric oxide coated<br>(b) Endothelial progenitor cell capturing |
| BRS | | (a) Nondrug eluting<br>(b) Everolimus, myolimus, and sirolimus eluting |

*BMS* bare-metal stent, *DES* drug-eluting stent, *BAS* bioactive stent, *BRS* bioresorbable scaffold

**Table 6.8** HAS-BLED score and associated risk of major bleeding/year [41]

| | Condition | Points | Total score | Risk of major bleeding/year (%) |
|---|---|---|---|---|
| H | Hypertension (uncontrolled blood pressure above 160/90 mmHg) | 1 | 0 | <1 |
| A | Renal (dialysis, transplant, creatinine > 2.6 mg/dL or >200 μmol/L) and/or liver (cirrhosis, bilirubin > 2x normal or AST/ALT/AP > 3x normal) disease | 1 or 2 | 1–2 | 2–3 |
| S | Stroke | 1 | ≥3 | 4–12 |
| B | Bleeding (previous or predisposition to) | 1 | | |
| L | Labile INR (unstable/high or TTR < 60 %) | 1 | | |
| E | Elderly (i.e., age > 65 years) | 1 | | |
| D | Drug usage predisposing to bleeding (antiplatelet agents, NSAIDs) and/or alcohol (≥8 drinks a week) | 1 or 2 | | |

*INR* international normalized ratio, *TTR* time in therapeutic range, *NSAID* nonsteroidal anti-inflammatory drugs, *AST* aspartate aminotranspherase, *ACT* alanine aminotranspherase, *AP* alkaline phosphatase

as of the superior efficacy compared to BMSs in preventing restenosis, and associated subsequent re-revascularization, DESs should be generally preferred also in NOAC patients, including in the context of the STEMI [15, 19, 24, 40]. At present, no individual DES appears preferable to others, although those approved for a DAPT duration of 1 month only may be of value, especially in patients at increased risk of bleeding in whom premature discontinuation (i.e., earlier than 3–6 months) may be required if a bleeding occurs. In selected patients deemed at particularly high risk of bleeding, such as those with a HAS-BLED score ≥ 3 [41] (Table 6.8), BMSs may be considered instead [15, 19, 24]. In this respect, it is, however, noteworthy that a recent trial showed that among patients at high risk for bleeding, a polymer-free umirolimus-coated stent was superior to a bare-metal stent with respect to the primary safety and efficacy end points when used with a 1-month course of dual antiplatelet therapy after PCI [42].

At present, it is unknown whether drug-eluting balloons (DEBs), which allow for a duration of DAPT as short as 1 month only [43], or bioresorbable scaffolds (BVSs), which also may allow limited duration of DAPT (apparently, however, not less than at least 6 months) [44] may be of value in patients at increased risk of

bleeding, such as those on NOAC undergoing emergency primary PCI for STEMI, and should therefore not be routinely considered.

### 6.3.1 Procedural Management

- The culprit lesion at the proximal RCA was easily crossed with a Pilot 50 Abbott Vascular guide wire (Fig. 6.5).
- Predilation was performed using the following balloons Maverick Boston Scientific in a sequence: 1.5×12 mm at 8 atm, 2.0×12 mm at 6 atm, and 3.0×12 mm at 6 atm. Antegrade flow was restored after the first predilation (Fig. 6.6). Significant stenosis was observed also in tortuous mid-RCA and a borderline stenosis in the crux of right posterolateral (RPL) and right posterior descending (RPD).
- Given the residual thrombus and recoil (Fig. 6.7), the procedure was finalized using cobalt-chromium BMS 3.5×16 mm (Rebel, Boston Scientific) starting from the ostium of RCA (Fig. 6.8). An excellent angiographic result was obtained with TIMI 3 flow and no angiographic dissection (Fig. 6.9).
- The femoral access site was sealed with Angio-Seal 6 F (St. Jude Medical) after the procedure.
- Clopidogrel loading with 600 mg orally was administered immediately after the procedure.

## 6.4 Post-procedural Issues

Given that DAPT of aspirin and clopidogrel has been shown significantly less effective than OAC (with warfarin) for stroke prevention in AF patients with at least one risk factor for stroke [45] and that OAC (with warfarin) has been shown significantly less effective than DAPT with aspirin and a thienopyridine in preventing subacute stent thrombosis [46], a combination therapy of OAC and antiplatelet(s) is indicated after PCI in AF patients at increased risk of stroke and therefore requiring OAC. Early stratification of the risk of stroke should be performed by using the $CHA_2DS_2$-VASc score [41] (Table 6.9): while individuals scoring 0 should be treated with DAPT only (as they have no indication for long-term OAC) and those scoring $\geq 2$ should receive combination OAC and antiplatelet(s) therapy, male patients scoring 1 and female patients scoring 2 should be considered for either DAPT or combination therapy of OAC and antiplatelet(s). Because of the limited risk of stroke, especially in the short term, associated with $CHA_2DS_2$-VASc score 1 (Tables 6.9 and 6.10), the net benefit (i.e., combined incidence of ischemic events, including death, myocardial infarction, repeat revascularization, stent thrombosis and stroke, and major bleeding events) of triple therapy (TT) may be lower than that

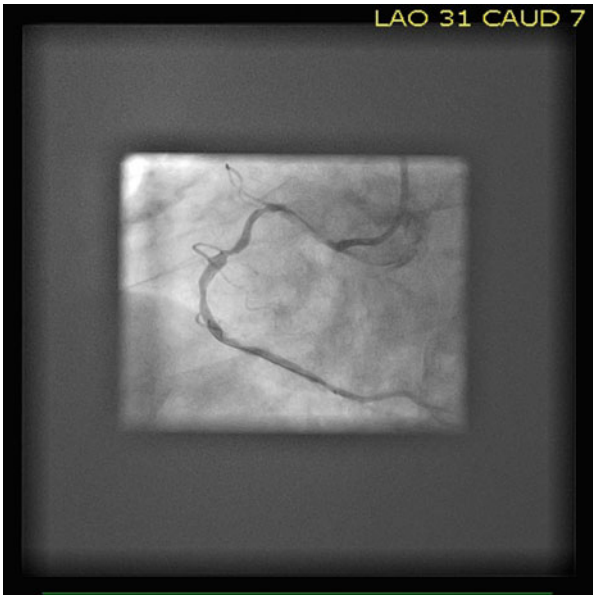


**Fig. 6.5** Coronary angiography (*LAO view*) of right coronary artery after crossing of the occlusion with the guide wire. *LAO* left anterior oblique

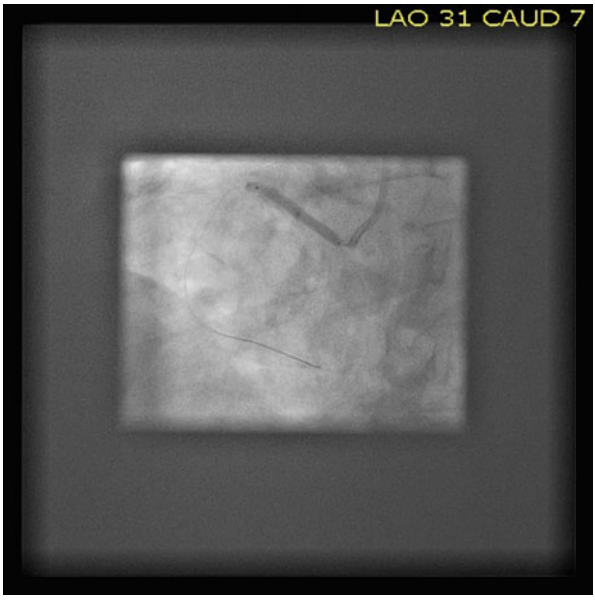


**Fig. 6.6** Balloon dilatation at proximal right coronary artery (*LAO view*). *LAO* left anterior oblique

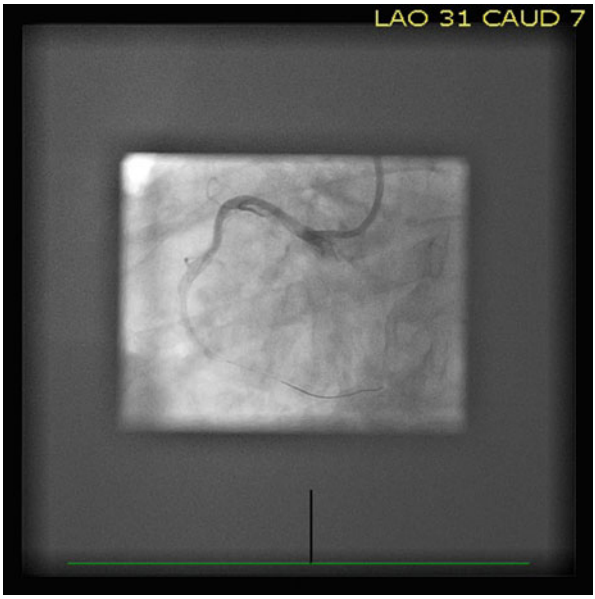


**Fig. 6.7** Coronary angiography of right coronary artery after balloon dilatation (*LAO view*). *LAO* left anterior oblique

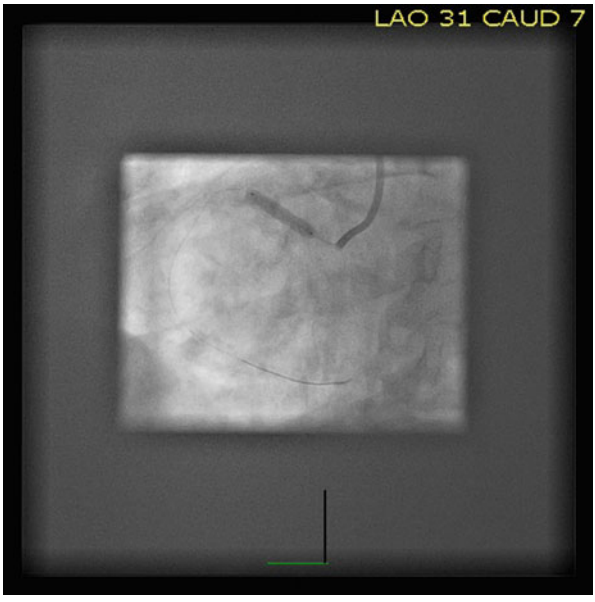


**Fig. 6.8** Stent deployment at proximal right coronary artery (*LAO view*). *LAO* left anterior oblique

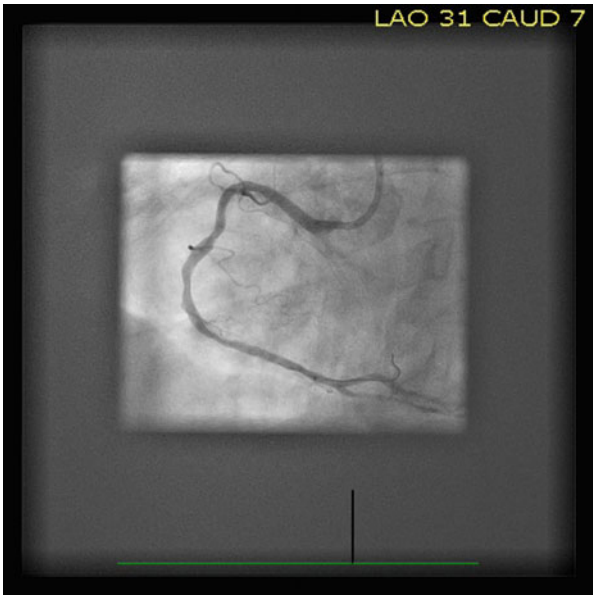


**Fig. 6.9** Final result after balloon angioplasty with stent implantation on proximal right coronary artery (*LAO view*). *LAO* left anterior oblique

**Table 6.9** $CHA_2DS_2$-VASc score and associated risk of stroke/year [41]

| | Condition | Points | Total score | Stroke risk/ year (%) |
|---|---|---|---|---|
| C | Congestive heart failure (or left ventricular ejection fraction ≤ 35 %) | 1 | 0 | 0 |
| H | Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication) | 1 | 1 | 1.3 |
| $A_2$ | Age ≥ 75 years | 2 | 2 | 2.2 |
| D | Diabetes mellitus | 1 | 3 | 3.2 |
| $S_2$ | Prior stroke or TIA or thromboembolism | 2 | 4 | 4.0 |
| V | Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque) | 1 | 5 | 6.7 |
| A | Age 65–74 years | 1 | 6 | 9.8 |
| Sc | Sex category (i.e., female sex) | 1 | 7 | 9.6 |
| | | | 8 | 6.7 |
| | | | 9 | 15.2 |

*TIA* transient ischemic attack

of temporary DAPT, especially in patients at increased risk of bleeding. Early stratification of the risk of (major) bleeding should therefore also be performed by using the HAS-BLED score (Table 6.8) [19, 41].

Based on pooled analyses of available data [47–49], TT appears superior to DAPT, OAC, and single antiplatelet and non-TT regimens on various outcomes.

**Table 6.10** Relative risk of stroke of the individual components of $CHA_2DS_2$-VASc score [41]

| | Hazard ratio (95 % confidence intervals) |
|---|---|
| Age (years) | |
| <65 | 1.0 (reference) |
| 65–74 | 2.97 (2.54–3.48) |
| ≥75 | 5.28 (4.57–6.09) |
| Female gender | 1.17 (1.11–1.22) |
| Previous stroke | 2.81 (2.68–2.85) |
| Vascular disease | 1.14 (1.06–1.23) |
| Previous myocardial infarction | 1.09 (1.03–1.15) |
| Previous coronary artery bypass | 1.19 (1.06–1.33) |
| Peripheral artery disease | 1.22 (1.12–1.32) |
| Hypertension | 1.17 (1.11–1.22) |
| Congestive heart failure | 0.98 (0.93–1.03) |
| Diabetes | 1.19 (1.13–1.26) |

Such increased efficacy, however, comes at the price of an (approximately two- to threefold compared to DAPT) increase in the risk of major bleeding. Whereas these results have been reported with warfarin (or other vitamin K antagonists) as OAC, they are currently considered valid also for NOACs [14, 15]. In AF clinical trials, NOACs have been consistently shown (at least) comparably effective and safe as warfarin [4–7] (Table 6.11). Also, in a post hoc analysis of the RE-LY trial [50], the subset of patients who received either one or two antiplatelet agents in addition to the study OAC showed a comparable increase in the risk of (major) bleeding independent of the type of OAC (i.e., warfarin or dabigatran), as well as of the dose of dabigatran (i.e., 110 or 150 mg twice daily). In the light of the above, NOACs are also considered largely similar in efficacy and safety when combined with DAPT, and therefore no indication is currently given to switch to a different NOAC in a patient who was on a specific NOAC at the time of STEMI [14, 15, 19, 24]. Nor it is given an indication to switch a NOAC patient to warfarin [14, 15, 19, 24]. Although larger experience has been obtained with the management of warfarin in general, with warfarin as OAC in TT combination after PCI, and in the management of complications of warfarin therapy, switching from a NOAC (who had likely been chosen for long-term treatment because of its advantages over warfarin) to warfarin for only some weeks after PCI appears hardly justified [15]. In addition to that, the induction phase of warfarin therapy, especially in naïve patients, is known to be associated to a substantial increase in bleeding risk [51, 52]. The recent availability of antidotes to NOACs [53, 54] will also make the concern of unopposed bleeding with these agents of lesser importance. Available data nonetheless suggest that even in the absence of specific reversal agents, conventional management of bleeding occurring during NOAC (namely, dabigatran) therapy tends to be associated to a better outcome compared to warfarin [55].

Whereas several observations consistently report that dual therapy (DT) of OAC and aspirin is largely ineffective in preventing adverse events in, and therefore is not suitable for, AF patients undergoing PCI [56, 57], DT of OAC

**Table 6.11** Efficacy and safety of non-vitamin K antagonist oral anticoagulants vs. warfarin in clinical trials (Hazard ratio; 95 % confidence intervals) [4–7]

| | Dabigatran 110 mg BID | Dabigatran 150 mg BID | Rivaroxaban 20 mg[a] OD | Apixaban 5 mg[b] BID | Edoxaban 30 mg BID | Edoxaban 60 mg BID |
|---|---|---|---|---|---|---|
| Stroke or systemic embolism | 0.91[c] (0.74–1.11) | 0.66[d] 0.53–0.82) | 0.88[c] (0.74–1.03) | 0.79[d] (0.66–0.95) | 1.07[c] (0.87–1.31) | 0.79[c] (0.63–0.99) |
| Major bleeding | 0.80[e] (0.69–0.93) | 0.93 (0.81–1.07) | 1.04 (0.90–1.20) | 0.69[e] (0.60–0.80) | 0.47[e] (0.41–0.55) | 0.80[e] (0.71–0.91) |
| Intracranial bleeding | 0.31[e] (0.20–0.47) | 0.40[e] (0.27–0.60) | 0.67[e] (0.47–0.93) | 0.42[e] (0.30–0.58) | 0.30[e] (0.21–0.43) | 0.47[e] (0.34–0.63) |
| Gastrointestinal bleeding | 1.10 (0.86–1.41) | 1.50[e] (1.19–1.89) | 1.60[e] (1.29–1.98) | 0.89 (0.70–1.15) | 0.67[e] (0.53–0.83) | 1.23[e] (1.02–1.50) |

*BID* twice daily, *OD* once daily

[a]15 mg OD in patients with creatinine clearance 30–50 ml/min

[b]2.5 mg BID in patients with two of the following three features: age ≥ 80 years, weight ≤ 60 kg, creatinine ≥ 1.5 ml/min

[c]significant for non-inferiority; [d]significant for superiority; [e]statistically significant

and clopidogrel may be an option. Such combination (with vitamin K antagonist as OAC) has been, in fact, proven superior to TT both in terms of efficacy and safety in the randomized, prospective, multicenter WOEST study [58]. Because of the several limitations of the study, however, including small size, open-label design, difference in bleeding essentially driven by nonmajor events, and undersizing for efficacy end points [59, 60], the lack of confirmation of the results in other analyses (where, nonetheless, DT of OAC and clopidogrel resulted in comparably effective and safe outcomes as TT) [49, 57], and the undefined pharmacological background (implying that clopidogrel has a more potent antiplatelet effect than aspirin, which as yet has not been demonstrated), the routine use of DT of OAC and clopidogrel is currently not recommended. Only in selected patients at increased risk of bleeding, and concomitant low risk of stent thrombosis (e.g., elective setting, large and short stent implanted, absence of diabetes), DT of OAC and clopidogrel may be considered as initial antithrombotic therapy [15, 19, 24]. Based on the considerations previously discussed and in the absence of specific data (which are however underway) [61, 62], warfarin and NOACs are considered comparable, and therefore, when selected, DT of OAC and clopidogrel may be carried out with the ongoing OAC. Uncertainty surrounds the efficacy and safety of DT of OAC and a newer $P2Y_{12}$-receptor inhibitor. While specific data are awaited [61, 62], initial observations suggest that both efficacy and safety may be comparable to those of TT [63].

Regardless of the regimen chosen, NOAC should be restarted a few hours (i.e., 3–6) after completion of PCI, provided however that the anticoagulant effect of intraprocedural heparins (or bivalirudin) is expected to be vanished.

### 6.4.1 Post-procedural Management

- Both stroke and bleeding risk were calculated by $CHA_2DS_2$-VASc and HAS-BLED score, which were 6 and 3, respectively.
- TT of apixaban, aspirin, and clopidogrel was prescribed.

## 6.5 Medium-Term Issues

Because of the increased risk of bleeding associated with combined OAC and antiplatelet therapy, and especially TT [64, 65], implementation of bleeding-avoiding strategies are warranted upon discharge (Table 6.12).

Based on both the concept that the longer the exposure to TT the higher the risk of bleeding and previous observations [66, 67], the duration of TT should be kept as short as possible to minimize the risk of bleeding [14, 15, 19, 24] (Table 6.12). While this is in contrast with the indication currently given for DAPT after an ACS, corresponding to 12 months (and possibly even longer) [3, 68], it should be noted that both the incidence of adverse cardiac events and stent thrombosis occur early after (i.e., within few weeks or months) the index event and procedure [3, 69]. Thus, in patients requiring OAC, a duration of TT of 3–6 months, based on the risk of bleeding, stent thrombosis, and recurrent cardiac events, should be generally sufficient [14, 15, 19, 24]. A further reduction or, on the contrary, prolongation of TT may be individually driven by the risk of ischemic and hemorrhagic adverse events [14] (see Fig. 6.4 in Chap. 2). How strictly this recommendation should be followed is currently unknown, as the only prospective evaluation of the relationship between duration of TT therapy (i.e., 6 weeks compared to 6 months) and adverse events in OAC patients undergoing DES implantation failed to report significant differences [70].

Based on the observation that reduced-intensity OAC with warfarin (i.e., target INR 2.0-2.5) appears associated with a survival free from bleeding events comparable to that of DAPT [71] and the dose-dependent efficacy and safety of NOACs (namely, dabigatran and edoxaban) documented in clinical trials [4, 7], the dose of the NOAC ongoing at the time of emergency primary PCI for STEMI should be reduced for as long as TT is administered [14, 15, 19] (Table 6.12). Whereas the lower dose of dabigatran (i.e., 110 mg twice daily) has indeed been shown safer than the higher dose (i.e., 150 mg twice daily), no data regarding the efficacy and safety of the reduced dose of rivaroxaban (i.e., 15 mg once daily) and apixaban (i.e., 2.5 mg twice daily) when given to patients without indications for dose reduction (i.e., creatinine clearance 30–49 ml/min for rivaroxaban and the presence of at least two out of serum creatinine $\geq$ 1.5 ml/min, body weight $\leq$ 60 kg, and age 80 years for apixaban) are currently available. Given that 25–50 % dose reduction of NOACs has been shown to be associated with an approximately 30 % reduction of the plasma exposure to the drug (and of its pharmacological effect) [72–74] and, in turn, that an

**Table 6.12** Medium- to long-term (i.e., up to 12 months after PCI) management recommendations

| Issue | Recommendations |
|---|---|
| Initial antithrombotic treatment | Triple therapy (NOAC + aspirin[a, b] + clopidogrel) |
| Duration of triple therapy | 3–6 months[c] |
| Intensity of OAC throughout triple therapy | Reduced[d] |
| Special care throughout triple therapy | Frequent (e.g., 1 a month) monitoring of CrCl and CBC[e]<br>Routine gastric protection[f] |
| Subsequent antithrombotic treatment[g] | NOAC[h] + either clopidogrel[i] or aspirin |

*PCI* percutaneous coronary intervention, *BMS* bare-metal stent, *DES* drug-eluting stent, *ACS* acute coronary syndrome, *OAC* oral anticoagulation, *CrCl* creatinine clearance, *CBC* complete blood count, *NOAC* non-vitamin *K* antagonist oral anticoagulant, *OD* once daily, *BID* twice daily, *TT* triple therapy, *PPI* proton pump inhibitor

[a]75–100 mg once daily

[b]May be omitted in selected patients at high risk of bleeding and concomitant low risk of stent thrombosis

[c]1 month only may be considered when the risk of bleeding is high, and new-generation DES has been implanted

[d]Lower tested dose: dabigatran 110 mg BID, rivaroxaban 15 mg OD, apixaban 2.5 mg BID

[e]Every 2 weeks

[f]Preferably with PPI not interfering with clopidogrel metabolism (e.g., pantoprazole, dexlansoprazole)

[g]After the initial course of 1 to 3–6 months of TT has been completed

[h]Standard dose, i.e., dabigatran 150 mg BID, rivaroxaban 20 mg BID, or apixaban 5 mg BID, should be resumed, unless indications for reduced dose are present

[i]Preferred due to its superior gastric tolerability

approximately 30 % reduction in the risk of stroke is expected with DAPT [75], a combination of low-dose NOAC and DAPT is considered comparably effective to standard OAC for stroke prevention. Because, however, of the lack of evidence, such combination should again be continued for as short as possible.

In order to limit the risk of bleeding and to early detect it in case of occurrence, close monitoring of the patient should be carried throughout TT. Accordingly, determination of complete blood count and creatinine clearance should be arranged approximately once a month and whenever conditions possibly impacting on renal function (e.g., dehydration, fever, etc.) occur [15] (Table 6.12).

Given that most (major) bleeding events during TT occur at the gastrointestinal site [19], gastric protection with proton-pump inhibitors (PPIs) should be routinely used for as long as TT is carried out (14, 15, 19). At present, however, no data are available regarding whether this strategy is effective or not. PPIs not interfering with the metabolism of clopidogrel, including pantoprazole and dexlansoprazole, should generally be preferred, given the reported, albeit still controversial, decrease of effect of clopidogrel when omeprazole is administered in conjunction [76].

Following the initial period of 3–6 months of TT, DT of NOAC and single antiplatelet agent should be implemented and carried out up to 12 months from the index event (Table 6.12). Again, no specific data are available in this regard.

Previous, albeit indirect, evidence has shown that a combination of OAC (with warfarin) and aspirin is as effective as DAPT in secondary prevention after an ACS [77]. Accordingly, such combination should be used to complete the recommended 12-month duration of aggressive antithrombotic therapy after an ACS [14, 15, 19]. Based on the same evidence and considerations, DT of OAC and single antiplatelet agent should be used in those OAC patients who suffer from an ACS but do not undergo PCI [78]. Whether aspirin or clopidogrel should be the antiplatelet to be withdrawn upon completion of TT may be questioned. On the one hand, aspirin has a much larger body of evidence regarding secondary prevention in ischemic heart disease, but on the other, clopidogrel has been shown safer, especially at the gastrointestinal site, than aspirin [79] and should therefore generally be preferred [14, 15, 19]. While acknowledging once again the lack of data, the dose of NOAC may be returned to standard (unless other reasons for continuing lower dose are present) as soon as TT is downgraded to DT. Gastric protection with PPIs should generally be continued for as long as combined OAC and antiplatelet therapy is carried out.

### 6.5.1 Medium-Term Management

- The discharge antithrombotic regimen included apixaban 2.5 mg twice daily, aspirin 100 mg once daily, and clopidogrel 75 mg once daily, which were given together with losartan 50 mg mg twice daily, long-acting isosorbide mononitrate 60 mg once daily, estradiol 1 mg twice daily, bisoprolol 5 mg twice daily, lercanidipine 20 mg once daily, simvastatin 40 mg once daily, salmeterol/fluticasone 50/500 mg twice daily, 1–2 × 2 and salbutamol 4 mg twice daily. Apixaban was restarted the next morning of PCI.
- Recommendation was given to withdraw aspirin after 3 months and then continue with apixaban 5 mg twice daily and clopidogrel 75 mg once daily up to 12 months. Owing to the combination therapy of apixaban and antiplatelet agents, recommendation was also given to evaluate hemoglobin levels and creatinine clearance monthly.

## 6.6 Long-Term Issues

After 12 months have elapsed from the index event and the patient is on combined NOAC and single antiplatelet agent, the question arises whether such antithrombotic regimen should be continued indefinitely or not. When the risk of stroke is substantial, i.e., when the $CHA_2DS_2$-VASc score is $\geq 2$ [41], OAC cannot be interrupted. Therefore, the question is whether or not the ongoing single antiplatelet agent should be confirmed long term. Historical data have shown that OAC (with warfarin) monotherapy after an ACS is at least as effective as aspirin in secondary prevention [80, 81]. While possibly being more effective than

aspirin, combination therapy of OAC and single antiplatelet agent is undoubtedly associated with an increased risk of bleeding [80–82]. Thus, monotherapy with OAC should generally be instituted after the 12-month course of combination therapy of OAC and antiplatelet agent(s) has been completed (Table 6.13). Possible exceptions are those conditions where the risk of recurrent events and/or coronary thrombosis is considered high and/or the occurrence of coronary thrombosis is expected to have catastrophic consequences, such as stent in the left main or last remaining vessel, multiple stenting, severe and diffuse coronary artery disease, especially in association with diabetes, and decreased left ventricular function (Table 6.13). The issues above may be of even more concern when dealing with an NOAC rather than warfarin, given the complete lack of data in this setting. In general, however, the same suggestions valid for warfarin should also be applied to NOACs, whose mechanism of action is to inhibit coagulation as also warfarin does.

### 6.6.1 Long-Term Management

- At 12 months, in the absence of further adverse cardiovascular events, clopidogrel was stopped and apixaban 5 mg twice daily continued indefinitely.

**Table 6.13** Long-term (i.e., > 12 months after PCI, in the absence of recurrent events) management recommendations

| Issue | Recommendation |
|---|---|
| Antithrombotic treatment | NOAC monotherapy[a] |
| Intensity of OAC | Standard[b] |

*PCI* percutaneous coronary intervention, *NOAC* non-vitamin K antagonist oral anticoagulant, *ASA* aspirin, *BID* twice daily, *OD* once daily

[a]Indefinite combination with either low-dose ASA (75–100 mg once daily) or clopidogrel 75 mg (depending on the individual risk of bleeding, especially gastrointestinal, and stent thrombosis) may be considered in special situations (e.g., left main/last remaining vessel stenting, history of stent thrombosis/recurrent cardiac events, diffuse CAD coronary artery disease), when bleeding risk is low

[b]That is, dabigatran 150 mg BID, rivaroxaban 20 mg OD, apixaban 5 mg BID, and edoxaban 60 mg BID, unless other indications for reduced dose are present

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# Atrial Fibrillation Early Complicating Acute Coronary Syndrome Treated with Percutaneous Coronary Intervention

7

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## 7.1 Case Presentation

### 7.1.1 Baseline Characteristics

- Gender: male.
- Age: 74 years.
- Cardiovascular risk factors: type 2 diabetes mellitus, hypertension, former cigarette smoker (approximately 1 pack/day, stopped 6 years ago).
- Associated diseases: anxiety.
- Previous history: 3 years earlier, atypical chest pain and subsequent exercise testing inconclusive. Upon subsequent coronary angiography, mild (<50 %) stenosis in the proximal right coronary artery (RCA) was found. Medical treatment was then decided.
- Current history: after a prolonged period of clinical stability, with no cardiologic symptoms during ordinary activity, patient had prolonged chest pain prompting hospitalization in coronary care unit 2 h later. Upon admission, the patient still had chest pain, and blood pressure was 140/80 mmHg, whereas other vital signs and arterial oxygen saturation were within normal limits. An

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electrocardiogram (ECG) showed sinus rhythm at heart rate 73/min with some premature ventricular complexes and 3 mm ST segment depression in the inferior and lateral leads (Fig. 7.1). Based on history, clinical presentation, and admission ECG, the diagnosis of non-ST-elevation acute coronary syndrome (NSTE-ACS) was made and proper management arranged. Ongoing treatment upon admission included bisoprolol 2.5 mg/day, aspirin 75 mg/day, simvastatin 20 mg/day, ramipril 2.5 mg/day, amlodipine 5 mg/day, and metformin 850 mg/day.

## 7.2 Early Management Issues

In the acute phase of NSTE-ACS, anti-ischemic drugs should immediately be given for both chest pain and ischemia relief. Accordingly, early initiation of beta-blocker treatment, or continuation of chronic beta-blocker therapy, is recommended, unless Killip class ≥3 or contraindications to beta-blocker therapy are present [1] (Table 7.1). Sublingual and/or intravenous (IV) nitrates are also recommended [1] (Table 7.1).

Given the pathophysiology of NSTE-ACS, generally involving nonocclusive thrombus formation at the site of a ruptured atherosclerotic plaque, early and effective antithrombotic therapy, including both platelet and thrombin inhibition, is warranted [1]. Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$

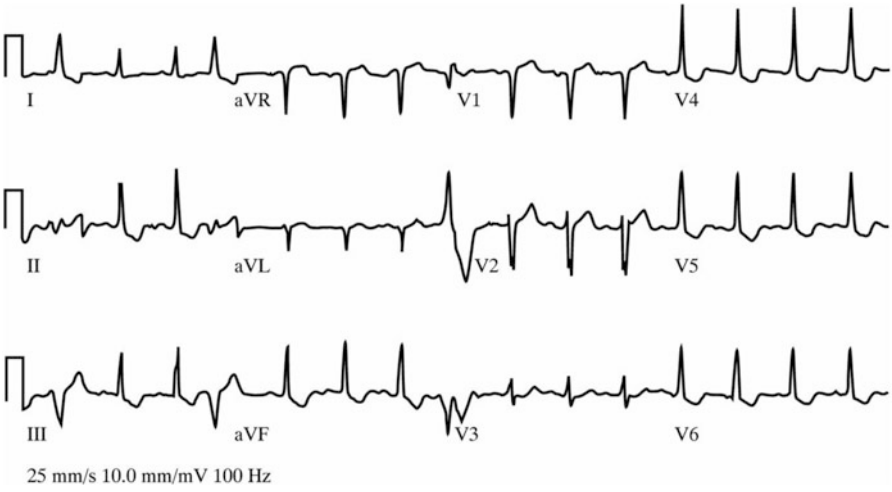


**Fig. 7.1** Electrocardiogram (ECG) on admission

**Table 7.1** Early pharmacological management of NSTE-ACS [1]

| | |
|---|---|
| Ischemia and pain relief | Oral beta-blocker initiation (or continuation if ongoing) |
| | Sublingual or IV nitrates |
| | Oral calcium channel blockers (and beta-blockers avoided) if confirmed/suspected vasospastic angina |
| Platelet inhibition and anticoagulation | Oral aspirin |
| | Oral $P2Y_{12}$ receptor inhibitor (either ticagrelor, prasugrel, or clopidogrel) |
| | Parenteral anticoagulation (either SC fondaparinux, IV bivalirudin, IV UFH, or SC enoxaparin) |

*NSTE-ACS* non-ST-elevation acute coronary syndrome, *IV* intravenous, *SC* subcutaneous, *UFH* unfractionated heparin

receptor inhibitor, including ticagrelor, prasugrel, or clopidogrel, is recommended soon after the diagnosis (Table 7.1), to be continued for 12 months, unless there are contraindications, such as excessive risk of bleeding [1]. Parenteral anticoagulation is recommended at the time of NSTE-ACS diagnosis to inhibit thrombin generation and/or activity [1] (Table 7.1). Either subcutaneous fondaparinux or enoxaparin or intravenous bivalirudin or unfractionated heparin (UFH) should be given [1] (Table 7.1).

### 7.2.1 Early Pharmacological Treatment

- Immediate IV nitroglycerin infusion was started, and the dose of bisoprolol increased to 5 mg once daily, while the remaining ongoing therapy upon admission was left unchanged.
- Aspirin therapy was continued at the dose of 75 mg once daily, and a loading dose of 180 mg of ticagrelor was given to be subsequently continued at the dose of 90 mg twice daily.
- Subcutaneous fondaparinux 2.5 mg once daily was started.
- As a result, chest pain promptly relieved and ECG changes normalized.

## 7.3 Risk Stratification

In NSTE-ACS patients, stratification of short-term ischemic and bleeding risk should be performed at presentation based on the combination of clinical history, symptoms, vital signs, other physical findings, ECG, and laboratory results, including troponin test [1]. Established risk scores, including GRACE (Table 7.2) and CRUSADE (Table 7.3), should be used for such early

**Table 7.2** GRACE score calculation [1]

| Background | Findings at the time of admission | Findings during hospital stay | | | |
|---|---|---|---|---|---|
| *1. Age (years)* | Points | *4. Heart rate at admission (bpm)* | Points | *7. Serum creatinine at admission (ml/min)* | Points |
| ≤29 | 0 | ≤49.9 | 0 | 0.0–0.39 | 1 |
| 30–39 | 0 | 50–69.9 | 3 | 0.4–0.79 | 3 |
| 40–49 | 18 | 70–89.9 | 9 | 0.8–1.19 | 5 |
| 50–59 | 36 | 90–109.9 | 14 | 1.2–1.59 | 7 |
| 60–69 | 55 | 110–149.9 | 23 | 1.6–1.99 | 9 |
| 70–79 | 73 | 150–199.9 | 35 | 2.0–3.99 | 15 |
| 80–89 | 91 | ≥200 | 43 | ≥4.0 | 20 |
| ≥90 | 100 | | | | |
| | | *5. SAP at admission (mmHg)* | | *8. Elevated enzymes or markers* | 15 |
| *2. History of heart failure* | 24 | ≤79.9 | 24 | | |
| | | 80–99.9 | 22 | *9. No percutaneous revascularization* | 14 |
| *3. History of myocardial infarction* | 12 | 100–119.9 | 18 | | |
| | | 120–139.9 | 14 | | |
| | | 140–159.9 | 10 | | |
| | | 160–199.9 | 4 | | |
| | | ≥200 | 0 | | |
| | | *6. Depressed ST segment* | 11 | | |

*SAP* systolic arterial pressure

stratification [1]. In-hospital invasive coronary angiography (CORO) is generally performed in patients with NSTE-ACS to (a) confirm the diagnosis; (b) identify the culprit lesion; (c) establish the indication for coronary revascularization, while assessing at the same time the suitability of coronary anatomy for percutaneous coronary intervention (PCI) and/or coronary bypass (CABG) surgery; and (d) stratify the patient's short- and long-term risk [1]. Such routine invasive strategy has been shown to improve clinical outcomes and reduce recurrent ACS episodes, subsequent rehospitalization, and revascularization compared to selective invasive strategy (where invasive coronary angiography and revascularization when indicated are driven by nonresponsiveness to initial

**Table 7.3** CRUSADE bleeding risk score ([7])

| | Points | Bleeding risk category | In-hospital bleeding rate (%) |
|---|---|---|---|
| *Baseline hematocrit, %* | | Very low, ≤20 | 3.0 |
| <31 | 9 | Low, 21–30 | 5.5 |
| 31–33.9 | 7 | Moderate, 31–40 | 9.0 |
| 34–36.9 | 3 | High, 41–50 | 12.0 |
| 37–39.9 | 2 | Very high, >50 | 19.0 |
| ≥40 | 0 | | |
| *Creatinine clearance,[a]mL/min* | | | |
| ≤15 | 39 | | |
| >15–30 | 35 | | |
| >30–60 | 28 | | |
| >60–90 | 17 | | |
| >90–120 | 7 | | |
| >120 | 0 | | |
| *Heart rate (bpm)* | | | |
| ≤70 | 0 | | |
| 71–80 | 1 | | |
| 81–90 | 3 | | |
| 91–100 | 6 | | |
| 101–110 | 8 | | |
| 111–120 | 10 | | |
| ≥121 | 11 | | |
| *Sex* | | | |
| Male | 0 | | |
| Female | 8 | | |
| *Signs of CHF at presentation* | | | |
| No | 0 | | |
| Yes | 7 | | |
| *Prior vascular disease†* | | | |
| No | 0 | | |
| Yes | 6 | | |
| Diabetes mellitus | | | |
| No | 0 | | |
| Yes | 6 | | |
| *Systolic pressure, mmHg* | | | |
| ≤90 | 10 | | |
| 91–100 | 8 | | |
| 101–120 | 5 | | |
| 121–180 | 1 | | |
| 181–200 | 3 | | |
| ≥201 | 5 | | |

*CHF* congestive heart failure
[a]According to Cockroft-Gault formula
[†]History of peripheral artery disease or prior stroke

**Table 7.4** Risk criteria mandating for, and recommended timing of, invasive strategy in NSTE-ACS [1]

| |
|---|
| Very-high-risk criteria (within 2 h when at least one is present) |
| Hemodynamic instability or cardiogenic shock |
| Recurrent or ongoing chest pain refractory to medical treatment |
| Life-threatening arrhythmias or cardiac arrest |
| Mechanical complications of myocardial infarction |
| Acute heart failure |
| Recurrent dynamic ST- or T-wave changes, particularly with intermittent ST elevation |
| High-risk criteria (within 24 h when at least one is present) |
| Rise or fall in cardiac troponin compatible with myocardial infarction |
| Dynamic ST- or T-wave changes (symptomatic or silent) |
| GRACE score >140 |
| Intermediate-risk criteria (within 72 h when at least one is present) |
| Diabetes mellitus |
| Renal insufficiency (eGFR < 60 ml/min/1.73 $m^2$) |
| LVEF <40 % or congestive heart failure |
| Early postinfarction angina |
| Prior PCI |
| Prior CABG |
| GRACE risk score >109 and <140 |
| Low-risk criteria |
| Any characteristics not mentioned above |

*NSTE-ACS* non-ST-elevation acute coronary syndrome, *eGFR* estimated glomerular filtration rate, *LVEF* left ventricular ejection fraction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting

medical treatment and/or early recurrence of ACS) [1]. Timing of invasive strategy should be based on the early risk of adverse events, as estimated by the presence or not of distinct features, namely, (1) within 2 h (analogous to ST-elevation myocardial infarction management) for very-high-risk patients, (2) within 24 h for high-risk patients, and (3) within 72 h for intermediate-risk patients (Table 7.4). In low-risk patients, that is, with none of the characteristics qualifying the above mentioned categories, a noninvasive stress test (preferably with imaging) for inducible ischemia is recommended before deciding on invasive strategy [1]. While percutaneous coronary intervention (PCI) with stent should be performed on the culprit lesion and generally also on all significant lesions in multivessel disease patients, conservative treatment should be offered to those patients who show either nonobstructive coronary artery disease, coronary artery disease not amenable to revascularization, or normal angiogram [1].

When PCI is performed, the radial vascular approach and the use of new-generation drug-eluting stents (DES) (Table 7.5), generally allowing a duration of DAPT of only 6 months or less, are recommended, to reduce the overall risk of bleeding [1].

**Table 7.5** General classification of coronary stents/scaffolds

| | | |
|---|---|---|
| BMS | | (a) Stainless steel |
| | | (b) Non-stainless steel, cobalt- or platinum-chrome alloy |
| DES | Early generation | (a) Durable polymer: sirolimus, paclitaxel eluting |
| | New generation | (a) Durable polymer: zotarolimus, everolimus-eluting |
| | | (b) Biodegradable polymer: biolimus A9-and everolimus eluting |
| | | (c) Polymer-free: amphilimus, biolimus A9-eluting |
| BAS | | (a) Diamond-like carbon-coated, titanium nitric oxide-coated |
| | | (b) Endothelial progenitor cells-capturing |
| BVS | | (a) Nondrug-eluting |
| | | (b) Everolimus, myolimus, sirolimus-eluting |

*BMS* bare-metal stent, *DES* drug-eluting stent, *BAS* bioactive stent, *BVS* bioresorbable vascular scaffold

### 7.3.1 Early Management

- Risk stratification was performed: GRACE score 153 and CRUSADE score 25 (given that hematocrit was above 40 % and creatinine clearance was 79).
- Troponin T levels were found increased at serial determination, therefore qualifying the current event as a non-ST-elevation myocardial infarction (NSTEMI).
- An early invasive strategy (<24 h) was therefore selected and the patient referred for CORO/PCI.
- The radial access site was selected, and an IV bolus of UFH 6000 IU (approximately corresponding to 70 IU/kg) was given through the arterial sheath upon start of procedure to prevent radial artery occlusion.
- Upon CORO, no significant lesions were detected in left coronary artery, whereas a severe (>90 %) stenosis was found at the proximal right coronary artery (RCA) (Fig. 7.2a). PCI with a new-generation DES (Xience, 3.0×15 mm, Abbott vascular) was performed on the proximal RCA with optimal result (Fig. 7.2b). Radial hemostasis was then obtained by means of elastic bandage.
- Following PCI, the prescribed antithrombotic therapy included fondaparinux 2.5 mg once daily up to 7 days, ticagrelor 90 mg twice daily up to 12 months, and aspirin 75 mg once daily lifelong.
- Post-procedural clinical course was uneventful until 36 h later when the patient started to complain of palpitations. Subsequent ECG showed AF at a heart rate of approximately 80/min (Fig. 7.3) which persisted over the subsequent hours.

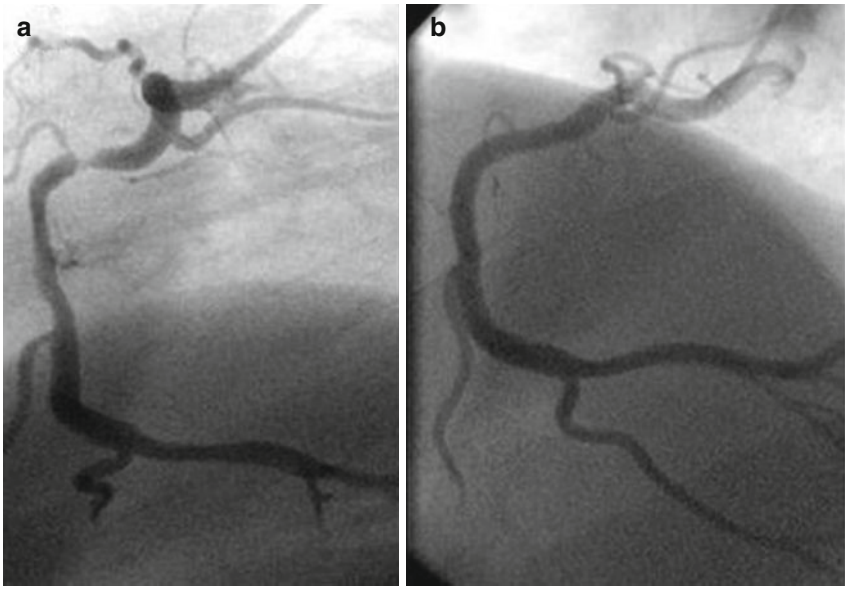


**Fig. 7.2** Angiography of tight coronary artery (LAO view) before (**a**) end after (**b**) PCI with stent. LAO left anterior oblique

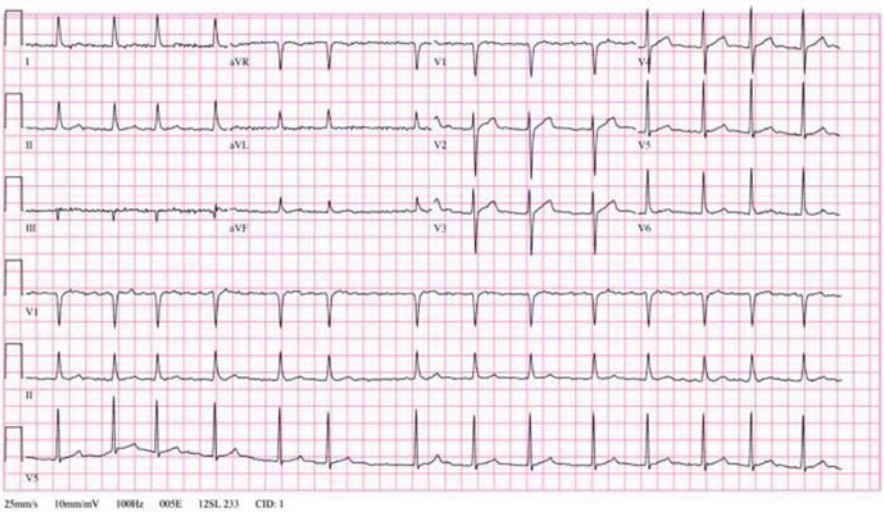


**Fig. 7.3** ECG upon development of palpitations 36 hours after PCI

## 7.4 The Issue of Choice and Management of Antithrombotic Therapy

AF complicates the course of ACS in approximately 10 % of cases [2]. Possible underlying mechanisms of AF in this setting include atrial ischemia or infarction, acute hypoxia or hypokalemia, pericardial inflammation, increased left ventricular (LV) diastolic pressure and left atrial pressure, and hemodynamic impairment secondary to LV dysfunction [3]. New-onset AF in ACS is associated with an increased risk of in-hospital and long-term mortality [3]. Also, AF complicating ACS is associated with an increased risk of subsequent "spontaneous" AF and also with an increased risk of ischemic stroke both during hospitalization and during follow-up, even if the AF is transient and reverses back to sinus rhythm before hospital discharge [3]. Adequate rate control represents the most important first therapeutic approach, whereas direct current electrical cardioversion should generally be reserved to patients with severe hemodynamic instability or intractable ischemia or when adequate rate control cannot be achieved with pharmacologic agents [3].

Given that patients with either permanent, persistent, or paroxysmal AF and ACS are a special subgroup with an increased risk for ischemic and embolic events, as well as bleeding complications, proper risk stratification should be promptly carried out. Based on $CHA_2DS_2$-VASc scoring (Table 7.6), all patients with a score ≥2 should be offered oral anticoagulation (OAC) [4]. Of note, DAPT with aspirin and a $P2Y_{12}$ receptor inhibitor, including ticagrelor, prasugrel, or clopidogrel, is also recommended in patients with ACS and especially when PCI-S has been performed (which occurs in over 90 % of patients with STEMI and approximately 50–60 % of those with NSTE-ACS) [3]. Stratification of bleeding risk should also be carried out in patients with AF (with or without associated ACS) by using the HAS-BLED score (Table 7.7) [3, 4]. Whereas a score ≥3 identifies patients at high risk of

**Table 7.6** $CHA_2DS_2$-VASc score and associated risk of stroke/year [4]

| | Condition | Points | Total score | Stroke risk/ year (%) |
|---|---|---|---|---|
| C | Congestive heart failure (or left ventricular ejection fraction ≤35 %) | 1 | 0 | 0 |
| H | Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication) | 1 | 2 | 1.3 |
| $A_2$ | Age ≥ 75 years | 2 | 2 | 2.2 |
| D | Diabetes mellitus | 1 | 3 | 3.2 |
| $S_2$ | Prior stroke or TIA or thromboembolism | 2 | 4 | 4.0 |
| V | Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque) | 1 | 5 | 6.7 |
| A | Age 65–74 years | 1 | 6 | 9.8 |
| Sc | Sex category (i.e., female sex) | 1 | 7 | 9.6 |
| | | | 8 | 6.7 |
| | | | 9 | 15.2 |

*TIA* transient ischemic attack

**Table 7.7** HAS-BLED score and associated risk of major bleeding/year [4]

| | Condition | Points | Total score | Risk of major bleeding/year (%) |
|---|---|---|---|---|
| H | Hypertension (uncontrolled blood pressure above 160/90 mmHg) | 1 | 0 | <1 |
| A | Renal (dialysis, transplant, creatinine >2.6 mg/dL or >200 μmol/L) and/or liver (cirrhosis, bilirubin >2× normal or AST/ALT/AP >3× normal) disease | 1 or 2 | 1–2 | 2–3 |
| S | Stroke | 1 | ≥3 | 4–12 |
| B | Bleeding (previous or predisposition to) | 1 | | |
| L | Labile INR (unstable/high or TTR < 60 %) | 1 | | |
| E | Elderly (i.e., age >65 years) | 1 | | |
| D | Drug usage predisposing to bleeding (antiplatelet agents, NSAIDs) and/or alcohol (≥8 drinks a week) | 1 or 2 | | |

*INR* international normalized ratio, *TTR* time in therapeutic range, *NSAID* nonsteroidal anti-inflammatory drugs, *AST* aspartate aminotranspherase, *ALT* alanine aminotranspherase, *AP* alkaline phosphatase

bleeding, the HAS-BLED score should be used not to select the antithrombotic therapy but essentially to identify patients potentially at risk of bleeding and to help identify and correct the potentially reversible bleeding risk factors (including uncontrolled hypertension, suboptimal quality of oral anticoagulation (OAC), concomitant use of aspirin or nonsteroidal anti-inflammatory drugs, and alcohol excess and/or abuse) [4, 5].

Given that DAPT with aspirin and a $P2Y_{12}$ receptor inhibitor, including ticagrelor, prasugrel, or clopidogrel, is recommended in patients with ACS, and especially when PCI has been performed, the question is how to carry out prevention of both stroke and recurrent cardiac events and stent thrombosis in patients with both AF and PCI performed in the context of NSTE-ACS [3]. Whereas DAPT has been shown significantly less effective than OAC with adjusted-dose warfarin, targeted to an international normalized ratio (INR) 2.0–3.0, for stroke prevention in AF [6], OAC with adjusted-dose warfarin targeted to an INR 2.0–3.0 has been shown in turn, significantly less effective than DAPT for prevention of stent thrombosis and recurrent cardiac events following PCI [7]. As a consequence, combined OAC and antiplatelet therapy is warranted.

In general, an initial period of triple therapy (TT) of OAC, aspirin, and clopidogrel should be prescribed to AF patients who have undergone PCI because of ACS [8]. Such TT has been rather consistently shown as the most effective regimen for prevention of major adverse cardiac events (MACE), including combined death, nonfatal myocardial infarction, urgent re-revascularization, stent thrombosis, and stroke [8]. Such TT however is associated to an increased risk of bleeding compared to other antithrombotic regimens and particularly two- to threefold higher compared to DAPT [8]. In the attempt to limit the risk of bleeding, the following general measures are recommended: (a) limit the duration of TT for as short as possible, based on clinical setting (i.e., elective versus acute), type of stent implanted (bare metal versus drug eluting), risk of major adverse cardiovascular events (MACE), and especially

stent thrombosis and risk of bleeding; (b) reduce the intensity of OAC by targeting the INR to 2.0–2.5 when warfarin is the OAC or by using the lower-tested dose of non-vitamin K antagonist oral anticoagulant (NOAC), that is, dabigatran 110 mg twice daily, rivaroxaban 15 m once daily, and apixaban 2.5 mg twice daily, when they are used; (c) strive to keep the time in therapeutic range (TTR) >70 % during OAC with warfarin; and (d) extensively use gastric protection with proton pump inhibitors [8–10]. Also, newer, more potent $P2Y_{12}$ receptor inhibitors, including ticagrelor and prasugrel, which in clinical trials in patients with ACS have been shown to be associated to an approximate 30 % increase in major bleeding compared to clopidogrel [11, 12], should generally not be used as part of TT [8–10]. Indeed, both in a small observational experience and a large multicenter registry where prasugrel was the $P2Y_{12}$ receptor inhibitor combined to OAC with vitamin K antagonist and aspirin following PCI, the incidence of total bleeding has been shown significantly higher than for clopidogrel, with no benefit on the occurrence of MACE [13, 14]. Because of that, switching from ticagrelor or prasugrel to clopidogrel should generally be performed when the indication for TT arises with either of the two above agents ongoing [8–10]. Whereas it needs to acknowledge that the clinical effect of most switching strategies is not fully determined, available data consistently show adequate safety and efficacy profiles with no evidence of drug interaction when the switching approach was used [15]. While waiting for the results of ongoing studies investigating the best strategies when a switch between P2Y12-inhibiting therapies is required, a practical algorithm both for the acute and chronic phase of treatment is provided in Fig. 7.4 [15].

In patients deemed at high risk of bleeding, dual therapy (DT) of OAC and clopidogrel may be considered instead of TT. While remarking that such regimen was tested, albeit prospectively and in a randomized fashion, in a relatively small population, including only approximately 30 % of ACS patients, it is of note that DT was

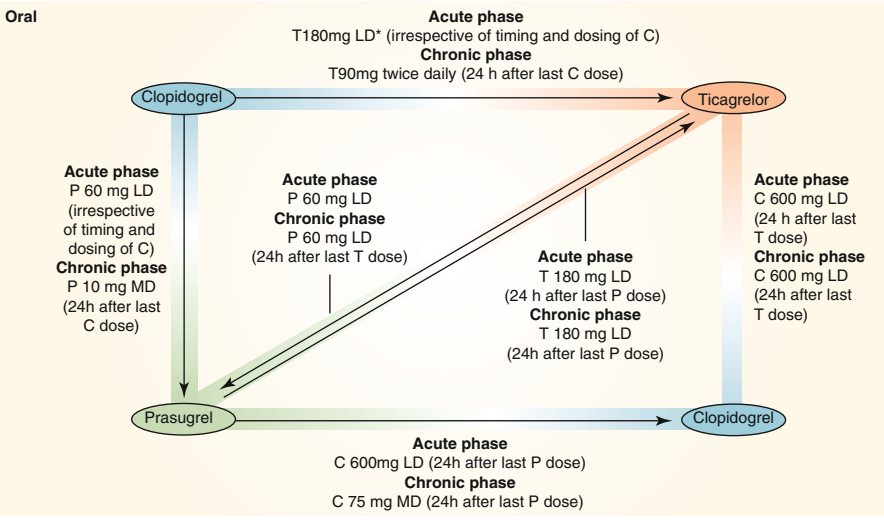


**Fig. 7.4** Modalities of switching between $P2Y_{12}$ receptor inhibitors. (Reproduced with permission from Rollini et al. [15])

significantly safer than TT of vitamin K antagonist, aspirin, and clopidogrel regarding the occurrence of total bleeding, as well as significantly more effective on the occurrence of MACE [16]. Given the study limitations mentioned above, the observation that the difference in total bleeding was essentially driven by the occurrence of nonmajor bleeding and the known variable and suboptimal efficacy of clopidogrel, the routine use of DT in AF patients undergoing PCI-S in the context of ACS is however currently not recommended [8]. Whether DT with OAC and a more potent $P2Y_{12}$ receptor inhibitor, such as ticagrelor or prasugrel, which show also a more predictable effect on platelet inhibition, may be of value is uncertain. Initial, limited, observational data suggest however that this may be the case, given the reported comparable efficacy and safety of conventional TT and DT with vitamin K antagonist and ticagrelor [17]. The efficacy and safety of DT with a NOAC (namely, rivaroxaban and dabigatran) and either ticagrelor or prasugrel (and even clopidogrel) is being tested in large, international, multicenter, randomized trials [18, 19].

In AF patients at intermediate risk of stroke, that is, with $CHA_2DS_2$-VASc score 1 (by virtue of their vascular disease only), DAPT with OAC, aspirin, and a $P2Y_{12}$ receptor inhibitor (either clopidogrel, ticagrelor, or prasugrel) may be considered instead of TT, particularly for patients at high risk of bleeding [8].

### 7.4.1 Choice and Management of Antithrombotic Therapy

- Stroke and bleeding risk stratification was performed: $CHA_2DS_2$-VASc score 4 and HAS-BLED score 3.
- TT therapy with OAC, aspirin 75 mg once daily, and clopidogrel 75 mg once daily was selected, and indication to be continued for 3 months was given.
- Switching from ticagrelor to clopidogrel was performed with a loading dose of clopidogrel 600 mg due to the quick offset of ticagrelor.
- Gastric protection with pantoprazole 20 mg was started, and indication to be continued for as long as TT was ongoing was given.
- Remaining therapy with bisoprolol at the increased dose of 5 mg once daily (for optimal rate control of AF), simvastatin 20 mg once daily, ramipril 2.5 mg once daily, and metformin 850 mg once daily was confirmed.

## 7.5 The Issue of the Choice of the Oral Anticoagulant to Be Added to DAPT

In AF patient on OAC with either a vitamin K antagonist or a NOAC undergoing PCI-S because of either stable coronary artery disease or ACS, the ongoing OAC should generally be confirmed [8–10]. Initial, albeit limited, data suggest in fact

that there is essentially no interaction as regards efficacy when a NOAC (namely, dabigatran at either 110 or 150 mg twice daily) is used instead of warfarin in association with DAPT (and also single antiplatelet therapy) [20]. Also, there is apparently no significant interaction neither as regards safety, given that the relative risk of major bleeding compared to DAPT is similar, and about 1.5- and 2.5-fold higher when single antiplatelet therapy and DAPT, respectively, are added, irrespective of whether a NOAC (namely, dabigatran at either 100 or 150 mg twice daily) or warfarin is used [20]. In addition, data derived from populations of patients with ACS treated with DAPT, in whom OAC has been added to enhance secondary prevention, largely appear to confirm the above profile of safety [21, 22]. Temporary (i.e., as long as TT is required) switching to warfarin, regarding which it needs however to be acknowledged that most of available data are derived, neither appears routinely justified, given the established increased risk of bleeding (and thromboembolic complications) upon initiation of OAC with vitamin K antagonists and management advantages of NOACs over the long term [23, 24].

On the other hand, when AF develops in a patient already on DAPT because of recent PCI, a choice between warfarin and a NOAC needs to be performed. Again, warfarin might be chosen as the preferred agent, given the larger experience and evidence regarding TT with warfarin rather than a NOAC as OAC are larger, as are the experience and the evidence regarding OAC with warfarin in general. The availability of a specific antidote, namely, vitamin K1, and established nonspecific reversal agents, including prothrombin complex concentrates, recombinant factor VIIa, and fresh frozen plasma, has long been considered additional factors supporting the choice of warfarin. Nonetheless, the importance of this issue should nowadays be considered reduced given both the, at least partial, efficacy reported with the same nonspecific agents used for VKA (i.e., including prothrombin complex concentrates, recombinant factor VIIa, and fresh frozen plasma) [25] and the recent availability of specific reversal factors for both dabigatran [26] and factor Xa inhibitors [27]. Also, warfarin requires several days before being effective, so that it may be questionable whether to start an anticipated short course of warfarin when a NOAC has been identified as the best option for long-term treatment [24]. Finally, an estimation of the likely quality of OAC with warfarin, that is, a predicted TTR >70 %, should be performed by preferentially using the SAMe-$TT_2$ $R_2$ score [28] (Table 7.8), with a score of 0–2 and ≥3 being predictive of high quality and low quality, respectively, of OAC with warfarin [29]. Whereas OAC with warfarin may be considered with a SAMe-$TT_2$ $R_2$ score of 0–2, a NOAC would generally appear a better option with a SAMe-$TT_2$ $R_2$ score ≥3. The risk of stroke and bleeding, as estimated by $CHA_2DS_2$-VASc and HAS-BLED scores [4], as well as patient's preferences, should then be taken into account when choosing between warfarin and a NOAC in addition to DAPT. An estimation of renal function, as evaluated by the Cockroft-Gault formula, should finally be performed in order to further guide the choice between warfarin and NOACs (which all are excreted, albeit in a variable amount, by the kidney) (Table 7.9) [30].

While the choice between warfarin and NOAC to be added to DAPT in a patient developing AF early after PCI should generally be guided by the same considerations

**Table 7.8** Definition of SAMe-$TT_2R_2$ score [28]

| | Definitions | Points |
|---|---|---|
| S | Sex (female) | 1 |
| A | Age (<60 years) | 1 |
| M | Medical history[a] | 1 |
| e | – | – |
| T | Treatment (interacting Rx[b]) | 1 |
| T | Tobacco use (within 2 years) | 2 |
| R | Race (non-white) | 2 |
| Maximum points | – | 8 |

SAMe-$TT_2R_2$=Sex female, Age less than 60, Medical history, Treatment strategy (rhythm control), Tobacco use (doubled), Race (doubled)

[a]Two of the following: hypertension, diabetes, coronary artery disease, myocardial infarction, peripheral artery disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease

[b]e.g., amiodarone for rhythm control

**Table 7.9** Main pharmacological properties of warfarin and non-vitamin K antagonist oral anticoagulants

| | Warfarin | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|---|
| Target | Factors II, VII, IX, X | Factor IIa (thrombin) | Factor Xa | | |
| Prodrug | No | Yes | No | No | No |
| Bioavailability | 100 % | 6 % | 66[a]/100 %[b] | 50 % | 62 % |
| Plasma protein binding | 97 % | 35 % | 93 % | 87 % | 50 % |
| Time to peak | 4–5 days | 1.5–2 h | 2–3 h | 2–3 h | 1–2 h |
| Elimination half-life | 36–42 h | 12–17 h | 5–9[c]/11–13[d] h | 12 h | 10–14 h |
| Route of clearance | Multiple | 80 % renal | 35 % renal | 27 % renal | 50 % renal |

[a]Without food, [b]with food, [c]in the young, [d]in the elderly

valid for patients not on DAPT, an important issue is what NOAC and what dose should be selected once the decision to give a NOAC has been taken. Based on the strength of available evidence, as well as the pharmacological properties of the various NOACs, dabigatran 110 mg twice daily should likely be considered as first option [24]. The concern about an increase in myocardial infarction, which has been shown about 30 % higher than with warfarin [31], should not influence the choice, given the lack of both negative prognostic impact [32] and confirmation in real-world settings [33, 34]. Alternative choices may include either rivaroxaban 15 mg once daily or apixaban 2.5 mg twice daily, for which on the other hand an increase in adverse cardiac events has never been reported. Should these latter regimens be chosen however, it should be kept in mind that at variance from dabigatran, no efficacy and safety data are available for rivaroxaban 15 mg once daily and apixaban 2.5 mg twice daily when they are given to patients without the clinical features in which these reduced doses were studied, namely, creatinine clearance 30–49 ml/min for rivaroxaban and two out of the following: age ≥80 years, body weight ≤60 kg, and serum creatinine ≥1.5 mg/

dl for apixaban. It should nonetheless be considered that the approximately 30 % reduction in stroke risk provided by DAPT of aspirin and clopidogrel, as estimated by available, albeit indirect, data [35, 36], may however add some protection to reduced-dose NOAC [24].

### 7.5.1 Choice and Management of Oral Anticoagulation

- Likelihood of good OAC quality, that is, predicted TTR >70 %, was estimated by means of SAMe-$TT_2R_2$ score: 1.
- Renal function was estimated by Cockroft-Gault formula: 64 ml/min.
- Rivaroxaban 15 mg once daily was then initiated, despite the fact that within 48 h from onset, AF has spontaneously cardioverted to sinus rhythm.
- Remaining therapy with bisoprolol 5 mg once daily, simvastatin 20 mg once daily, ramipril 2.5 mg once daily, pantoprazole 20 mg once daily, and metformin 850 mg once daily was confirmed.

## 7.6 The Issue of Post-discharge Management of Antithrombotic Therapy

In the attempt to optimize efficacy and safety of TT, duration of such combination should be prolonged for as short as possible (Table 7.10). Whereas DAPT should be prolonged up to 12 months after ACS, irrespective of whether a bare-metal or a DES has been implanted and even irrespective of whether a stent has been implanted, it appears that most of the benefit is observed early, that is, within the first 3 months [37]. Because of that and of the low propensity for stent thrombosis (especially late, i.e., between 30 days and 12 months from PCI) (Table 7.11) of currently available, new-generation DES (Table 7.5), a 3–6-month duration of TT would generally be sufficient [8–10]. In the presence of a particularly high risk of bleeding, even a 1-month only duration of TT may be considered [38].

After the initial, mandatory period of TT, one antiplatelet agent may, and should, be withdrawn, and DT of OAC and single antiplatelet agent continued up to 12 months [8–10] (Table 7.10). The choice of the antiplatelet agent to discontinue, that is, aspirin or clopidogrel, should be taken based on an estimation of the individual risk of stent thrombosis, recurrent cardiac events, and bleeding, although aspirin should generally be the one given the superior gastric tolerability of clopidogrel [8–10]. Throughout DT of OAC and single antiplatelet agent, the dose of NOAC should generally be increased to standard, unless an increased risk of bleeding is present (Table 7.10).

**Table 7.10** Medium- to long-term (i.e., up to 12 months after PCI) management recommendations after NSTE-ACS

| Issue | Recommendations |
|---|---|
| Initial antithrombotic treatment | Triple therapy (OAC + aspirin[a,b] + clopidogrel) |
| Duration of triple therapy | Either BMS or DES in ACS setting: 3–6 months[c] |
| Intensity of OAC throughout triple therapy | Reduced[d] |
| Special care throughout triple therapy | VKAs: frequent INR monitoring[e] and attention to high-quality OAC[f] |
| | NOACs: frequent[g] CrCl and CBC monitoring |
| | Both VKAs and NOACs: routine gastric protection[h] |
| Subsequent antithrombotic treatment[i] | OAC[k] + either clopidogrel[j] or aspirin |

*PCI* percutaneous coronary intervention, *BMS* bare-metal stent, *DES* drug-eluting stent, *ACS* acute coronary syndrome, *OAC* oral anticoagulation, *INR* international normalized ratio, *VKA* vitamin K-antagonists, *OD* once daily, *BID* twice daily, *TT* triple therapy, *OAC* oral anticoagulation, *PPIs* proton pump inhibitors

[a]75–100 mg once daily

[b]May be omitted in selected patients at high risk of bleeding and concomitant low risk of stent thrombosis

[c]1 month only may be considered when the risk of bleeding is high, and either a BMS or a new-generation DES has been implanted

[d]Target INR 2.0–2.5 with VKAs or lower dose with NOAC (dabigatran 110 mg BID, rivaroxaban 15 mg, OD, apixaban 2.5 mg BID)

[e]Every 2 weeks

[f]Aiming at an average INR >70 %

[g]Once a month for as long as TT is continued

[h]Preferably with PPI not interfering with clopidogrel metabolism (e.g., pantoprazole, dexlansoprazole)

[i]After the initial course of 1 to 3–6 months of TT has been completed

[j]Standard intensity of OAC, i.e., INR 2.0–3.0 with VKAs or dabigatran 150 mg BID, rivaroxaban 20 mg BID, and apixaban 5 mg BID with NOACs, should generally be resumed

[k]Preferred due to its superior gastric tolerability

**Table 7.11** Academic Research Consortium (ARC) definitions of stent thrombosis [41]

| | |
|---|---|
| Event certainty | (a) Definite: acute coronary syndrome with angiographic or autopsy confirmation of stent thrombosis |
| | (b) Probable: |
| | (i) Unexplained death within 30 days of stent implantation without autopsy |
| | (ii) Acute myocardial infarction in the territory of target vessel where stent was implanted without angiographic confirmation |
| Time frame | (a) Early: |
| | (i) Acute – within 24 h of stent implantation |
| | (ii) Subacute – between 24 h and 30 days of stent implantation |
| | (b) Late: between 30 days and 1 year of stent implantation |
| | (c) Very late: after 1 year of stent implantation |

**Table 7.12** Long-term (i.e., >12 months after PCI, in the absence of recurrent events) management recommendations

| Issue | Recommendation |
|---|---|
| Antithrombotic treatment | OAC monotherapy[a] |
| Intensity of OAC | Standard[b] |

*PCI* percutaneous coronary intervention, *OAC* oral anticoagulation, *ASA* aspirin, *CAD* coronary artery disease, *INR* international normalized ratio, *BID* twice daily, *OD* once daily, *VKA* vitamin K-antagonists, *NOAC* non-vitamin K-antagonist oral anticoagulant

[a]Indefinite combination with either low-dose ASA (75–100 mg once daily) or clopidogrel 75 mg (depending on the individual risk of bleeding, especially gastrointestinal and stent thrombosis) may be considered in special situations (e.g., left main/last remaining vessel stenting, history of stent thrombosis/recurrent cardiac events, diffuse CAD), when bleeding risk is low

[b]Target INR 2.0–3.0 with VKAs and dabigatran 150 mg BID, rivaroxaban 20 mg OD, apixaban 5 mg BID with NOACs

After 12 months, the remaining single antiplatelet agent should also be discontinued, and OAC monotherapy with NOAC at the standard dose continued lifelong (Table 7.12). Even though specific data on secondary prevention after ACS with NOAC monotherapy are lacking, historical evidence with warfarin in this context showed at least comparable efficacy to aspirin monotherapy [38, 40]. Given that there is no apparent reason for NOACs to act differently from warfarin in this context and that prolonged combination therapy of OAC (with warfarin) and single antiplatelet agent (with aspirin) appears to substantially increase the risk of bleeding, with no benefit on efficacy [42], long-term DT of OAC and single antiplatelet agent is not routinely recommended [8–10]. Exceptions however may include situations where stent thrombosis may have catastrophic consequences, like previous PCI in left main or last remaining vessel.

### 7.6.1 Post-procedural Management

- The patient was discharged with the indication to continue TT for 1 month and then drop aspirin while continuing clopidogrel up to 12 months in combination with rivaroxaban at the dose of 15 mg once daily throughout TT and 20 mg once daily after aspirin has been interrupted.
- Because of the treatment with rivaroxaban, an evaluation of renal function (i.e., creatinine clearance) was planned at 3 months and then every 6 months after discharge. Outpatient cardiology visits were scheduled at 3, 6, and 12 months.

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# New-Onset Atrial Fibrillation in a Stable Patient with Remote Percutaneous Coronary Intervention

8

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## 8.1 Case Presentation

### 8.1.1 Baseline Characteristics

- Gender: female.
- Age: 73 years.
- Cardiovascular risk factors: type 2 diabetes mellitus, hypertension, hypercholesterolemia.
- Previous history: 3 years earlier, anterior ST-elevation myocardial infarction (STEMI) because of which percutaneous coronary intervention (PCI) with implantation of two new-generation drug (zotarolimus)-eluting stents (Resolute, Medtronic, 3×22 and 2.5×18 mm) (Table 8.1) in the left anterior descending (LAD) was performed, followed after 48 h by another PCI with implantation of two new-generation drug (zotarolimus)-eluting stents (Resolute, Medtronic, 3.5×22 and 3.5×15 mm) (Table 8.1) in the right coronary artery (RCA) that was performed in two separate sessions

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(Figs. 8.1, 8.2, and 8.3). The left circumflex (LCX) was considered chronically occluded, and it was therefore decided to treat the lesion only if symptoms would occur during follow-up. Pre-discharge echocardiography showed a hypertrophic left ventricle with mild anterior hypokinesia and slightly decreased ejection fraction (50 %), together with mild dilatation of left atrium. Therapy at discharge included aspirin 100 mg once daily and prasugrel 10 mg once daily, together with bisoprolol 5 mg once daily, ramipril 10 mg once daily, atorvastatin 80 mg once daily, metformin 850 mg twice daily, and insulin. After 12 months, in the absence of recurrent coronary events and bleeding, prasugrel was withdrawn, and aspirin only continued lifelong.

- Current history: the patient referred herself to the emergency department because of tiredness, dizziness, and occasional palpitations over the previous 2 weeks. Indeed, short self-limiting episodes of palpitations first occurred several months earlier, with progressive worsening over the last 2 weeks. Upon physical examination, blood pressure was 165/91 mmHg, and an irregularly irregular and accelerated pulse was detected. An electrocardiogram (ECG) showed atrial fibrillation (AF) with ventricular rate approximately 89 bpm and pathological Q waves in precordial leads V1–V2 (Fig. 8.4). Ongoing therapy included aspirin 100 mg once daily, bisoprolol 5 mg once daily, ramipril 10 mg once daily, amlodipine 10 mg once daily, atorvastatin 80 mg once daily, metformin 850 mg twice daily, and insulin. The patient was admitted to hospital for rate control and start of antithrombotic therapy. Upon echocardiography, moderate left ventricular hypertrophy, mild anterior hypokinesia with normal ejection fraction (55 %), and a moderate dilatation of the left atrium were detected.

**Table 8.1** General classification of coronary stents/scaffolds

| | | |
|---|---|---|
| BMS | | (a) Stainless steel<br>(b) Non-stainless steel, cobalt-, or platinum-chrome alloy |
| DES | Early generation | (a) Durable polymer: sirolimus, paclitaxel eluting |
| | New generation | (a) Durable polymer: zotarolimus, everolimus eluting<br>(b) Biodegradable polymer: biolimus A9 and everolimus eluting<br>(c) Polymer-free: amphilimus, biolimus A9 eluting |
| BAS | | (a) Diamond-like carbon coated, titanium nitric oxide coated<br>(b) Endothelial progenitor cell capturing |
| BVS | | (a) Nondrug eluting<br>(b) Everolimus, myolimus, sirolimus eluting |

*BMS* bare-metal stent, *DES* drug-eluting stent, *BAS* bioactive stent, *BVS* bioresorbable vascular scaffold

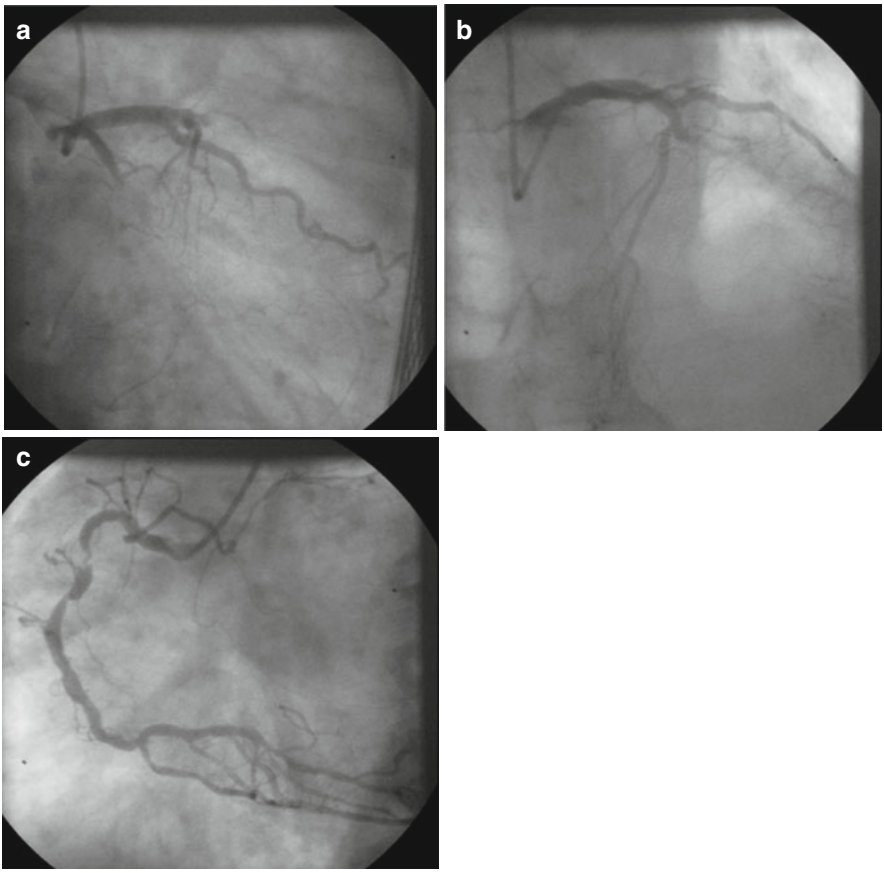


**Fig. 8.1** (**a**) RAO projection. Thrombotic occlusion of the left anterior descending. Chronic total occlusion of the circumflex artery. (**b**) AP cranial projection to visualize the acute occlusion of the LAD. (**c**) LAO projection of the right coronary artery showing critical stenosis of the medium segment. *RAO* right anterior oblique, *AP* antero-posterior, *LAO* left anterior oblique

## 8.2 Management Issues

In a patient presenting with presumably new-onset, symptomatic AF, urgent electrical cardioversion is not mandatory when hemodynamic impairment (i.e., myocardial ischemia, heart failure, symptomatic arterial hypotension, or cardiogenic shock) is not present [1]. In the presence, however, of disabling symptoms, that is, class III of the European Heart Rhythm Association (EHRA) classification (Table 8.2), pharmacological control of the rate of ventricular response of AF is advised [1].

Immediately next, decision is to be taken regarding the indication for oral anticoagulation (OAC). In this regard, stratification of the risk of stroke associated with

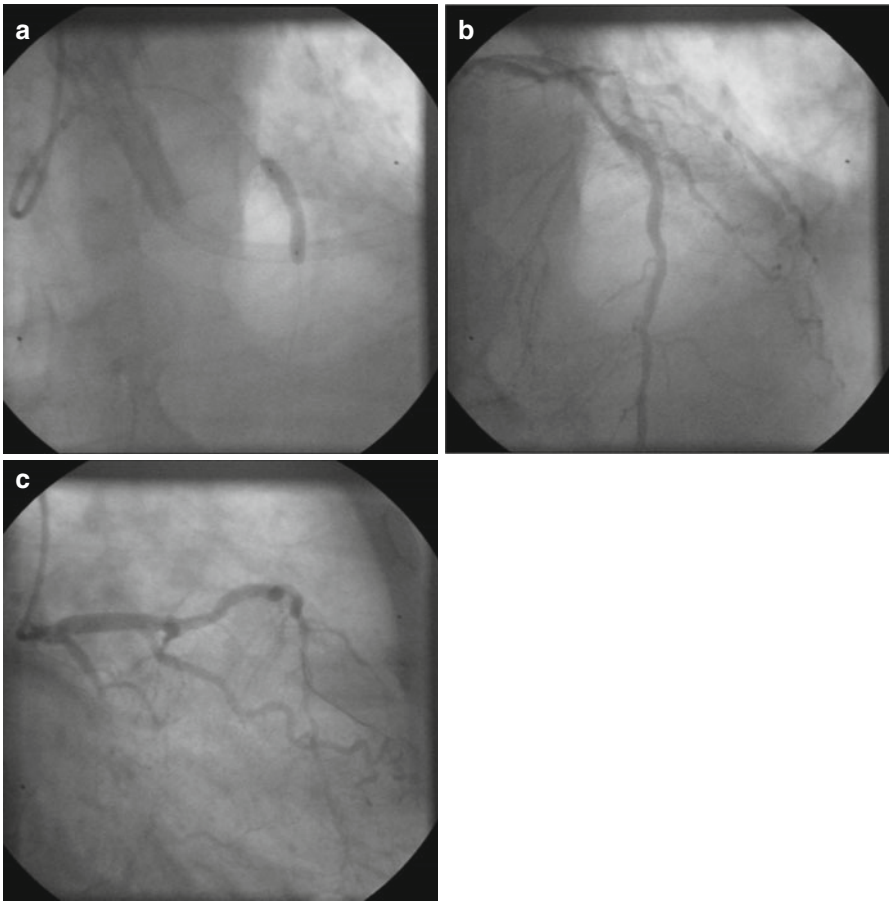


**Fig. 8.2** Primary angioplasty of the left anterior descending. (**a**): Stent implantation. (**b**): AP cranial projection: final result of the primary PCI. (**c**): RAO projection that shows a good result with TIMI 3 flow. *AP* antero-posterior, *RAO* right anterior oblique

AF needs to be carried out, preferably by using the validated $CHA_2DS_2$-VASc score [1] (Table 8.3). According to available evidence and current guidelines, for a $CHA_2DS_2$-VASc score $\geq 2$, OAC is indicated unless a prohibitive risk of bleeding is present [1]. AF pattern, that is, paroxysmal, persistent, long-standing persistent, and permanent (Fig. 8.5), should not impact on the decision to prescribe OAC, given the reported comparable risk of stroke of the different types of AF [1]. To properly manage OAC during follow-up, stratification of the risk of bleeding associated with OAC should be performed [1]. Among the several scores which have been proposed, the HAS-BLED score has been shown to be the most predictive of major bleeding complications while also being very much user-friendly (Table 8.4) [1]. The presence of a high risk of major bleeding, as identified by a HAS-BLED score $\geq 3$, however, should not lead per se to withhold OAC while mandating instead

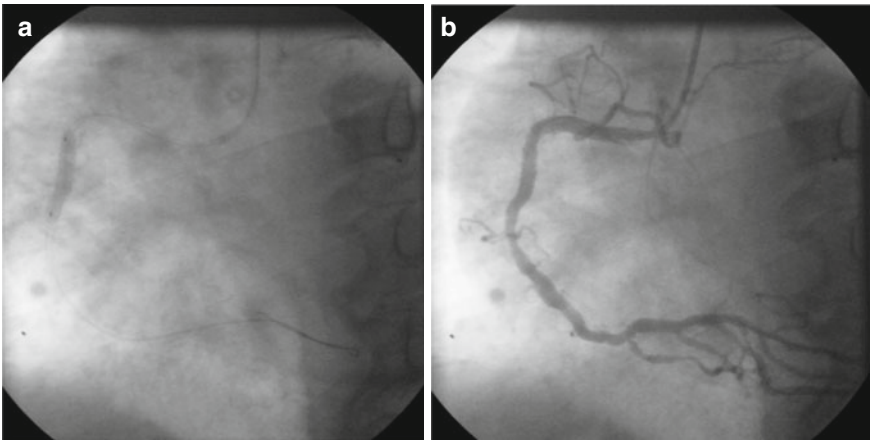


**Fig. 8.3** Angioplasty of the right coronary artery (second time). (**a**) Stent implantation. (**b**) LAO: final result of the PCI of the right coronary artery. *LAO* left anterior oblique

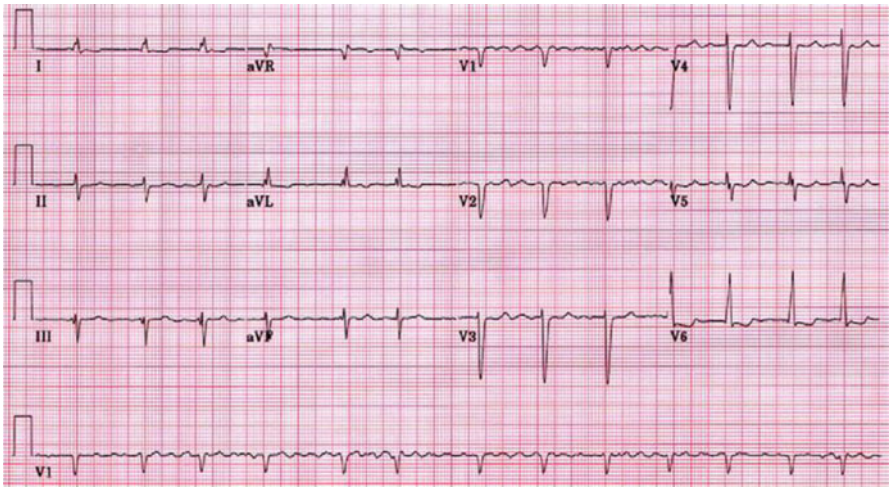


**Fig. 8.4** Electrocardiogram (ECG) at Emergency Department

attention and careful management of the correctable factors associated with increased risk of bleeding as well as careful and close patient monitoring during follow-up [2].

While continuation of antiplatelet therapy with aspirin only might be considered in a patient with new-onset AF and remote (i.e., > 1 year) implantation of either bare-metal (BMS) or drug-eluting (DES) coronary stent when the $CHA_2DS_2$-VASc score is 1 (i.e., male patient with vascular disease as the only risk factor for stroke), in the remaining categories of stroke risk, that is, $CHA_2DS_2$-VASc score $\geq 2$ (likely also including female patient with vascular disease as the only risk factor

**Table 8.2** EHRA score of AF-related symptoms [1]

| Classification of AF-related symptoms (EHRA score) | |
|---|---|
| EHRA class | Explanation |
| EHRA I | "No symptoms" |
| EHRA II | "Mild symptoms"; normal daily activity not affected |
| EHRA III | "Severe symptoms"; normal daily activity affected |
| EHRA IV | "Disabling symptoms"; normal daily activity discontinued |

**Table 8.3** $CHA_2DS_2$-VASc score and associated risk of stroke/year [1])

| | Condition | Points | Total score | Stroke risk/ year (%) |
|---|---|---|---|---|
| C | Congestive heart failure (or left ventricular ejection fraction $\leq 35\%$) | 1 | 0 | 0 |
| H | Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication) | 1 | 2 | 1.3 |
| $A_2$ | Age $\geq 75$ years | 2 | 2 | 2.2 |
| D | Diabetes mellitus | 1 | 3 | 3.2 |
| $S_2$ | Prior stroke or TIA or thromboembolism | 2 | 4 | 4.0 |
| V | Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque) | 1 | 5 | 6.7 |
| A | Age 65–74 years | 1 | 6 | 9.8 |
| Sc | Sex category (i.e., female sex) | 1 | 7 | 9.6 |
| | | | 8 | 6.7 |
| | | | 9 | 15.2 |

*TIA* transient ischemic attack

for stroke), the question is whether or not aspirin should be continued together with OAC. In accordance with available evidence and current guidelines, OAC monotherapy should be prescribed to patients with stable coronary artery disease (defined as $\geq 1$ year without recurrent events after an acute coronary syndrome and/or PCI and/or coronary bypass graft surgery) developing AF (Table 8.5) [1, 3, 4]. Combining aspirin to OAC (with vitamin K antagonists (VKAs)) in this context, in fact, appears not to bring additional benefit compared to OAC alone with respect to the prevention of stroke and recurrent cardiac events [5]. On the contrary, the risk of bleeding associated with the combination of OAC (with VKAs) and aspirin is substantially increased in comparison to monotherapy with either of the two drugs [5, 6]. Therefore, routine combination of OAC and aspirin in patient with stable coronary artery disease developing AF is discouraged while possibly being considered only in selected cases at low bleeding risk in whom stent thrombosis and/or recurrent cardiac event may have catastrophic consequences (such as previous stenting of the left main or last remaining vessel or recurrent cardiac events, especially in patients with diabetes) (Table 8.5) [1, 3, 4]. The type of stent, that is, BMS

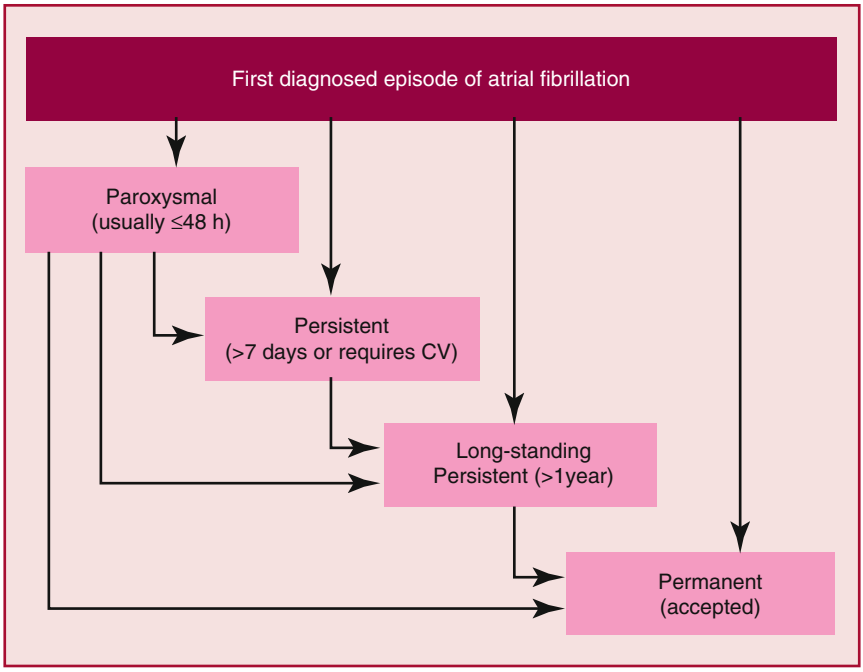


**Fig. 8.5** Definition of AF pattern [1]

**Table 8.4** HAS-BLED score and associated risk of major bleeding/year [1]

| | Condition | Points | Total score | Risk of major bleeding/year (%) |
|---|---|---|---|---|
| H | Hypertension (uncontrolled blood pressure above 160/90 mmHg) | 1 | 0 | <1 |
| A | Renal (dialysis, transplant, creatinine > 2.6 mg/dL or >200 μmol/L) and/or liver (cirrhosis, bilirubin > 2x normal or AST/ALT/AP > 3x normal) disease | 1 or 2 | 1–2 | 2–3 |
| S | Stroke | 1 | ≥ 3 | 4–12 |
| B | Bleeding (previous or predisposition to) | 1 | | |
| L | Labile INR (unstable/high or TTR < 60 %) | 1 | | |
| E | Elderly (i.e., age > 65 years) | 1 | | |
| D | Drug usage predisposing to bleeding (antiplatelet agents, NSAIDs) and/or alcohol (≥ 8 drinks a week) | 1 or 2 | | |

*INR* international normalized ratio, *TTR* time in therapeutic range, *NSAID* nonsteroidal anti-inflammatory drugs, *AST* aspartate aminotranspherase, *ACT* alanine aminotranspherase, *AP* alkaline phosphatase

or (new-generation) DES (Table 8.1), previously implanted, should generally not to impact on the choice to combine or not aspirin and OAC because the incidence of very late (i.e., > 12 months after implantation) stent thrombosis (Table 8.6) appears limited (i.e., in the range of approximately 0.5 % per year) and comparable with the two types of stent [7].

**Table 8.5** Long-term (i.e., > 12 months after PCI, in the absence of recurrent events) management recommendations

| Issue | Recommendation |
|---|---|
| Antithrombotic treatment | OAC monotherapy[a] |
| Intensity of OAC | Standard[b] |

*PCI* percutaneous coronary intervention, *OAC* oral anticoagulation, *ASA* aspirin, *CAD* coronary artery disease, *NOAC* Non-vitamin K-antagonist oral anticoagulant, *VKA* vitamin K antagonist, *INR* international normalized ratio, *BID* twice daily, *OD* once daily

[a]Indefinite combination with either low-dose ASA (75–100 mg once daily) or clopidogrel 75 mg (depending on the individual risk of bleeding, especially gastrointestinal and stent thrombosis) may be considered in special situations (e.g., left main/last remaining vessel stenting, history of stent thrombosis/recurrent cardiac events, diffuse CAD), when bleeding risk is low or when the NOAC used is dabigatran

[b]Target INR 2.0–3.0 with VKAs and dabigatran 150 mg BID, rivaroxaban 20 mg OD, and apixaban 5 mg BID with NOACs

**Table 8.6** Academic Research Consortium (ARC) definitions of stent thrombosis [8]

| | |
|---|---|
| Event Certainty | (a) Definite: acute coronary syndrome with angiographic or autopsy confirmation of stent thrombosis<br>(b) Probable:<br>(i) Unexplained death within 30 days of stent implantation without autopsy<br>(ii) Acute myocardial infarction in the territory of target vessel where stent was implanted without angiographic confirmation |
| Time frame | (a) Early:<br>(i) Acute – within 24 h of stent implantation<br>(ii) Subacute – between 24 h and 30 days of stent implantation<br>(b) Late: between 30 days and 1 year of stent implantation<br>(c) Very late: after 1 year of stent implantation |

### 8.2.1 In-hospital Management

- No indication for electrical cardioversion was given, and control of the ventricular response was pursued by increasing bisoprolol to 10 mg once daily.
- Stratification of both the risk of stroke and bleeding was performed: $CHA_2DS_2$-VASc score 5 and HAS-BLED score 2.
- Indication for OAC was then given and aspirin treatment discontinued.

## 8.3 Choice and Management of Oral Anticoagulation

While acknowledging that the evidence regarding OAC for secondary prevention in patients with coronary artery disease (without AF) is essentially obtained from datasets where a vitamin K antagonist, namely, warfarin, was the anticoagulant [9, 10],

**Table 8.7** Definition of SAMe-$TT_2R_2$ score [14]

| | Definitions | Points |
|---|---|---|
| S | Sex (female) | 1 |
| A | Age (<60 years) | 1 |
| M | Medical history[a] | 1 |
| e | | |
| T | Treatment (interacting Rx[b]) | 1 |
| T | Tobacco use (within 2 years) | 2 |
| R | Race (non-white) | 2 |
| Maximum points | | 8 |

*SAMe-TT2R2* sex female, age less than 60, medical history, treatment strategy (rhythm control), tobacco use (doubled), race (doubled)

[a]Two of the following: hypertension, diabetes, coronary artery disease, myocardial infarction, peripheral artery disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease

[b]For example, amiodarone for rhythm control

at present no specific recommendation is given regarding the OAC to choose in this setting. There is, in fact, no apparent reason why a non-vitamin K antagonist oral anticoagulant (NOAC) should act differently from VKAS, which as monotherapy after an acute coronary syndrome has been shown, in turn, to be at least as effective as aspirin [9, 10]. Available data on the combination of a NOAC with one (or two) antiplatelet agents [11–13] essentially show no interaction relative to efficacy and safety of NOAC compared to warfarin. Therefore, also in these patients with stable coronary artery disease and previous PCI, the selection of a VKA or a NOAC should be based on the same considerations valid for AF patients without associated coronary artery disease, including the individual risk of stroke and bleeding (as estimated by the $CHA_2DS_2$-VASc and HAS-BLED scores, respectively) [1], the anticipated quality of OAC with vitamin K antagonists (as evaluated by the SAMe-$TT_2R_2$ score) [14] (Table 8.7), and the anticipated compliance to OAC.

The question might on the other hand be which of the various NOACs to be chosen when a NOAC rather than warfarin has been selected. Data from randomized trials comparing NOACs to warfarin for stroke prevention in AF have shown that the use of dabigatran at both doses of 110 and 150 mg twice daily may be associated with an approximately 30 % increase in the incidence of myocardial infarction, while this finding has not been reported with rivaroxaban, apixaban, and edoxaban [15–18]. Such effect, which may be attributed to the recognized cardioprotective action of warfarin [19], appears nonetheless to have no significant impact on prognosis [20]. Also, subsequent real-world data did not confirm the finding of an increased incidence of myocardial infarction, which instead was (significantly) reduced [21, 22]. At present therefore, the fear of a higher risk of myocardial infarction with dabigatran as compared to rivaroxaban, apixaban, and edoxaban should not be a factor for the selection of a NOAC rather than another for secondary prevention after a remote acute coronary syndrome in patients also with AF [23, 24].

Finally, when NOAC rather than VKA monotherapy has been selected for both stroke prevention and secondary prevention of recurrent coronary events in a patient with previous acute coronary syndrome and PCI developing AF, the NOAC dose considered to optimize the individual net clinical benefit should be chosen. Again, both the individual risk of stroke and bleeding, as estimated by the $CHA_2DS_2$-VASc (Table 8.3) and HAS-BLED (Table 8.4) scores, respectively [1], should be evaluated, together with an estimation of renal function, as calculated by the Cockroft-Gault formula [24].

Proper follow-up should then be arranged to check for adherence to treatment, occurrence of adverse either thromboembolic or bleeding events, treatment side effects, and use of co-medications [24].

### 8.3.1 Discharge Therapy and Recommendations

- Based on the overall picture, namely, $CHA_2DS_2$-VASc score 5, HAS-BLED score 2, and SAMe-$TT_2R_2$ score 2, OAC with a NOAC rather than warfarin was selected.
- Among available NOACs, apixaban was chosen, and Cockroft-Gault formula calculated for estimation of renal function: 61 ml/min.
- Apixaban 5 mg twice daily was prescribed long term, together with bisoprolol 10 mg once daily, ramipril 5 mg twice daily, amlodipine 10 mg once daily, atorvastatin 80 mg once daily, metformin 850 mg twice daily, and insulin.
- Follow-up visit was arranged at 30 days together with blood sampling for complete blood count and glomerular filtration rate determination.

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# 9 Urgent Surgery Early After Percutaneous Coronary Intervention in a Patient with Atrial Fibrillation on Triple Therapy with a Vitamin K Antagonist, Aspirin, and Clopidogrel

Nikolaus Sarafoff, Jens Walldorf, and Axel Schlitt

## 9.1 Case Presentation

### 9.1.1 Baseline Characteristics

- Gender: male.
- Age: 66 years.
- Cardiovascular risk factors: hypertension.
- Associated diseases: permanent atrial fibrillation (AF) on chronic oral anticoagulation (OAC) with warfarin.
- Previous history: hospitalization about 1 week earlier because of acute non-ST-elevation myocardial infarction (NSTEMI) because of which urgent coronary angiography (CORO) was performed with documentation

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of severe high-grade stenosis of the left anterior descending (LAD) and no other significant stenosis (Fig. 9.1). Percutaneous coronary intervention (PCI) was then performed with implantation of a new-generation drug-eluting stent (DES) (Promus Premier, Boston Scientific, 3.0×24 mm). Owing to the estimated thromboembolic risk ($CHA_2DS_2$-VASc score 3) [1] (Table 9.1) and hemorrhagic risk (HAS-BLED score 2) [1] (Table 9.2), triple therapy (TT) with warfarin, targeting an international normalized ratio (INR) of 2.0–2.5, aspirin 100 mg once daily for 6 months, and clopidogrel 75 mg once daily for 12 months was prescribed, and a combination of hydrochlorothiazide 12.5 mg plus amlodipine 5 mg once daily, atorvastatin 40 mg once daily, and pantoprazole 20 mg once daily was added. The hospital course was uneventful and after 5 days the patient was discharged home with an application for an in-patient cardiology rehabilitation program, where he was electively admitted after 3 days.

- Current history: 5 days after hospitalization for rehabilitation, severe rectal blood loss developed, therefore prompting urgent gastroscopy and colonoscopy. Upon this latter examination, a stenotic tumor of the descending colon was found (Fig. 9.2) and multiple biopsies were taken (INR 2.2). Histologically an adenocarcinoma of the colon was diagnosed. After blood transfusion of two red blood cell concentrates, abdominal and chest computed tomographies and abdominal sonography were performed with no signs of metastasis. Indication for urgent surgical removal of the tumor was then given.

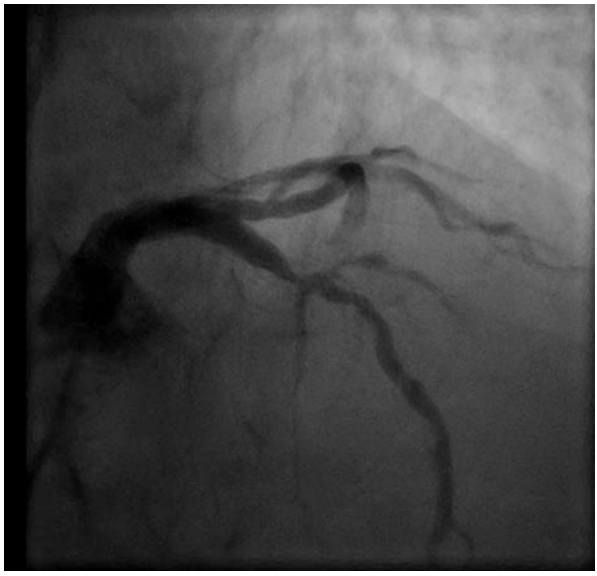


**Fig. 9.1** Coronary angiography of the left coronary artery (AP view cranial) showing high-grade stenosis of the left anterior descending (LAD). *AP* antero-posterior

**Table 9.1** $CHA_2DS_2$-VASc score and associated risk of stroke/year [1]

| | Condition | Points | Total score | Stroke risk/ year (%) |
|---|---|---|---|---|
| C | Congestive heart failure (or left ventricular ejection fraction ≤ 35 %) | 1 | 0 | 0 |
| H | Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication) | 1 | 2 | 1.3 |
| $A_2$ | Age ≥ 75 years | 2 | 2 | 2.2 |
| D | Diabetes mellitus | 1 | 3 | 3.2 |
| $S_2$ | Prior stroke or TIA or thromboembolism | 2 | 4 | 4.0 |
| V | Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque) | 1 | 5 | 6.7 |
| A | Age 65–74 years | 1 | 6 | 9.8 |
| Sc | Sex category (i.e., female sex) | 1 | 7 | 9.6 |
| | | | 8 | 6.7 |
| | | | 9 | 15.2 |

*TIA* transient ischemic attack

**Table 9.2** HAS-BLED score and associated risk of major bleeding/year [1]

| | Condition | Points | Total score | Risk of major bleeding/year (%) |
|---|---|---|---|---|
| H | Hypertension (uncontrolled blood pressure above 160/90 mmHg) | 1 | 0 | <1 |
| A | Renal (dialysis, transplant, creatinine > 2.6 mg/dL or >200 μmol/L) and/or liver (cirrhosis, bilirubin > 2x normal, or AST/ALT/AP > 3x normal) disease | 1 or 2 | 1–2 | 2–3 |
| S | Stroke | 1 | ≥3 | 4–12 |
| B | Bleeding (previous or predisposition to) | 1 | | |
| L | Labile INR (unstable/high or TTR < 60 %) | 1 | | |
| E | Elderly (i.e., age > 65 years) | 1 | | |
| D | Drug usage predisposing to bleeding (antiplatelet agents, NSAIDs) and/or alcohol (≥8 drinks a week) | 1 or 2 | | |

*INR* international normalized ratio, *TTR* time in therapeutic range, *NSAID* nonsteroidal anti-inflammatory drugs, *AST* aspartate aminotranspherase, *ACT* alanine aminotranspherase, *AP* alkaline phosphatase

## 9.2 Peri-procedural Issues

When not deferrable surgery is indicated in a patient on antithrombotic therapy, the overall management is complex. Ideally, antithrombotic therapy should be on the one hand interrupted to prevent perioperative bleeding complications and, on the other hand, continued to prevent perioperative ischemic complications, which may be even more harmful [2, 3]. Therefore, stratification of both the risk of bleeding associated with surgery and the risk of thrombosis and/or thromboembolism associated with the interruption and/or modification of antithrombotic therapy should be carried out [2, 3]. Further complexity to the perioperative management of antithrombotic therapy is added when it comprises both OAC and antiplatelet agents.

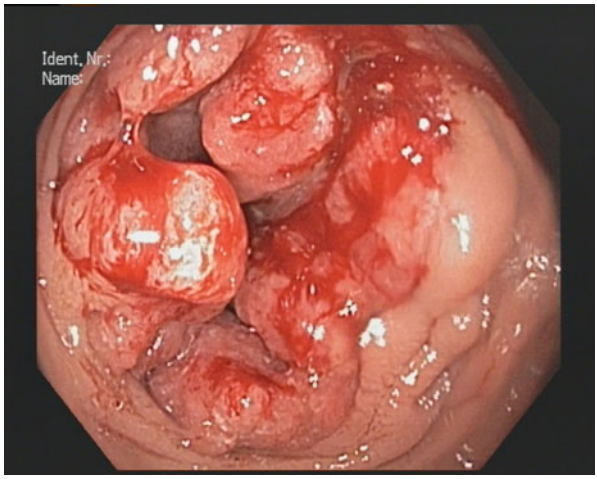



**Fig. 9.2** Colonoscopy of the descending colon showing large tumoral mass

For practical purposes, the inherent risks associated with the management of the two classes of antithrombotic agents should be evaluated (and managed) separately.

There is a high mortality rate (up to 8 %) associated with postoperative bleeding in patients undergoing surgery while on OAC with warfarin (as a result of blood transfusion, possible wound infection, occasional need for reoperation, and delayed resumption of antithrombotic therapy) [4]. Therefore, only when bleeding risk is low, it is advisable to perform surgery while being on effective OAC (i.e., INR $\geq$ 2.0) [3, 5] (Table 9.3). In patients at intermediate or high bleeding risk, timely interruption and/or reversal of OAC (depending on whether it is an elective of emergent procedure) seems reasonable [3, 5] (Table 9.4). In the elective setting, consideration should also be given to whether bridging anticoagulation with low-molecular-weight heparin (LMWH) may be required during interruption of OAC [2, 3]. Because of the increase in major bleeding complications, with no associated benefit on the incidence of thromboembolic events, perioperative bridging therapy with LMWH in patients with AF undergoing invasive procedures [2, 3] should generally not be performed. Possible exceptions may include a very high risk of stroke (such as a $CHA_2DS_2$-VASc score $\geq$ 6) and/or a history of previous stroke [3], given that interruption of OAC with warfarin has indeed been proven not to be without risks [6]. An algorithm of warfarin interruption for elective surgery is provided in Fig. 9.3 [2]. In the urgent/emergency setting, there is no time for warfarin interruption, and therefore reversal of OAC with the specific antidote vitamin K and/or nonspecific reversal agents [6] (Table 9.4) should be considered when the estimated risk of bleeding of surgery is high (or even intermediate) [2].

The perioperative management of antiplatelet therapy in patients with coronary artery disease is also complex and depends on the indication for and intensity of antiplatelet therapy. Of note, a 1.5 increase in the risk of bleeding has been reported for surgery on ongoing aspirin therapy compared to no aspirin [7], whereas that of dual antiplatelet therapy (DAPT) with aspirin and clopidogrel may be 3.4 times higher than with aspirin alone [8]. A 4 % and 21 % absolute rate of severe bleeding

**Table 9.3** Surgical procedures classified according to the associated risk of bleeding (Modified from Ref. [5])

| | High risk | Intermediate risk | Low risk |
|---|---|---|---|
| General surgery | Hepatic resection<br>Duodeno-cefalo-pancreasectomy | Hemorrhoidectomy<br>Splenectomy<br>Gastrectomy<br>Obesity surgery<br>Rectal resection<br>Thyroidectomy | Hernioplasty<br>Plastic surgery of incisional hernias<br>Cholecystectomy<br>Appendectomy<br>Colectomy<br>Gastric/intestinal resection<br>Breast surgery |
| Vascular surgery | Open thoracic and thoracoabdominal surgery | Open abdominal aorta surgery | Carotid endarterectomy<br>Bypass or endarterectomy of lower extremity<br>EVAR<br>TEVAR<br>Limb amputations |
| Cardiac surgery | Reintervention<br>Endocarditis<br>CABG in PCI failure<br>Aortic dissection | Minithoracotomy<br>TAVI (apical approach)<br>OPCAB<br>CABG<br>Valve replacement | Pacemaker, ICD, and CRT operations |
| Orthopedic surgery | Major prosthetic surgery (hip or knee)<br>Major traumatology (pelvis, long bones)<br>Fractures of the proximal femur in the elderly | Prosthetic shoulder surgery<br>Major spine surgery<br>Knee surgery (anterior cruciate ligament, osteotomies)<br>Foot surgery | Hand surgery<br>Shoulder and knee arthroscopy<br>Minor spine surgery |
| Urology surgery | Radical and partial nephrectomy<br>Percutaneous nephrostomy<br>Percutaneous lithotripsy<br>Cystectomy and radical prostatectomy<br>TURP<br>TURBT<br>Penectomy<br>Partial orchiectomy | Prostate biopsy<br>Orchiectomy<br>Circumcision | Flexible cystoscopy<br>Ureteral catheterization<br>Ureteroscopy |
| Thoracic surgery | Esophagectomy<br>Pleuropneumonectomy<br>Decortication of the lung | Lobectomy<br>Pneumonectomy<br>Mediastinoscopy<br>Sternotomy<br>Mediastinal mass excision | Wedge resection<br>Diagnostic videothoracoscopy<br>Chest wall resection |

(continued)

**Table 9.3** (continued)

| | High risk | Intermediate risk | Low risk |
|---|---|---|---|
| Digestive endoscopy | Dilatation in achalasia<br>Mucosectomy/submucosal resection<br>Echography with fine needle aspiration biopsy of pancreatic cystic lesions<br>Vater ampullectomy | Endoscopy + fine needle aspiration biopsy for solid lesions<br>Stenosis dilatation (esophageal, colorectal)<br>Gastroenteric stents<br>Argon plasma coagulation treatment<br>Polypectomy (polyps >1 cm)<br>PEG (percutaneous endoscopic gastrostomy)<br>Binding/variceal sclerosis<br>Binding/hemorrhoid sclerosis | EGD or colonoscopy +/− biopsy<br>Echoendoscopy without biopsy<br>Polypectomy (polyps <1 cm)<br>ERCP, stent, dilated papilla without sphincterotomy |

**Table 9.4** Characteristics of therapies for warfarin reversal [6]

| | Time to effect (after administration) | Duration of effect | Evidence of efficacy for warfarin reversal | Risk of thrombosis |
|---|---|---|---|---|
| Oral vitamin K | 24 h | Days | ++++ | Not significant |
| Intravenous vitamin K | 8–12 h | Days | ++++ | Not significant |
| Fresh frozen plasma | Immediate | 12–24 h | ++ | Not significant |
| Prothrombin complex concentrates | Immediate | 12–24 h | +++ | +[a] |
| Recombinant factor VII | Immediate | 2–6 h | + | ++ |

[a]Higher with activated prothrombin complex concentrates

with ongoing single and DAPT, respectively, have been reported within 30 days of noncardiac surgery [9]. In addition to that, consideration to perform surgery on DAPT precludes the use of locoregional anesthesiological techniques (namely, neuroaxial), which are currently preferred due to their greater ability to lower sympathetic stimulation and give better control of perioperative pain [10]. Of note, perioperative withdrawal of aspirin in patients at risk of, or with proven, coronary artery disease increases the risk of adverse cardiac events by a factor of three [3]. General recommendations for the perioperative management of antiplatelet therapy in patients with coronary artery disease are given in Table 9.5 [11].

Given that every year > 1 million PCI (with stent implantation in approximately 85 % of cases) are performed in Europe and the USA and that 4–8 % of these patients undergo surgery within 1 year and 25 % within 5 years [12, 13], the management of antiplatelet therapy in this setting is an issue of great relevance. Early interruption of antiplatelet therapy is in fact the most potent predictor of stent thrombosis [14], which is in turn, associated with a rate of myocardial infarction and death of 50–70 %

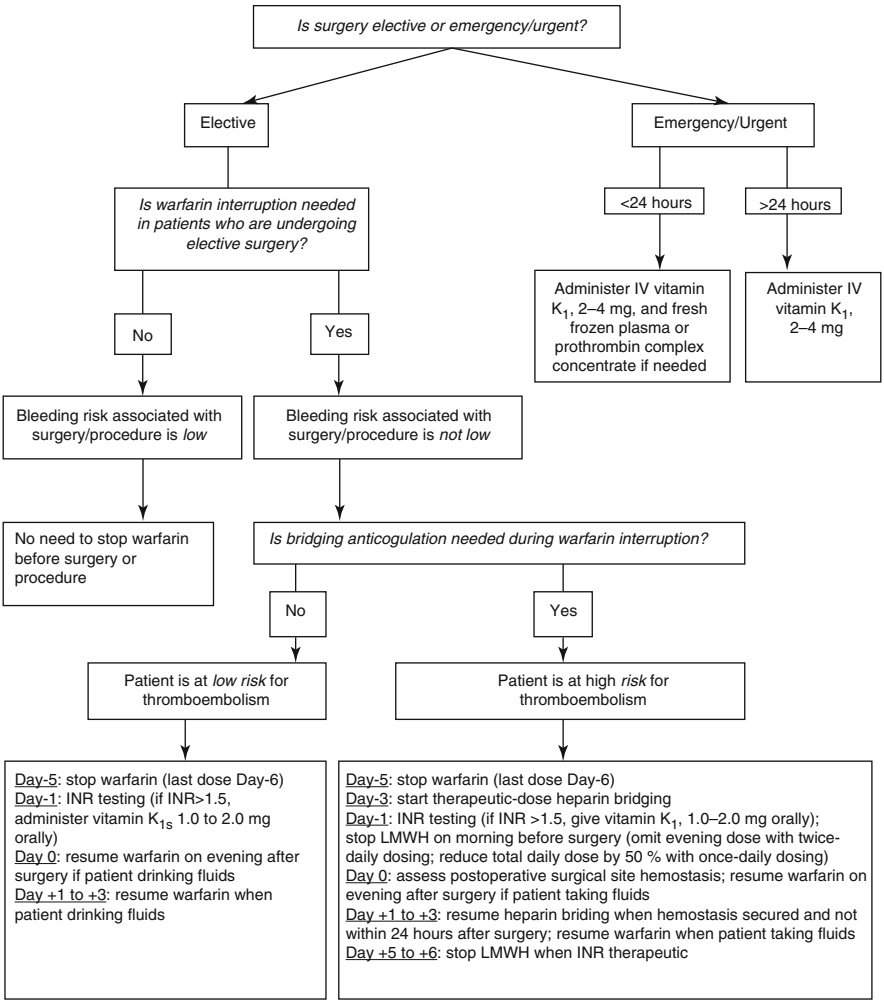



**Fig. 9.3** Algorithm for the perioperative management of oral anticoagulation with warfarin [2]

and 20–40 %, respectively [14]. In addition, surgery leads to an inflammatory, hypercoagulable, and hypoxic condition, which may result in plaque instability and perioperative arterial thrombosis [13]. These factors contribute to increased rates of adverse cardiac events, including death myocardial infarction and need for revascularization, when surgery is performed early after stent implantation, especially within the first month [15, 16].

In AF patients after coronary stent implantation who receive TT consisting of warfarin, aspirin, and clopidogrel in whom surgery is planned, the risk of stent thrombosis, surgical bleeding (Table 9.3), and thromboembolism (Table 9.1) needs to be estimated. The time elapsed from stent implantation and the type of stent implanted are the main variables to be considered for such risk stratification [5] (Table 9.6). Two new large-scale randomized studies have impressively shown that

**Table 9.5** Suggested perioperative management of antiplatelet therapy [11]

◆ Extends also to patients on clopidogrel monotherapy

**Minor surgery:** do not stop antiplatelet therapy

Implement **multidisciplinary consult** in patients with ( potential) bleeding complications.
Low molecular weight heparin: NOT a substitute for platelet inhibting drugs.
Avoid plasmatic anticoagulation (LMWH, OAC) during surgery.

| Major surgery and | How to proceed | Exception | How to proceed with exception |
|---|---|---|---|
| Aspirin for primary prevention ◆ | Stop aspirin 5 days before surgery ◆ | | |
| Aspirin in high-risk patients ◆ (diabetes, history of CV events, documented CV disease, increased global risk | Continue aspirin ◆ | Surgery in closed space expected major bleeding complications | • Stop aspirin 5 days before surgery ◆<br>• Consider restarting within 24 h◆ |
| Aspirin plus clopidogrel in high risk patients<br>© HICC | 1. Electric surgery: delay until no dual inhibition necessary<br>2. Semi-urgent surgery: continue aspirin ± clopidogrel on a case by case basis<br>3. Urgent surgery (within 24 h); continue aspirin and clopidogrel | Surgery in closed space, expected major bleeding complications | *if delaying surgery not possible / semi-urgent surgery necessary:*<br>• Stop clopidogel 5 days before surgery, consider bridging (short acting GPIIb/IIIa antagonist<br>• Consider stopping also aspirin in particular patients<br>• Consider resuming dual antiplatelet therapy asap |

**Table 9.6** Timing of surgery and risk of stent thrombosis

| High risk | Intermediate risk | Low risk |
|---|---|---|
| <1 month after PCI with BMS<br><1 month after PCI with new-generation DES<br><3 months after complex PCI with new-generation DES (long stents, multiple stents, overlapping, small vessels, bifurcations, left main, last remaining vessel)<br><6 months after PCI with first-generation DES | 1–6 months after PCI with BMS<br>1–6 months after PCI with new-generation DES<br>3–12 months after complex PCI with new-generation DES (long stents, multiple stents, overlapping, small vessels, bifurcations, left main, last remaining vessel)<br>6–12 months after PCI with first-generation DES | >6 months after PCI with BMS or new-generation DES<br>>12 months after PCI with first-generation DES |

Modified from Refs. [5, 17, 18]

among patients at high risk for bleeding using a new-generation drug-eluting stent is superior to a bare-metal stent with respect to MACE and revascularization rates even when used with a shorter 1-month course of DAPT [17, 18]. In addition, new-generation DES (Table 9.7) may confer a lower thrombotic risk as compared to first-generation DES, thus allowing an earlier discontinuation (<6 months) of DAPT, when necessary [19, 20]. Especially in the setting of TT, current European Society of Cardiology (ESC) guidelines recommend only 1 month of DAPT after implantation of new-generation DES when the bleeding risk is high [21]. An algorithm to determine the risk of stent thrombosis is provided in Fig. 9.4 [22].

**Table 9.7** General classification of coronary stents/scaffolds

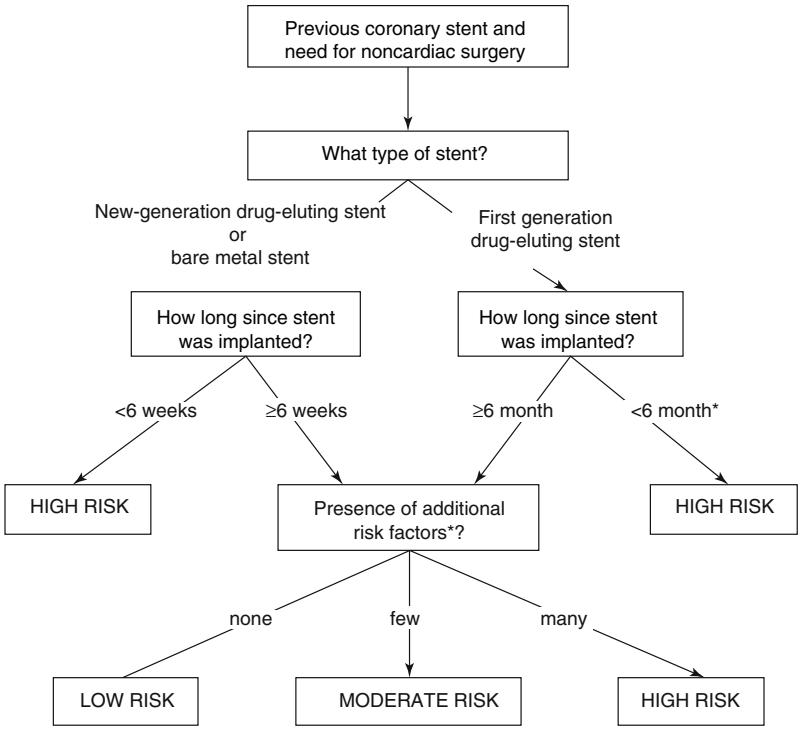
| | | |
|---|---|---|
| BMS | | (a) Stainless steel<br>(b) Non-stainless steel, cobalt- or platinum-chrome alloy |
| DES | Early-generation | (a) Durable polymer: sirolimus-, paclitaxel-eluting |
| | New-generation | (a) Durable polymer: zotarolimus-, everolimus-eluting<br>(b) Biodegradable polymer: biolimus A9 and everolimus-eluting<br>(c) Polymer-free: amphilimus-, biolimus A9-eluting |
| BAS | | (a) Diamond-like carbon-coated, titanium nitric oxide-coated<br>(b) Endothelial progenitor cell-capturing |
| BVS | | (a) Nondrug-eluting<br>(b) Everolimus-, myolimus-, sirolimus-eluting |

*BMS* bare-metal stent, *DES* drug-eluting stent, *BAS* bioactive stent, *BVS* bioresorbable vascular scaffold

Discontinuation of DAPT should not be performed for surgical procedures at low bleeding risk, especially if the risk of stent thrombosis is high or moderate [3, 5] (Tables 9.3 and 9.6). In some cases, however, discontinuation of DAPT is necessary when the risk of bleeding is very high (Tables 9.3 and 9.6). While continuing aspirin is mostly possible, bridging antiplatelet therapy with intravenous short-acting glycoprotein IIb/IIIa inhibitors, including tirofiban and eptifibatide, may be considered to limit the risk of stent thrombosis [3, 5, 22]. In observational, non-randomized studies in which this strategy was adopted, no adverse cardiac events were observed, with low rates of bleeding and transfusion (in relation to the types of surgery) and no bleeding complications requiring reoperation [23–26]. Stopping both aspirin and clopidogrel should only be performed in patients for whom a bleeding complication could be catastrophic, such as patients undergoing neurosurgical procedures. An algorithm of bridging therapy with intravenous, short-acting glycoprotein IIb/IIIa inhibitors is provided in Fig. 9.5.

### 9.2.1 Peri-procedural Management

- Oral administration of vitamin K 2 mg was performed and DAPT with aspirin and clopidogrel continued.
- Surgical intervention was planned for the next day upon reversal of OAC.
- Hemicolectomy with nearby lymph node removal was performed the next morning after confirmation of INR < 1.5 and under general anesthesia. Great care was put in intraoperative hemostasis and multiple drainages were inserted to monitor bleeding.
- Histologic examination of the removed mass yielded a final diagnosis of colorectal adenocarcinoma stage IIA (T3, N0, M0), i.e., the cancer has grown into the outermost layers of the colon or rectum but has not gone through them (T3), has not reached nearby organs, and has not yet spread to nearby lymph nodes (N0) or to distant sites (M0). Accordingly, oncological follow-up care was advised.




***Additional risk factors for stent thrombosis**

| **Coronary anatomy** | **Stent-Indication** | **Patient** |
|---|---|---|
| Bifurcation stenting | Acute coronary syndrome | Diabetes |
| Ostial stenting | | Renal impairment |
| Small (<2.0 mm) stent diameter | | Advanced age |
| Long (>18 mm) stent length | | Low ejection fraction |
| Overlapping stents | | Prior brachytherapy |
| Multiple stents | | |
| Suboptimal result | | |

**Fig. 9.4** Stratification of the perioperative risk of stent thrombosis (Modified from Ref. [22])

## 9.3 Post-procedural Issues

Following surgery, the key issue is when and how to restart antithrombotic therapy. Again, the decision should be based on the risk of perioperative bleeding, stent thrombosis and adverse cardiac events, and thromboembolism. Provided that effective hemostasis has been obtained, and the risk of post-procedural bleeding is

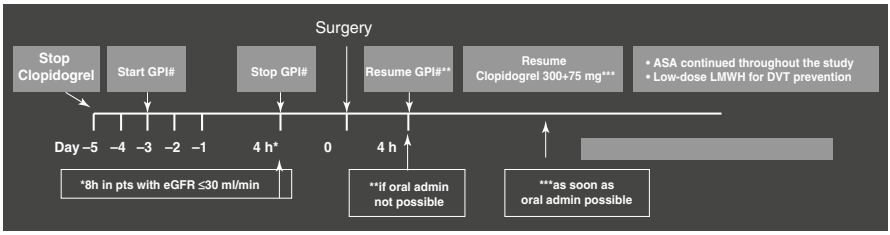



**Fig. 9.5** Scheme for bridging infusion of short-acting glycoprotein IIb/IIIa inhibitors in patients candidates for early surgery after coronary artery stenting

deemed low, OAC with warfarin should be restarted as soon as fluid drinking is allowed. A 5 mg dose should generally be given for the first 2 days with subsequent doses adjusted based on the INR values of the following days. In the absence of a very high risk of stroke (i.e., a $CHA_2DS_2$-VASc score $\geq 6$ and/or a history of previous stroke), no full-dose, bridging therapy with LMWH is generally required [2, 3]. Instead, prophylaxis of venous thromboembolism with subcutaneous, low-dose (i.e., enoxaparin 4.000 IU/day) LMWH is recommended [3, 27]. Upon reaching a therapeutic INR value (i.e., > 2.0), LMWH should be discontinued. When restarting OAC, consideration may be given nowadays to use a newer, non-vitamin K antagonist oral anticoagulant (NOAC), including dabigatran, rivaroxaban, apixaban, or edoxaban. These agents have been generally shown to be safer than and at least as effective as warfarin when used for stroke prevention in AF [28–31] (Table 9.8). While being more convenient than warfarin because of the less cumbersome dosing schedule, the more predictable dose-response relationship, the absence of food interaction, the few drug interactions, and the need for no routine monitoring, such option may be of questionable value when considered after a bleeding event associated with the presence of an organic lesion. In this context in fact, bleeding is likely to occur regardless of the OAC used as long as the lesion is not removed. Also, it should be considered that while consistently and dramatically reducing the incidence of intracranial bleeding, NOACs (with the exception, however, of dabigatran 110 mg twice daily and apixaban 5 mg twice daily) have been shown overall to increase the risk of gastrointestinal bleeding compared to warfarin [32] (Table 9.8).

Regarding post-procedure antiplatelet therapy, either continuation of DAPT, if not previously interrupted, or resumption of clopidogrel (in addition to ongoing aspirin), if previously withheld, should be carried out as long as indicated by the clinical condition because of which PCI has been performed (i.e., stable effort angina vs. acute coronary syndrome) and the type of stent implanted (i.e., bare-metal and new-generation DES vs. first-generation DES). Restarting of clopidogrel should be carried out as soon as possible when fluid drinking is allowed [2, 3].

When surgery has been performed close to the time when TT should be downgraded to dual combination of OAC and a single antiplatelet agent (either aspirin or clopidogrel), that is, 1–6 months from the index event [21, 33, 34], consideration may be given not to resume DAPT.

**Table 9.8** Efficacy and safety of non-vitamin K antagonist oral anticoagulants vs. warfarin in clinical trials (hazard ratio, 95 % confidence intervals) [28–31]

| | Dabigatran 110 mg BID | Dabigatran 150 mg BID | Rivaroxaban 20 mg[a] OD | Apixaban 5 mg[b] BID | Edoxaban 30 mg BID | Edoxaban 60 mg BID |
|---|---|---|---|---|---|---|
| Stroke or systemic embolism | 0.91[c] (0.74–1.11) | 0.66[d] 0.53–0.82) | 0.88[c] (0.74–1.03) | 0.79[d] (0.66–0.95) | 1.07[c] (0.87–1.31) | 0.79[c] (0.63–0.99) |
| Major bleeding | 0.80[e] (0.69–0.93) | 0.93 (0.81–1.07) | 1.04 (0.90–1.20) | 0.69[e] (0.60.0.80) | 0.47[e] (0.41–0.55) | 0.80[e] (0.71–0.91) |
| Intracranial bleeding | 0.31[e] (0.20–0.47) | 0.40[e] (0.27–0.60) | 0.67[e] (0.47–0.93) | 0.42[e] (0.30–0.58) | 0.30[e] (0.21–0.43) | 0.47[e] (0.34–0.63) |
| Gastrointestinal bleeding | 1.10 (0.86–1.41) | 1.50[e] (1.19–1.89) | 1.60[e] (1.29–1.98) | 0.89 (0.70–1.15) | 0.67[e] (0.53–0.83) | 1.23[e] (1–02–1.50) |

*BID* twice daily, *OD* once daily
[a]115 mg OD in patients with creatinine clearance 30–50 ml/min
[b]22.5 mg BID in patients with two of the following three features: age ≥ 80 years, weight ≤ 60 kg, creatinine ≥ 1.5 ml/min
[c]Significant for non-inferiority
[d]Significant for superiority
[e]Statistically significant

### 9.3.1 Post-procedural Management

- Following surgery, the patient was first admitted to the intensive care unit and then transferred to the surgery ward, before being transferred again to the rehabilitation clinic.
- Warfarin was restarted 2 days after surgery when the drainages were removed and no bleeding was observed. No bridging anticoagulation was performed, but the patient received subcutaneous enoxaparin (4000 IU once daily) for thromboprophylaxis until the INR reached 2.0.
- DAPT with aspirin and clopidogrel was continued with the indication to stop clopidogrel 12 months and aspirin 6 months after index PCI.
- Remaining therapy with combination of hydrochlorothiazide 12.5 mg plus amlodipine 5 mg once daily, atorvastatin 40 mg once daily, and pantoprazole 20 mg once daily was confirmed.

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# 10 Urgent Surgery Early After Percutaneous Coronary Intervention in a Patient with Atrial Fibrillation on Triple Therapy of Non-vitamin K Antagonist Oral Anticoagulant, Aspirin, and Clopidogrel

Giuseppe Patti and Ilaria Cavallari

## 10.1 Case Presentation

### 10.1.1 Baseline Characteristics

- Gender: female.
- Age: 75 years.
- Cardiovascular risk factors: hypertension, type 2 diabetes, previous smoker (20 cigarettes/day for 40 years, quit 10 years before, and obesity) (body mass index 30.2 kg/m$^2$).
- Associated diseases: chronic obstructive pulmonary disease.
- Previous history: new-onset atrial fibrillation (AF) approximately 18 months before, unresponsive to both pharmacological (with amiodarone) and electrical cardioversion. A rate-control strategy was then selected and, after an echocardiogram, showing left ventricular hypertrophy with no dilatation, no wall motion abnormalities, normal ejection fraction and no significant valvular heart disease, and evaluation of renal function, showing a mild reduction of the estimated glomerular filtration rate (GFR) (55 ml/min) [1] (Table 10.1), oral anticoagulation (OAC) with the non-vitamin K antagonist oral anticoagulant (NOAC) rivaroxaban at the dose of 20 mg/day and bisoprolol 5 mg/day were prescribed. Ongoing therapy with insulin, ramipril 10 mg once daily, and bronchial dilators was confirmed.

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- Recent history: five weeks before current admission, the patient underwent primary coronary intervention (PCI) with implantation of a new-generation drug-eluting stent (DES) (Promus Premiere 3.0×20 mm, Boston Scientific) (Table 10.2) in a large marginal branch (Fig. 10.1) because of an acute, lateral ST-elevation myocardial infarction (STEMI) (Fig. 10.2). Due to the high risk of stroke ($CHA_2DS_2$-VASc score 6) [2] (Table 10.3), OAC with rivaroxaban was maintained at the reduced dose however of 15 mg once daily because of the addition of dual antiplatelet therapy (DAPT) with aspirin (300 mg load followed by 100 mg once daily orally) and clopidogrel (600 mg load followed by 75 mg once daily orally) [3–5]. In-hospital course was uneventful and predischarge echocardiogram showed mild dilation of the left atrium, left ventricular ejection fraction 50 %, without LV enlargement, and with hypokinesia of the lateral LV wall. The patient was discharged on triple antithrombotic therapy [3–5] associated with ramipril 10 mg/day, bisoprolol 5 mg/day, pantoprazole 20 mg/day, and atorvastatin 80 mg/day (in addition to insulin and bronchial dilators). Based on the thromboembolic and bleeding risk (HAS-BLED 3) [2] (Table 10.4), triple therapy was intended to be continued for 6 months and then substituted by aspirin 100 mg once daily and rivaroxaban at the standard dose of 20 mg once daily up to 1 year after index event when rivaroxaban 20 mg once daily monotherapy was to be continued lifelong [3–5].
- Current history: while at home, the patient tripped over the carpet when trying to reach the ringing phone and fell down. The ambulance service was called, and the patient was transported to the emergency department, where she continued complaining of severe right shoulder pain together with bruising and swelling around that area. Clinical and X-ray examination showed a three-part fracture of the proximal humerus. Pain killers were prescribed and early surgical treatment was considered indicated.

**Table 10.1** Stages of chronic kidney disease (www.kdigo.org)

| CKD stage | Description | GFR (ml/min per 1.73 $m^2$) |
|---|---|---|
| 1 | Kidney damage with normal or increased GFR | ≥90 |
| 2 | Kidney damage with mild decreased GFR | 60–89 |
| 3 | Moderate decreased GFR | 30–59 |
| 4 | Severe decreased GFR | 15–29 |
| 5 | Kidney failure | <15 (or dialysis) |

*GFR* glomerular filtration rate

**Table 10.2** General classification of coronary stents/scaffolds

| | | |
|---|---|---|
| BMS | | (a) Stainless steel<br>(b) Non-stainless steel, cobalt- or platinum-chrome alloy |
| DES | Early-generation | (a) Durable polymer: sirolimus-, paclitaxel-eluting |
| | New-generation | (a) Durable polymer: zotarolimus-, everolimus-eluting<br>(b) Biodegradable polymer: biolimus A9 and everolimus-eluting<br>(c) Polymer-free: biolimus A9-, amphilimus-eluting |
| BAS | | (a) Diamond-like carbon-coated, titanium nitric oxide-coated<br>(b) Endothelial progenitor cell-capturing |
| BVS | | (a) Nondrug-eluting<br>(b) Everolimus-, myolimus-, sirolimus-eluting |

*BMS* bare-metal stent, *DES* drug-eluting stent, *BAS* bioactive stent, *BVS* bioresorbable vascular scaffold

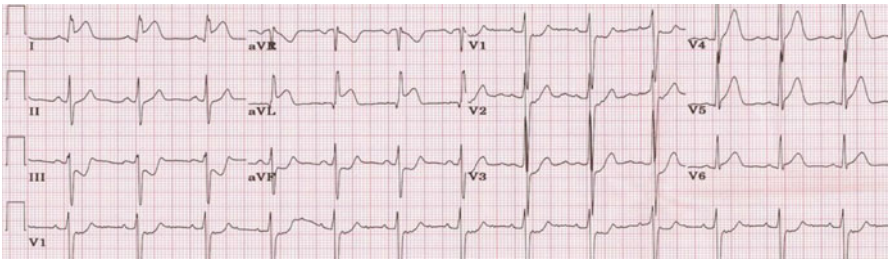


**Fig. 10.1** Electrocardiogram (ECG) on admission

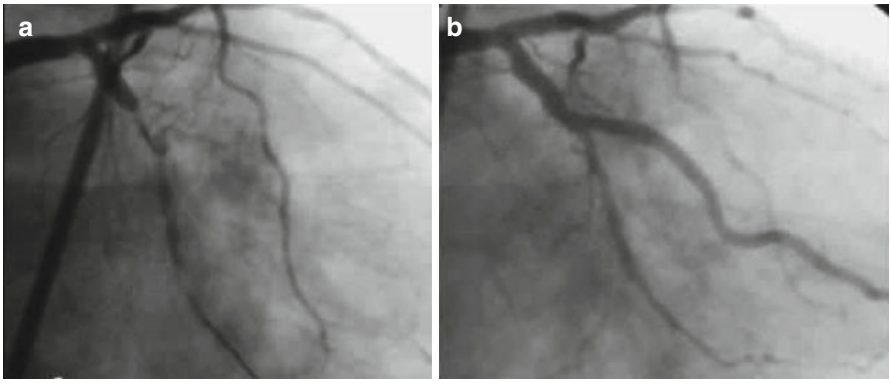


**Fig. 10.2** Coronary angiography of the left coronary artery (*RAO view*) at baseline (**a**) and after stent implantation (**b**). RAO: right anterior oblique

**Table 10.3** $CHA_2DS_2$-VASc score and associated risk of stroke/year [37]

| | Condition | Points | Total score | Stroke risk/ year (%) |
|---|---|---|---|---|
| C | Congestive heart failure (or left ventricular ejection fraction ≤ 35 %) | 1 | 0 | 0 |
| H | Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication) | 1 | 1 | 1.3 |
| $A_2$ | Age ≥ 75 years | 2 | 2 | 2.2 |
| D | Diabetes mellitus | 1 | 3 | 3.2 |
| $S_2$ | Prior stroke or TIA or thromboembolism | 2 | 4 | 4.0 |
| V | Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque) | 1 | 5 | 6.7 |
| A | Age 65–74 years | 1 | 6 | 9.8 |
| Sc | Sex category (i.e., female sex) | 1 | 7 | 9.6 |
| | | | 8 | 6.7 |
| | | | 9 | 15.2 |

*TIA* transient ischemic attack

**Table 10.4** HAS-BLED score and associated risk of major bleeding/year [37]

| | Condition | Points | Total score | Risk of major bleeding/year (%) |
|---|---|---|---|---|
| H | Hypertension (uncontrolled blood pressure above 160/90 mmHg) | 1 | 0 | <1 |
| A | Renal (dialysis, transplant, creatinine > 2.6 mg/dL or >200 μmol/L) and/or liver (cirrhosis, bilirubin > 2x normal, or AST/ALT/AP > 3x normal) disease | 1 or 2 | 1–2 | 2–3 |
| S | Stroke | 1 | ≥3 | 4–12 |
| B | Bleeding (previous or predisposition to) | 1 | | |
| L | Labile INR (unstable/high or TTR < 60 %) | 1 | | |
| E | Elderly (i.e., age > 65 years) | 1 | | |
| D | Drug usage predisposing to bleeding (antiplatelet agents, NSAIDs) and/or alcohol (≥8 drinks a week) | 1 or 2 | | |

*INR* international normalized ratio, *TTR* time in therapeutic range, *NSAID* nonsteroidal anti-inflammatory drugs, *AST* aspartate aminotranspherase, *ACT* alanine aminotranspherase, *AP* alkaline phosphatase

## 10.2 Perioperative Issues

The perioperative management of DAPT and OAC in patients with AF candidates to surgery early after coronary stenting is challenging, because a balance between the competing risks of thromboembolism (after interruption of OAC), cardiac events (after interruption of antiplatelet therapy), and perioperative bleeding is required. Both ischemic and bleeding events are known to adversely affect survival, and therefore an inadequate or excessive antithrombotic therapy may contribute to higher mortality [6]. Thus, a careful stratification of the patient's risk profile for bleeding and thrombotic events (related to either in situ coronary thrombosis or cardiac thromboembolism) appears crucial. This assessment, in particular, also

includes the type of operation in addition to the persistent indication for both antiplatelet therapy and OAC and to patient-specific factors predisposing to either bleeding or thrombosis.

As regards the risk of bleeding, surgery can be classified as high risk (i.e., 2–4 % two-day risk of major bleeding) or very low/low risk (i.e., 0–2 % two-day risk of major bleeding) [7] (Table 10.5). Furthermore, specific patient-related factors, including advanced age, low body weight, uncontrolled hypertension, reduced liver and/or kidney function, history of bleeding, and concomitant antithrombotic medications, should be considered when stratifying the surgical risk of bleeding [8].

As regards the risk of cardiac ischemic events, it has been established that premature discontinuation of DAPT is associated with an increased occurrence of stent thrombosis, a serious complication with mortality rates of 20–45 % [9–12]. The magnitude of the risk essentially depends on the timing of discontinuation and on the type of stent implanted. Moving away from the time of coronary intervention, the risk of perioperative death, myocardial infarction, and stent thrombosis has been shown to decrease from 30 % in the first month (regardless of the type of stent implanted), to

**Table 10.5** Bleeding risk according to the type of surgery (Adapted from Ref. [3])

| |
|---|
| Operations/procedures with very low bleeding risk |
| Dental interventions (extraction of one to three teeth, paradontal surgery, incision of abscess) |
| Cataract or glaucoma intervention |
| Endoscopy without biopsy |
| Superficial surgery (abscess incision, small dermatologic excisions) |
| Operations/procedures with low bleeding risk |
| Endoscopy with biopsy |
| Prostate, thyroid, breast, or bladder biopsy |
| Electrophysiological study or catheter ablation of the right-side heart |
| Pacemaker or ICD implantation |
| Shoulder/foot/hand surgery and arthroscopy |
| Hemorrhoidal surgery |
| Operations/procedures with high bleeding risk |
| Catheter ablation of the left-side heart |
| Spinal or epidural anesthesia |
| Procedures with puncture of a major artery |
| Lumbar puncture |
| Liver or kidney biopsy |
| Extracorporeal shockwave lithotripsy |
| Polypectomy |
| Transurethral prostate/bladder resection |
| Thoracic or abdominal surgery |
| Major orthopedic surgery |
| Cardiac or vascular surgery |
| Head and neck surgery |
| Neurosurgery |

10–15 % between 2 and 6 months, and to <10 % after 6 months [13–17]. Early stent thrombosis (i.e., in the first 30 days after PCI) (Table 10.6) occurs with both bare-metal stents (BMS) and DES and may be related to residual target lesion thrombus or dissection, stasis, or stent underexpansion [18]. Late stent thrombosis (i.e., between 1 month and 1 year after PCI) and very late stent thrombosis (>1 year after PCI) are most often observed in DES, especially with early-generation devices (Table 10.2), and thought to be related to incomplete healing or inadequate neo-intimal coverage [19]. Independently of stent thrombosis, other patient-related and procedure-related predictors of further cardiac ischemic events in patients undergoing PCI include intervention for an acute coronary syndrome (ACS), concomitant diabetes mellitus, presence of diffuse coronary artery disease, implantation of small stents or long/multiple stents, intervention for in-stent restenosis, and large areas of jeopardized myocardium [20, 21]. Of note, the risk of recurrence of major cardiac events after an ACS is higher in the first weeks.

Optimal duration of DAPT after PCI is currently a matter of debate. In patients undergoing coronary revascularization for ACS, DAPT is recommended for 1 year, irrespective of the stent type [5, 22], with the aim to decrease the occurrence of re-infarction and cardiovascular mortality related to either stent thrombosis or events unlinked to the target vessel (i.e., multifocal coronary plaque instability, progression of coronary atherothrombosis) [23]. On the other hand, in the setting of stable coronary artery disease, a routine prolongation of DAPT beyond 6 months after new-generation DES implantation cannot be recommended, given the well-established risk of bleeding and the lack of evidence that extended duration DAPT may further prevent ischemic events [22]. Recent data with new-generation zotarolimus-eluting and everolimus-eluting stents suggest that even a shorter DAPT duration (i.e., 3 months) does not expose the patient to higher incidence of stent thrombosis [24–26]. However, to date a 3-month (or shorter) duration of DAPT after new-generation DES implantation should be reserved for patients at high risk of bleeding or requiring OAC [5]. Additional data are needed to confirm and definitely extend this strategy in routine clinical practice.

When a patient on DAPT is undergoing surgery, the risk of bleeding inherent to surgery and individual patient should guide the management of antiplatelet therapy.

**Table 10.6** Academic research consortium (ARC) definitions of stent thrombosis [38]

| | |
|---|---|
| Event certainty | (a) Definite: acute coronary syndrome with angiographic or autopsy confirmation of stent thrombosis<br>(b) Probable:<br>(i) Unexplained death within 30 days of stent implantation without autopsy<br>(ii) Acute myocardial infarction in the territory of target vessel where stent was implanted without angiographic confirmation |
| Time frame | (a) Early:<br>(i) Acute – within 24 h of stent implantation<br>(ii) Subacute – between 24 h and 30 days of stent implantation<br>(b) Late: between 30 days and 1 year of stent implantation<br>(c) Very late: after 1 year of stent implantation |

DAPT should not be withdrawn for surgery at very low bleeding risk (Table 10.5), and aspirin should be continued in the large majority of surgical interventions [5]. Interruption of aspirin from 7 days prior to surgery at high bleeding risk may be considered only in patients who are not considered at high risk of cardiovascular events [27]. Current guidelines recommend before cardiac and noncardiac surgery interrupting clopidogrel and ticagrelor for at least 5 days and prasugrel at least 7 days before the operation and continuing aspirin [5]. Of note however, the relationship between the time of withdrawal of antiplatelet agent and incidence of postoperative bleeding appears uncertain [28]. Also, the increase in surgical blood loss associated with any single antiplatelet agent as well as DAPT appears doubtfully associated with patient mortality in orthopedic surgery [28].

After surgery, DAPT should be resumed, if possible, within 24 h including a loading dose [5]. Using low-molecular-weight heparin (LMWH) or unfractionated heparin as a bridging therapy is not recommended, as heparins do not have antiplatelet properties and could even increase platelet reactivity. In patients at high risk of cardiovascular events, such as those with ongoing myocardial ischemia and/or complex anatomy (e.g., left main or severe, proximal multivessel disease), candidates to early bypass surgery, withdrawal of clopidogrel is not recommended, and these patients should undergo the operation while on DAPT with special care to hemostasis [5]. Only in patients undergoing cardiac operations with very high bleeding risk, such as redo bypass surgery or combined interventions of bypass plus valve surgery, it may be reasonable to withhold clopidogrel for 3–5 days before surgery (i.e., even in patients with active myocardial ischemia), and bridging strategies can be considered [5].

In general, DAPT interruption should be evaluated on an individual basis considering the bleeding risk of surgery, the patient's cardiac risk profile (also including the time interval from PCI), and the type of stent. In patients on DAPT after coronary stenting candidates to operation/procedures at low bleeding risk, the $P2Y_{12}$ antagonist is generally interrupted if the cardiac ischemic risk is deemed to be low and the intervention, if possible, deferred if the ischemic risk is high. In patients undergoing high bleeding risk surgery who are also at high risk of ischemic events and in whom cessation of antiplatelet therapy is considered to be too hazardous (i.e., within the first weeks after stent implantation), it may be considered to switch from clopidogrel 5 days before surgery to a reversible antiplatelet agent with a short half-life, such as continuous infusion of the glycoprotein IIb/IIIa inhibitors tirofiban or eptifibatide [5] (Fig. 10.3). In an observational experience, such protocol has indeed been shown effective and safe [29]. Another emerging approach would consider the use of cangrelor, an intravenous antagonist of the $P2Y_{12}$ receptor characterized by rapid, potent, predictable, and reversible platelet inhibition with prompt offset of effect, but the lack of reliable efficacy and safety data makes this option still needing validation [30]. In common with glycoprotein IIb/IIIa inhibitors, cangrelor shares potency, rapid onset of action, and consistent platelet inhibition effects [31]. Short-acting glycoprotein IIb/IIIa antagonists (tirofiban and eptifibatide), however, have a slower offset of action, requiring at least 6 h to return to baseline platelet function, which is conversely achieved within 1 h after stopping cangrelor [31].

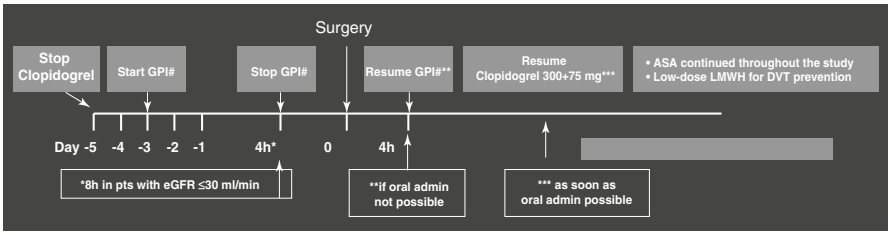


**Fig. 10.3** Scheme for bridging infusion of short-acting glycoprotein IIb/IIIa inhibitors in patients candidates for early surgery after coronary artery stenting. # tirofiban 0.4 mg/kg/min over 30 min + 0.1 mg/kg/min (0.05 mg/kg/min if CrCl < 30 ml/min) or eptifibatide 180 mcg/kg over 1-2 min + 2.0 mcg/kg/min (or 1.0 mcg/kg/min if CrCl < 50 ml/min). *CrCl* creatinine clearance

As regards the risk of thromboembolism associated with AF, either minimizing the interval without anticoagulation or delaying elective surgery if the risk is transiently increased (i.e., in case of stroke or transient ischemic attack within 3 months) should generally be considered for OAC patients needing surgery. The thromboembolic high-risk stratum includes patients with $CHA_2DS_2$-VASc score ≥6 (Table 10.3), those with prior thromboembolism during temporary interruption of OAC, or patients undergoing surgery "per se" associated with increased propensity for thromboembolic events (i.e., cardiac valve replacement, carotid endarterectomy, or major vascular surgery) [27].

Because of the fast onset of action and short half-life [32] (Table 10.7), non-vitamin K antagonist oral anticoagulants (NOACs) make them easier to discontinue and resume rapidly than warfarin and do not require routine laboratory monitoring.

In case of selected procedures carrying a very low bleeding risk, it may be suggested to continue anticoagulation, i.e., cataract surgery, minor dermatologic operations, selected procedures of electrophysiology, or minor dental procedures (Table 10.5); however, it is reasonable to perform the intervention at trough concentration of NOAC, i.e., 18–24 h after the last intake, and then restart it 6 h later (with skipping one dose for twice-daily NOACs) [3] (Table 10.8). For the other procedures/interventions, NOAC discontinuation is suggested, and the time of interruption depends on bleeding risk and on renal function. Of note, in patients at high thromboembolic risk, the period without anticoagulation should be as short as possible.

In patients without impairment of the renal function, the discontinuation scheme suggests interrupting NOACs at least 24 h before the operation if bleeding risk is low and at least 48 h for surgery at high bleeding risk (Table 10.8) [3]. In patients with creatinine clearance ≤50 mL/min, withdrawal of dabigatran, having the greatest proportion of renal clearance (80 %), is recommended at least 48 h and 96 h before the operation in case of low and high bleeding risk, respectively [3] (Table 10.8). For oral factor Xa inhibitors, having a lower renal clearance (25–50 %) (Table 10.7), time of interruption is irrespective of renal function in patients candidates to surgery at high bleeding risk, whereas a prolongation of cessation of ≥ 36 h is indicated in patients with severe renal impairment undergoing operation with low

**Table 10.7** Main pharmacological properties of warfarin and non-vitamin K antagonist oral anticoagulants

| | Warfarin | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|---|
| Target | Factors II, VII, IX, X | Factor IIa (thrombin) | Factor Xa | | |
| Prodrug | No | Yes | No | No | No |
| Bioavailability | 100 % | 6 % | 66[a]/100 %[b] | 50 % | 62 % |
| Plasma protein binding | 97 % | 35 % | 93 % | 87 % | 50 % |
| Time to peak | 4–5 days | 1.5–2 h | 2–3 h | 2–3 h | 1–2 h |
| Elimination half-life | 36–42 h | 12–17 h | 5–9[c]/11–13[d] h | 12 h | 10–14 h |
| Route of clearance | Multiple | 80 % renal | 35 % renal | 27 % renal | 50 % renal |

[a]Without food; [b]with food; [c]in the young; [d]in the elderly

**Table 10.8** Recommended last drug intake before elective surgical/invasive procedure (From Ref. [3])

| | Dabigatran | | Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) | |
|---|---|---|---|---|
| | Low risk[a] | High risk[b] | Low risk[a] | High risk[b] |
| CrCl ≥ 80 ml/min | ≥24 h | ≥48 h | ≥24 h | ≥48 h |
| CrCl 50–80 ml/min | ≥36 h | ≥72 h | ≥24 h | ≥48 h |
| CrCl 30–49 ml/min | ≥48 h | ≥96 h | ≥24 h | ≥48 h |
| CrCl 15–29 ml/min | Not indicated | Not indicated | ≥36 h | ≥48 h |
| CrCl < 15 ml/min | No official indication for use | | | |

*CrCl* creatinine clearance
NOTE: when no important bleeding risk and/or adequate local hemostasis is possible, perform procedure at trough level (i.e., ≥12 or 24 h after last intake)
NOTE: there is no need for bridging with low-molecular-weight/unfractionated heparin
[a]With a low frequency of bleeding and/or minor impact of a bleeding
[b]With a high frequency of bleeding and/or important clinical impact

bleeding risk (Table 10.8). If urgent surgery is needed, NOAC should be discontinued, and the operation should be deferred, if possible, until at least 12 h and ideally 24 h after the last dose [3]. If surgery cannot be delayed, reversal of the anticoagulant may be considered. Data in healthy volunteers have shown that prothrombin complex concentrate (PCC) or activated PCC dose dependently reverses the anticoagulant effects of NOACs. The dose suggested are 50 U/Kg for PCC (with additional 25 U/Kg if clinically needed) and 50 U/Kg, max 200 U/Kg/day, for activated PCC [3]. Reversal of NOAC effect by specific antidotes, like idarucizumab for dabigatran [33] and eventually andexanet alfa [34] for factor Xa inhibitors (including rivaroxaban, apixaban, and likely also edoxaban), might be considered although solid clinical experience is lacking. In the preoperative setting, coagulation tests, especially if specific (i.e., diluted thrombin time or specific anti-Xa activity), may be helpful in selected patients, such as those undergoing emergency procedures during anticoagulation or surgery at high risk of bleeding [3] (Table 10.9).

An overview of the perioperative management suggestions is given in Table 10.10.

**Table 10.9** Laboratory tests for evaluation of anticoagulation with NOACs

| NOAC | Preferred method | In an emergency |
|---|---|---|
| Dabigatran | 1. Ecarin clotting time | APPT (preferably with specific calibrated reagents) |
| | 2. Dilute thrombin time | |
| Rivaroxaban | Anti-factor Xa | PT (preferably with specific calibrated reagents) |
| Apixaban | Anti-factor Xa | Dilute PT |
| Edoxaban | Anti-factor Xa | Few firm data |

*APPT* activated partial thomboplastin time, *NOAC* non-vitamin K oral anticoagulant, *PT* prothrobin time

**Table 10.10** Overview of the perioperative suggestions for the management of antithrombotic therapy in patients on TT of NOAC, aspirin, and clopidogrel undergoing surgery

| | Risk of bleeding | | |
|---|---|---|---|
| Risk of stent thrombosis | High | Low | Very low |
| High | Stop NOAC[a]<br>Consider NOAC reversal[b]<br>Stop clopidogrel[c]<br>Consider short-acting GPIs[d]<br>Proceed to surgery<br>Resume NOAC as soon as possible[e]<br>Resume clopidogrel as soon as possible | Stop NOAC[a]<br>Continue clopidogrel + aspirin<br>Proceed to surgery<br>Resume NOAC as soon as possible[e] | Maintain NOAC<br>Continue clopidogrel + aspirin<br>Proceed to surgery |
| Intermediate | Stop NOAC[a]<br>Consider NOAC reversal[b]<br>Stop clopidogrel[c] (± aspirin)<br>Proceed to surgery<br>Resume NOAC as soon as possible[e]<br>Resume antiplatelet(s) as soon as possible | Stop NOAC[a]<br>Continue clopidogrel + aspirin<br>Proceed to surgery<br>Resume NOAC as soon as possible[e] | Maintain NOAC<br>Continue clopidogrel + aspirin<br>Proceed to surgery |
| Low | Stop NOAC[a]<br>Consider NOAC reversal[b]<br>Stop clopidogrel" (± aspirin)<br>Proceed to surgery<br>Resume NOAC as soon as possible[e]<br>Resume antiplatelet(s) as soon as possible | Stop NOAC[a]<br>Continue aspirin (± clopidogrel)<br>Proceed to surgery<br>Resume NOAC (± clopidogrel) as soon as possible[e] | Maintain NOAC<br>Continue aspirin (± clopidogrel)<br>Proceed to surgery<br>Resume clopidogrel (if interrupted) as soon as possible |

*NOAC* non-vitamin K antagonist oral anticoagulant, *GPI* glycoprotein IIb/IIIa inhibitors

[a]In a timely fashion, based on individual NOAC pharmacology and bleeding and thromboembolic risk of the patient (without routine bridging anticoagulation, which might be considered if $CHA_2DS_2$-VASc score $\geq 6$ and/or previous history of stroke)

[b]In emergency or urgent setting

[c]Ideally 5 days before

[d]Intravenous tirofiban or eptifibatide

[e]Provided that adequate hemostasis has been obtained

### 10.2.1 Perioperative Management

- Given the low bleeding risk of surgery, and the high risk of cardiac adverse events associated with the recent stent implantation in the context of an ACS, both aspirin and clopidogrel were continued.
- Because of the mild reduction of renal function, rivaroxaban was immediately interrupted and surgery scheduled approximately 36 h later.
- Surgical humerus fixation was performed without relevant complications, except for significant intraoperative blood loss. Because of that, and the associated decrease of approximately 2 g/dl of hemoglobin, transfusion of two units of packed red blood cells was performed postoperatively.

## 10.3 Postoperative Issues

The timing of postoperative NOAC resumption needs to take into account the type of surgery and adequacy of hemostasis. In patients undergoing low bleeding risk operations, NOAC can be resumed 12–24 h, whereas after high-risk surgery, resumption of anticoagulation should be deferred at 48–72 h and only if an adequate hemostasis is assured. Given some similar pharmacokinetic properties of NOACs compared to LMWH, such as short time to onset and short half-lives, the utility of bridging therapy after NOAC discontinuation is marginal. Bridging therapy may be considered only in patients unable to promptly resume NOACs in the postoperative period (i.e., those with postoperative ileus) [35, 36].

### 10.3.1 Postoperative Management

- Albeit not specifically labeled in the setting of orthopedic surgery performed to treat a bone fracture, the evening after operation, rivaroxaban was reinitiated at the dose of 10 mg once daily for prevention of venous thromboembolism because the patient was deemed at high risk for such complication (advanced age, immobilization, and concomitant chronic obstructive lung disease).
- After 48 h from intervention, the dose of rivaroxaban dose was increased to 15 mg once daily in combination with ongoing DAPT.
- As previously scheduled, triple therapy was continued up to 6 months after coronary stent implantation, then downgraded to rivaroxaban 20 mg once daily and aspirin 100 mg once daily up to 12 months, and finally to rivaroxaban 20 mg once daily as monotherapy lifelong.

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# 11 Major Bleeding Early After Percutaneous Coronary Intervention in a Patient with Atrial Fibrillation on Triple Therapy with Vitamin K Antagonist, Aspirin, and Clopidogrel

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## 11.1 Case Presentation

### 11.1.1 Baseline Characteristics

- Gender: female.
- Age: 80 years.
- Cardiovascular risk factors: diabetes.
- Associated diseases: permanent atrial fibrillation (AF) on oral anticoagulation (OAC) with warfarin.
- Previous history: new-onset effort angina since approximately 4 months earlier with subsequent percutaneous coronary intervention (PCI) with a new-generation drug-eluting stent (DES) (Synergy 3x24 mm, Boston Scientific) (Table 11.1) implantation on proximal left anterior descending (LAD), in the absence of further coronary lesions, 3 months earlier.
- Current history: hospitalization due to abrupt, massive, rectal blood loss. Treatment included warfarin, aspirin 75 mg once daily, clopidogrel 75 mg once daily, metoprolol 50 mg twice daily, and metformin 850 mg twice daily. Upon physical examination, blood pressure was 140/90 mmHg, and the pulse was irregular with an average heart rate of 78/min. Laboratory examination showed hemoglobin 10 g/dL, normal kidney function (serum creatinine 0.7 mg/dL), liver enzymes, and a blood glucose level of 100 mg/dL. The international normalized ratio (INR) was 2.4.

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**Table 11.1** General classification of coronary stents/scaffolds

| | | |
|---|---|---|
| BMS | | (a) Stainless steel<br>(b) Non-stainless steel, cobalt- or platinum-chrome alloy |
| DES | Early generation | (a) Durable polymer: sirolimus- and paclitaxel-eluting |
| | New generation | (a) Durable polymer: zotarolimus- and everolimus-eluting<br>(b) Biodegradable polymer: biolimus A9 and everolimus-eluting<br>(c) Polymer-free: biolimus A9- and amphilimus-eluting |
| BAS | | (a) Diamond-like carbon-coated, titanium nitric oxide-coated<br>(b) Endothelial progenitor cells-capturing |
| BVS | | (a) Nondrug-eluting<br>(b) Everolimus, myolimus, and sirolimus eluting |

*BMS* bare-metal stent, *DES* drug-eluting stent, *BAS* bioactive stent, *BVS* bioresorbable vascular scaffold

## 11.2 Early Evaluation Issues

When dealing with a bleeding event potentially having relevant clinical consequences, like hypovolemia and/or hemodynamic impairment, permanent damage in close spaces (e.g., skull, spinal cord, or joints), or ultimately death, the initial question is how rapidly the hemorrhagic event needs to be controlled. Whereas measures aiming to preserve organ perfusion, including fluid and/or plasma expander administration and vasopressors, together with specific maneuvers directed to the treatment of the cause of bleeding, such as surgical or endoscopic hemostasis and/or removal of the bleeding lesion, are used in a standard patient, the management is more complex when bleeding occurs in a patient on OAC with warfarin or on dual antiplatelet therapy (DAPT) with aspirin and a P2Y12-receptor inhibitor or, even more, on triple therapy (TT) of warfarin, aspirin, and clopidogrel [1]. In these latter cases, careful balance needs to be applied in order to effectively manage bleeding while not exposing the patient to an increased risk of thrombotic and/or thromboembolic events.

In a patient experiencing a clinically relevant bleeding [2–5] (Table 11.2), while on TT of warfarin, aspirin, and clopidogrel, the immediate question to be addressed is what is the risk of adverse outcome when continuing as opposed to interrupting one or more of, or even all, the components of combination antithrombotic therapy. Namely, the risk of permanent sequelae and/or death associated with the continuation of antithrombotic therapy needs to be balanced with that of stroke and/or stent thrombosis and/or recurrent coronary events associated with the interruption of OAC and/or antiplatelet agent (s). With this purpose, stratification of the above risks needs to be performed.

Although not standardized in a specific scoring system, the risk of (in-hospital) adverse outcome associated with bleeding appears dependent on several variables, including age, systolic blood pressure, impairment of consciousness, and preexisting comorbidities (including heart failure, cancer, peripheral artery disease, chronic obstructive lung disease), as well as type and location of bleeding and degree of over-anticoagulation with warfarin (when ongoing) [6, 7].

**Table 11.2** Most used classifications of bleeding

| | *ISTH* | *BARC* | *TIMI* | *GUSTO* |
|---|---|---|---|---|
| Major/severe | Fall in Hgb ≥ 2 g/dl, OR<br>Transfusion of ≥ 2 units of PRBC or whole blood, OR<br>In critical locations (i.e., intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, or pericardial), OR<br>That causes death | 3b: overt bleeding with Hgb drop ≥ 5 g/dl OR Bleeding requiring vasopressors or surgical intervention OR Cardiac tamponade<br>3c: intraocular or intracranial<br>4: CABG related, requiring transfusion of ≥ 5 units blood, repeat sternotomy, and chest output ≥ 2 liters within 24 hours<br>5: fatal | Intracranial, OR<br>Hgb drop ≥ 5 g/dl<br>Hct drop ≥ 15% | Intracranial, OR Causing hemodynamic compromise and requiring intervention |
| Clinically relevant nonmajor | That does not meet criteria for major bleeding, AND Requires any medical or surgical intervention to treat the bleeding | – | – | – |
| Moderate | – | – | – | Requiring transfusion, but not leading to hemodynamic instability |
| Minor/mild | – | 1: Bleeding that is not actionable<br>2: Any overt, actionable bleeding requiring nonsurgical medical intervention OR Leading to hospitalization or increased level of care OR Prompting evaluation<br>3a: Overt bleeding with Hgb drop 3–5 g/dl | Hgb drop ≥ 3 g/dl, OR<br>Hct drop ≥ 10%<br>No overt blood loss, but Hgb drop ≥ 4 g/dl or Hct drop ≥ 12% | Not meeting criteria for severe or moderate |
| Minimal | – | – | Any clinically overt bleeding with Hgb drop < 3 g/dl or Hct drop < 9% | – |

*Hgb* hemoglobin, *Hct* hematocrit, *CABG* coronary artery bypass graft, *PRBC* packed red blood cell

**Table 11.3** $CHA_2DS_2$-VASc score and associated risk of stroke/year [8]

| | Condition | Points | Total score | Stroke risk/ year (%) |
|---|---|---|---|---|
| C | Congestive heart failure (or left ventricular ejection fraction ≤ 35 %) | 1 | 0 | 0 |
| H | Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication) | 1 | 2 | 1.3 |
| $A_2$ | Age ≥ 75 years | 2 | 2 | 2.2 |
| D | Diabetes mellitus | 1 | 3 | 3.2 |
| $S_2$ | Prior stroke or TIA or thromboembolism | 2 | 4 | 4.0 |
| V | Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque) | 1 | 5 | 6.7 |
| A | Age 65–74 years | 1 | 6 | 9.8 |
| Sc | Sex category (i.e., female sex) | 1 | 7 | 9.6 |
| | | | 8 | 6.7 |
| | | | 9 | 15.2 |

*TIA* transient ischemic attack

The risk of stroke should be evaluated by means of the $CHA_2DS_2$-VASc score (Table 11.3) [8]. It gives an estimation of the annual risk of stroke and/or thromboembolism in the absence of antithrombotic treatment. While acknowledging that the predictive value of $CHA_2DS_2$-VASc score is modest (i.e., C-statistic range 0.64–0.79, median 0.673) [9], it nonetheless should be regarded as the standard tool for stroke risk stratification.

The risk of stent thrombosis is related to the type (i.e., bare-metal vs. drug-eluting) of stent, the generation (i.e., early vs. new) of drug-eluting stent, the clinical setting (elective vs. acute) where the stent has been implanted, and the time elapsed from stent implantation. Premature discontinuation of DAPT, however, should be regarded as the strongest predictor of stent thrombosis [10]. In this regard, it is considered safe to interrupt DAPT and continue with single antiplatelet therapy with aspirin (or clopidogrel) 1 month and, respectively, 6 months after bare-metal stent and new-generation drug-eluting stent implantation in an elective setting. A period of 12 months should be considered after an early-generation drug-eluting stent implantation, irrespective of the elective or acute clinical setting, and either bare-metal, early-, or new-generation drug-eluting stent implantation in an acute coronary syndrome (ACS) [11]. If needed, such as in the event of bleeding, a shorter duration of DAPT, that is, 3 or even 1 month, may be considered for (some) new-generation drug-eluting stents (Table 11.1). Care, however, should be put in not interrupting both antiplatelet agents at the same time, given that this has been associated with an increased risk of stent thrombosis (Fig. 11.1) [12]. The location where the stent was implanted (i.e., proximal in a main and/or largely distributed vessel vs. mid-distal in secondary and/or poorly distributed vessel) should also be taken into account when trying to foresee the potential consequences of stent thrombosis.

The risk of recurrent coronary events is higher after ACS compared to the elective setting. Over the first year after the former, an incidence of < 1 % may be expected, as compared to up to 10 % after the latter. Of note, however, the risk of adverse events (namely, death) after and ACS tends progressively to decrease as long as time passes

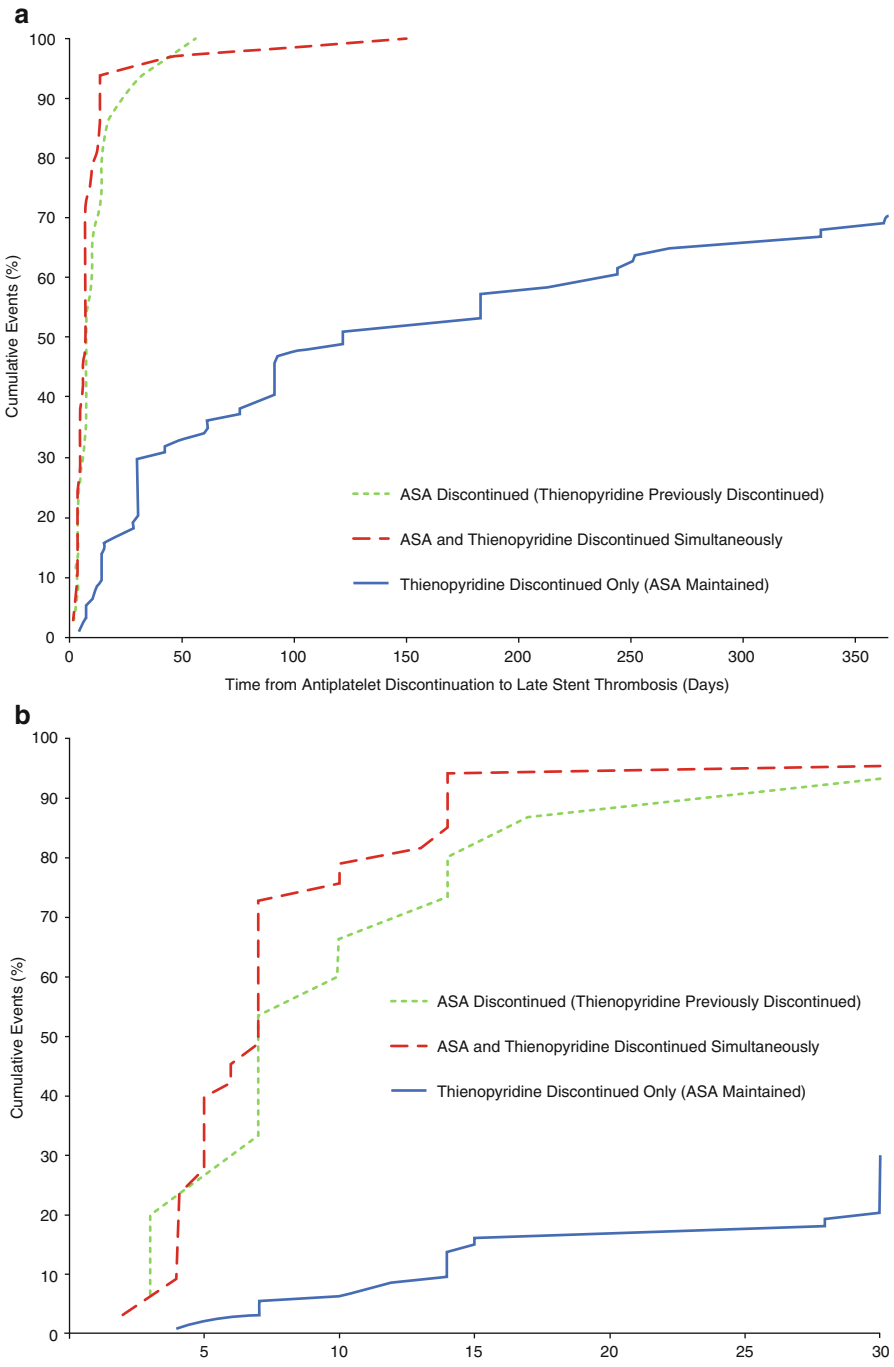


**Fig. 11.1** Cumulative proportion of stent thrombosis (>12 months from stent implantation) among patients who discontinued antiplatelet therapy: (**a**) within 1 year of discontinuation; (**b**) within 30 days of discontinuation (Reproduced with permission from Ref. [12])

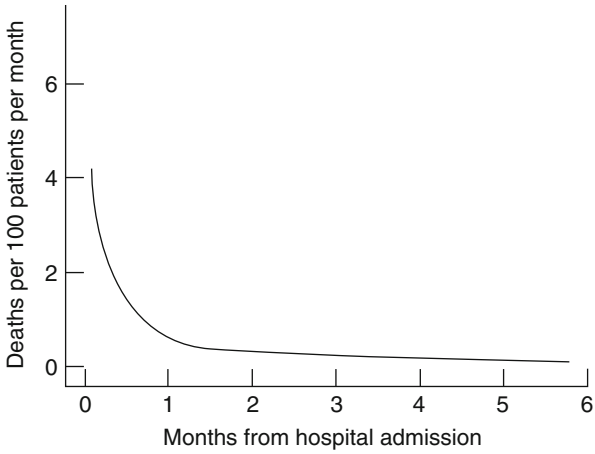


**Fig. 11.2** Mortality of patients with acute coronary syndrome over time (Reproduced with permission from Ref. [13])

from index event (Fig. 11.2) [13]. After 1 year (with no recurrence) from ACS, a patient is then considered stable, thereby generally requiring low-intensity (i.e., single-agent) antiplatelet therapy. In selected cases at high risk of recurrences, especially because of previous myocardial infarction, prolonged (i.e., up to 3 years) DAPT with aspirin and $P_2Y_{12}$-receptor inhibitor may be considered [14–16].

### 11.2.1 Initial Evaluation

- Because of the stable hemodynamics with no signs of organ hypoperfusion or severe anemia, the patient was considered at low risk of adverse outcome related to bleeding, thereby not requiring emergency intervention
- The risk of stroke, as estimated by a $CHA_2DS_2$-VASc score of 5, was high, corresponding with an incidence of 6.7 % per year.
- The risk of stent thrombosis was considered moderate as 3 months were elapsed since the implantation of a new-generation DES, which however was located in the proximal LAD.
- The risk of recurrent coronary events was considered moderate as 4 months were elapsed since the onset of stable effort angina.

## 11.3 Early Management Issues

In the absence of hemodynamic impairment and/or harmful location (e.g., intracranial and/or intraspinal and possibly also intra-articular) of bleeding, no fluid or plasma expander administration nor blood transfusion nor inotropic support nor reversal of OAC appears warranted. Oral or intravenous administration of vitamin K and/or prothrombotic agents, in the form of prothrombin complex concentrates or fresh frozen plasma (Tables 11.4 and 11.5), should generally be reserved to the emergency

**Table 11.4** Characteristics of therapies for warfarin reversal

| | Time to effect (after administration) | Duration of effect | Evidence of efficacy for warfarin reversal | Risk of thrombosis |
|---|---|---|---|---|
| Oral vitamin K | 24 h | Days | ++++ | Not significant |
| Intravenous vitamin K | 8–12 h | Days | ++++ | Not significant |
| Fresh frozen plasma | Immediate | 12–24 h | ++ | Not significant |
| Prothrombin complex concentrates | Immediate | 12–24 h | +++ | +[a] |
| Recombinant factor VII | Immediate | 2–6 h | + | ++ |

[a]Higher with activated prothrombin complex concentrates

**Table 11.5** Content of vitamin K-dependent coagulation factors in available reversal agents

| Factor | 3-Factor PCC | 4-Factor PCC | FFP | FEIBA | rFVIIa |
|---|---|---|---|---|---|
| II | ✓ | ✓ | ✓ | ✓ | |
| VII | | ✓ | | ✓ | ✓ |
| IX | ✓ | ✓ | ✓ | ✓ | |
| X | ✓ | ✓ | ✓ | ✓ | |

*PPC* prothrombin complex concentrates, *FFP* fresh frozen plasma, *FEIBA* factor eight bypass activity, *rFVIIa* Recombinant factor VII

management of life-threatening bleeding events (Table 11.6). With the exception of these circumstances, immediate warfarin withdrawal should generally be considered as the only measure to adopt. Even in the presence of an increased risk of stroke, which may range from about 0 % to 15 % per year based on the range of $CHA_2DS_2$-VASc scores between 0 and 9 (Table 11.3) [8], it is unlikely that such event will develop during a short (i.e., some days to a week or so) interruption of warfarin OAC. A possible exception may be represented by a very high (i.e., 7–9) risk of stroke, especially when a history of stroke is present as a variable contributing to the total $CHA_2DS_2$-VASc score. In this case, bridging warfarin interruption with (possibly reduced dose) subcutaneous low-molecular-weight heparin may be considered once bleeding has ceased in the light of the superior convenience of management in the event that the need for subsequent invasive or surgical intervention arises [17]. Indeed, interruption of warfarin performed as initial management strategy for bleeding also allows safe endoscopic (with biopsy) or surgical intervention when needed.

Regarding concomitant DAPT with aspirin and clopidogrel, every effort should be made not to interrupt both agents at the same time [12]. Withdrawal of one antiplatelet (generally clopidogrel) may generally be performed, provided that at least 1 and 3–6 months have elapsed from bare-metal and new-generation drug-eluting stent implantation, respectively. Within those time periods, the management should be individualized based on the actual risk of adverse events with antiplatelet interruption compared to no interruption. While there are no data available, consideration of platelet transfusions appears largely unfeasible due to the possible increase in adverse thrombotic events [18]. Withdrawal of antiplatelet therapy is likely of greater importance as regards to the risk of stent thrombosis rather than that of recurrent cardiac events, which is hardly affected by a short (some days to a week or so) interruption of secondary prevention with antiplatelet therapy.

**Table 11.6** Doses of reversal agents for (life-threatening) bleeding on warfarin

| | Warfarin | Vitamin K | PCC | FFP | rFVIIa |
|---|---|---|---|---|---|
| Measures | Stop | 5–10 mg IV | 25–50 IU/kg | 150–300 ml | 10–100 mcg/kg |

*PPC* prothrombin complex concentrates, *FFP* fresh frozen plasma, *rFVIIa* Recombinant factor VII
Note: assess patient continuously until INR < 5.0 and bleeding stops
If FFP unavailable, give vitamin K (5–10 mg IV) plus PCC (25–50 IU/kg)
If PCC unavailable, give vitamin K (5–10 mg IV) plus FFP (10–15 ml/kg)

**Table 11.7** Strategies for the management of major bleeding at various time points following PCI with stent

| | During TT | During warfarin + SAPT | During warfarin only |
|---|---|---|---|
| Warfarin interruption | Recommended | Recommended | Recommended |
| Warfarin reversal | To be considered[a] | To be considered[a] | To be considered[a] |
| Withdrawal of both antiplatelets | Not recommended | | |
| Withdrawal of one antiplatelet | To be considered | Recommended | |
| General measures to preserve circulation[b] | Recommended | Recommended | Recommended |
| Endoscopic and/or surgical hemostasis[c] | Recommended | Recommended | Recommended |

*TT* triple therapy, *SAPT* single antiplatelet agent, *PCI* percutaneous coronary intervention
[a]In life-threatening bleeding
[b]For example, plasma expanders, blood transfusions, inotropic support, etc.
[c]When feasible

A summary of the strategies suggested in response to a major bleeding event at various time points after PCI with stent in patients with AF is provided in Table 11.7.

### 11.3.1 Early Management

- Given the acceptable and stable clinical condition and laboratory findings, a conservative strategy was chosen with no circulatory support nor blood transfusion nor reversal of OAC with vitamin K administration.
- Because the rectal blood loss was considered originating from the lower gastrointestinal tract, a proton-pump inhibitor was not prescribed.
- Warfarin was immediately interrupted, while DAPT of aspirin and clopidogrel was continued, and urgent gastrointestinal endoscopy was arranged.
- At gastroduodenoscopy no bleeding source was identified, whereas a diverticulum in the descending colon filled with recent blood clots was identified at colonoscopy.
- Based on the advice of the attending gastroenterologist, a conservative strategy was chosen because of lack of ongoing symptoms and the apparent cessation of bleeding. A stool softener was prescribed.

## 11.4 Post-acute Issues

Once bleeding has been controlled, the issues are whether and how antithrombotic therapy should be modified and when should it be restarted.

The risk of (re)bleeding should guide the choice of subsequent antithrombotic therapy together with the residual risk of stent thrombosis and recurrent cardiac events. Given that the risk of stroke associated with AF does not change over time (and indeed increases only with advancing age up to 75 years) (Table 11.3), continuation of warfarin OAC should generally not be questioned. An issue on the other hand may be whether warfarin might be substituted by a newer, non-vitamin K-antagonist oral anticoagulant (NOAC), including the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors rivaroxaban, apixaban, and edoxaban. While generally showing a preserved, and in some cases superior, efficacy and safety in stroke and systemic embolism prevention and incidence of major bleeding compared to warfarin (Table 11.8), NOACs are associated overall to an approximately 25 % increase in the incidence of gastrointestinal bleeding [19]. This may make them a less valuable option compared to warfarin for patients on TT in whom the most frequent site of bleeding is indeed the gastrointestinal tract [20]. An exception may be represented by apixaban at the dose of 5 mg twice daily and possibly also by dabigatran 110 mg twice daily, for which the rate of gastrointestinal bleeding was, albeit non significantly, lower than with warfarin (Table 8). Whereas, however, NOACs appear as an uncertain option for patients experiencing a major (gastrointestinal or not) bleeding while on OAC with warfarin with an INR above 3.0 range, they may possibly be considered in the event that the bleeding complications occur with an INR within the therapeutic range of 2.0–3.0.

Whether dual, single, or even no antiplatelet therapy should be given in conjunction with OAC after a major bleeding event essentially depends once again on the time from and type of stent implantation, the clinical setting where PCI has been performed, and the individual risk of bleeding. Following a bleeding event occurring within the first 3–6 months from bare-metal or new-generation drug-eluting stent implantation in the context of ACS, DAPT of aspirin and clopidogrel should generally be given together with warfarin. Upon stratification of the risk of bleeding by applying the HAS-BLED score (Table 11.9), a shorter duration of 1 month only may be considered when the estimated bleeding risk is high (i.e., HAS-BLED score $\geq 3$), and either a bare-metal or new-generation drug-eluting stent (especially durable polymer zotarolimus-eluting or absorbable polymer everolimus-eluting) (Table 11.1) has been implanted, irrespective of whether PCI has been performed in the setting of stable vs. unstable coronary artery disease. Beyond the first 3–6 months of stent implantation, continuation of warfarin and single antiplatelet agent (either aspirin or clopidogrel) should generally be preferred as the risk of stent thrombosis, and/or recurrent cardiac events has largely decreased compared to the previous period. Should a major bleeding occur after the first 3–6 months of TT, when the patient is on dual therapy with warfarin and single antiplatelet agent (either aspirin or clopidogrel), restarting of both agents should generally be preferred after bleeding control up to 1 year from the index event. Indeed, while being associated with an increased risk of bleeding, the combination of warfarin and

**Table 11.8** Efficacy and safety of non-vitamin K-antagonist oral anticoagulants vs. warfarin in the major trials on stroke prevention in AF (hazard ratio; 95 % confidence intervals)

| | Dabigatran 110 mg BID | Dabigatran 150 mg BID | Rivaroxaban 20 mg[a] OD | Apixaban 5 mg[b] BID | Edoxaban 30 mg BID | Edoxaban 60 mg BID |
|---|---|---|---|---|---|---|
| Stroke or systemic embolism | 0.91[c] (0.74–1.11) | 0.66[d] 0.53–0.82) | 0.88[c] (0.74–1.03) | 0.79[d] (0.66–0.95) | 1.07[c] (0.87–1.31) | 0.79[c] (0.63–0.99) |
| Major bleeding | 0.80[e] (0.69–0.93) | 0.93 (0.81–1.07) | 1.04 (0.90–1.20) | 0.69[e] (0.60.0.80) | 0.47[e] (0.41–0.55) | 0.80[e] (0.71–0.91) |
| Intracranial bleeding | 0.31[e] (0.20–0.47) | 0.40[e] (0.27–0.60) | 0.67[e] (0.47–0.93) | 0.42[e] (0.30–0.58) | 0.30[e] (0.21–0.43) | 0.47[e] (0.34–0.63) |
| Gastrointestinal bleeding | 1.10 (0.86–1.41) | 1.50[e] (1.19–1.89) | 1.60[e] (1.29–1.98) | 0.89 (0.70–1.15) | 0.67[e] (0.53–0.83) | 1.23[e] (1–02–1.50) |

*BID* twice daily, *OD* once daily, *AF* atrial fibrillation
[a]15 mg OD in patients with creatinine clearance 30–50 ml/min
[b]2.5 mg BID in patients with two of the following three features: age ≥ 80 years, weight ≤ 60 kg, creatinine ≥ 1.5 ml/min
[c]Significant for non-inferiority
[d]Significant for superiority
[e]Statistically significant

**Table 11.9** HAS-BLED score and associated risk of major bleeding/year

| | Condition | Points | Total score | Risk of major bleeding/year (%) |
|---|---|---|---|---|
| H | Hypertension (uncontrolled blood pressure above 160/90 mmHg) | 1 | 0 | <1 |
| A | Renal (dialysis, transplant, creatinine > 2.6 mg/dL or >200 μmol/L) and/or liver (cirrhosis, bilirubin > 2x normal or AST/ALT/AP > 3x normal) disease | 1 or 2 | 1–2 | 2–3 |
| S | Stroke | 1 | ≥3 | 4–12 |
| B | Bleeding (previous or predisposition to) | 1 | | |
| L | Labile INR (unstable/high or TTR < 60 %) | 1 | | |
| E | Elderly (i.e., age > 65 years) | 1 | | |
| D | Drug usage predisposing to bleeding (antiplatelet agents, NSAIDs) and/or alcohol (≥8 drinks a week) | 1 or 2 | | |

*INR* international normalized ratio, *TTR* time in therapeutic range, *NSAID* nonsteroidal anti-inflammatory drugs, *AST* aspartate aminotranspherase, *ACT* alanine aminotranspherase, *AP* alkaline phosphatase

aspirin for secondary prevention after ACS has been shown comparably effective to the standard therapy of DAPT [21].

After effective management of bleeding (without interruption of DAPT), a further issue is when to restart warfarin. Because of its pharmacology (Table 11.10), based on which at least 48 h is required before a therapeutic effect is reached, warfarin may and should be restarted soon after effective hemostasis and bleeding control have been obtained. In the case that also clopidogrel had been previously

**Table 11.10** Elimination half-life of vitamin K-dependent coagulation factors and anticoagulant proteins

| | Half-life (hours) |
|---|---|
| Factor II | 42–72 |
| Factor VII | 4–6 |
| Factor IX | 21–30 |
| Factor X | 27–48 |
| Protein C | 8–14 |
| Protein S | 30–42 |

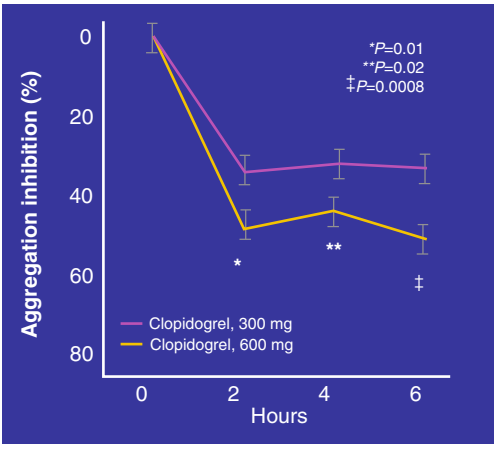


**Fig. 11.3** Degree and rapidity of platelet inhibition with clopidogrel 300 vs. 600 mg loading dose (From Ref. [22])

interrupted and there is indication for its reinstitution (based on the type of stent, the time elapsed from its implantation, and the clinical setting where PCI has been performed), this agent should be restarted as soon as possible either with no or 300–600 mg oral loading depending on the duration of interruption and the required rapidity for an effective antiplatelet effect ([22] Fig. 11.3).

Given the persistent increased risk of bleeding from the (high) gastrointestinal tract, adjunct proton-pump inhibitor gastric protection is advisable throughout combined OAC and (single or dual) antiplatelet therapy [23, 24].

### 11.4.1 Long-Term Management

- Because of the moderate risks of stent thrombosis and recurrent coronary events associated with the elective setting of the PCI which had been performed and the time elapsed, the HAS-BLED score of 3, as well as the conservative approach adopted in the management of bleeding, aspirin was permanently stopped, and dual therapy with warfarin and clopidogrel continued up to 12 months.
- Remaining therapy with metoprolol 50 mg twice daily and metformin 850 mg twice daily was confirmed long term, together with pantoprazole 20 mg once daily to be on the other hand stopped at 12 months when also clopidogrel was planned to be stopped and warfarin monotherapy to be continued lifelong.

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# 12 Major Bleeding Early After Percutaneous Coronary Intervention in a Patient with Atrial Fibrillation on Triple Therapy with a Non-vitamin K-Antagonist Oral Anticoagulant, Aspirin, and Clopidogrel

Giulia Renda, Marco Zimarino, and Raffaele De Caterina

## 12.1 Case Presentation

### 12.1.1 Baseline Characteristics

- Gender: male.
- Age: 69 years.
- Cardiovascular risk factors: hypertension, current cigarette smoking.
- Associated diseases: permanent atrial fibrillation (AF) on chronic oral anticoagulation (OAC) with dabigatran 150 mg twice daily since 2 years before.
- Previous history: hospitalization 6 months earlier because of non-ST-elevation myocardial infarction (NSTEMI) prompting urgent coronary angiography (CORO) with documentation of sub-occlusive stenosis of mid-left anterior descending (LAD). Percutaneous coronary intervention (PCI) with bioresorbable scaffold (BVS) (Absorb 3.0×28 mm, Abbott Vascular) implantation in the LAD was performed, and triple antithrombotic therapy with aspirin 100 mg once daily, clopidogrel 75 mg once daily, and dabigatran 110 mg twice daily was started together with ramipril 5 mg once daily and atorvastatin 40 mg once daily. Triple therapy was planned for 12 months, given the patient's high thromboembolic risk, with a $CHA_2DS_2$-VASc score of 3 (Table 12.1), and the moderate hemorrhagic risk, with a HAS-BLED score of 2 (Table 12.2).

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- Current history: rehospitalization due to angina and dyspnea on effort since a few weeks earlier. Both physical examination and noninvasive evaluation, including electrocardiogram and echocardiogram, were within normal limits, with the exception of pale skin. Blood sampling documented severe anemia (Hb 8 g/dL) and mild renal dysfunction (creatinine clearance 60 ml/min). Careful review of patient's history suggested the presence of melena prior to admission.

**Table 12.1** $CHA_2DS_2$-VASc score and associated risk of stroke/year [4]

| | Condition | Points | Total score | Stroke risk/year (%) |
|---|---|---|---|---|
| C | Congestive heart failure (or left ventricular ejection fraction ≤ 35%) | 1 | 0 | 0 |
| H | Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication) | 1 | 2 | 1.3 |
| $A_2$ | Age ≥ 75 years | 2 | 2 | 2.2 |
| D | Diabetes mellitus | 1 | 3 | 3.2 |
| $S_2$ | Prior stroke or TIA or thromboembolism | 2 | 4 | 4.0 |
| V | Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque) | 1 | 5 | 6.7 |
| A | Age 65–74 years | 1 | 6 | 9.8 |
| Sc | Sex category (i.e., female sex) | 1 | 7 | 9.6 |
| | | | 8 | 6.7 |
| | | | 9 | 15.2 |

*TIA* transient ischemic attack

**Table 12.2** HAS-BLED score and associated risk of major bleeding/year [4]

| | Condition | Points | Total score | Risk of major bleeding/year (%) |
|---|---|---|---|---|
| H | Hypertension (uncontrolled blood pressure above 160/90 mmHg) | 1 | 0 | <1 |
| A | Renal (dialysis, transplant, creatinine > 2.6 mg/dL or >200 μmol/L) and/or liver (cirrhosis, bilirubin > 2x normal or AST/ALT/AP > 3x normal) disease | 1 or 2 | 1–2 | 2–3 |
| S | Stroke | 1 | ≥3 | 4–12 |
| B | Bleeding (previous or predisposition to) | 1 | | |
| L | Labile INR (unstable/high or TTR < 60%) | 1 | | |
| E | Elderly (i.e., age > 65 years) | 1 | | |
| D | Drug usage predisposing to bleeding (antiplatelet agents, NSAIDs) and/or alcohol (≥8 drinks a week) | 1 or 2 | | |

*INR* international normalized ratio, *TTR* time in therapeutic range, *NSAID* nonsteroidal anti-inflammatory drugs, *AST* aspartate aminotranspherase, *ACT* alanine aminotranspherase, *AP* alkaline phosphatase

## 12.2 Early Management Issues

With a history of clinically relevant bleeding (Table 12.3) in a patient on antithrombotic therapy, assessment and evaluation of the potential clinical consequences should be made. A search for the source of bleeding and specific (endoscopic or surgical) management should be made. Withdrawal of ongoing antithrombotic agent is often performed, but the risk of (potentially serious) adverse outcomes when interrupting antithrombotic treatment should always be weighed against the risks of continuing it. The risk of stroke and/or stent thrombosis and/or recurrent coronary events may be associated with the interruption of all or part of ongoing antithrombotic therapy.

The risk of (in-hospital) adverse outcomes associated with bleeding depends on several variables, including age, uncontrolled blood pressure, pre-existing comorbidities, and concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) or alcohol excess, as well as type and location of bleeding and degree of over-anticoagulation with warfarin (when ongoing) [1–3].

The risk of stroke is assessed by calculation of the $CHA_2DS_2$-VASc score [4]. The risk of stroke associated with the absence and/or withdrawal of OAC as estimated by the CHA2DS2-VASc score, however, may not be linear, and therefore just dividing the risk per year by the duration of discontinuation may not provide an adequate estimation of the true risk. The risk of stent thrombosis is related to the type (i.e., bare-metal vs. drug-eluting) of stent, the generation (i.e., early vs. new) of drug-eluting stent, the clinical setting (elective vs. acute) where the stent has been implanted, and the time elapsed from stent implantation. Premature discontinuation of DAPT, however, is the strongest predictor of stent thrombosis [5]. It may be relatively safe to interrupt DAPT and continue with single antiplatelet therapy (preferably clopidogrel) for 1 month and 6 months after bare-metal stent and new-generation drug-eluting stent implantation, respectively. A period of 12 months should be considered after an early-generation drug-eluting stent implantation, irrespective of the elective or acute clinical setting, and either bare-metal, early-, or new-generation drug-eluting stent implantation in an acute coronary syndrome (ACS) [6].

In the event of bleeding, a shorter duration of DAPT, even 1 month, may be considered for (some) new-generation drug-eluting stents (Table 12.1). Care is needed in not interrupting both antiplatelet agents at the same time, given the increased risk of stent thrombosis [7]. The location where the stent was implanted (i.e., proximal in a main and/or largely distributed vessel vs. mid-distal in secondary and/or poorly distributed vessel) should also be taken into account when trying to foresee the potential consequences of stent thrombosis.

The risk of recurrent coronary events is higher after ACS compared to the elective setting. Over the first year after the former, an incidence of $<1\%$ may be expected, as compared to up to 10% after the latter. Of note, however, the risk of adverse events (namely, death) after an ACS tends progressively to decrease as long

**Table 12.3** Most used classifications of bleeding

| | ISTH | BARC | TIMI | GUSTO |
|---|---|---|---|---|
| Major/severe | Fall in Hgb ≥ 2 g/dl, OR Transfusion of ≥ 2 units of PRBC or whole blood, OR in critical locations (i.e., intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, or pericardial) OR That causes death | 3b: overt bleeding with Hgb drop ≥ 5 g/dl OR Bleeding requiring vasopressors or surgical intervention OR Cardiac tamponade 3c: intraocular or intracranial 4: CABG-related, requiring transfusion of ≥ 5 units blood, repeat sternotomy, and chest output ≥ 2 liters within 24 h 5: fatal | Intracranial, OR Hgb drop ≥ 5 g/dl OR Hct drop ≥ 15% | Intracranial, OR Causing hemodynamic compromise and requiring intervention |
| Clinically relevant non-major | That does not meet criteria for major bleeding, AND Requires any medical or surgical intervention to treat the bleeding | – | – | – |
| Moderate | – | – | – | Requiring transfusion, but not leading to hemodynamic instability |
| Minor/Mild | – | 1: bleeding that is not actionable 2: any overt, actionable bleeding requiring nonsurgical medical intervention OR Leading to hospitalization or increased level of care OR Prompting evaluation 3a: overt bleeding with Hgb drop 3–5 g/dl | Hgb drop ≥ 3 g/dl, OR Hct drop ≥ 10% No overt blood loss, but Hgb drop ≥ 4 g/dl or Hct drop ≥ 12% | Not meeting criteria for severe or moderate |
| Minimal | – | – | Any clinically overt bleeding with Hgb drop < 3 g/dl or Hct drop < 9% | – |

*Hgb* hemoglobin, *Hct* hematocrit, *CABG* coronary artery bypass graft, *PRBC* packed red blood cells

as time passes from index event. After 1 year (with no recurrence) from ACS, a patient is then considered stable, thereby generally requiring low-intensity (i.e., single-agent) antiplatelet therapy, in the non-AF setting. In selected cases at high risk of recurrences, especially because of previous myocardial infarction, prolonged (i.e., up to 3 years) DAPT with aspirin and $P2Y_{12}$-receptor inhibitor may be considered [8–10].

Once stratification of the risk associated with treatment interruption as compared to continuation has been carried out, proper management of the bleeding complication should be arranged. Management strategies are particularly difficult in patients on triple therapy (TT) of OAC, aspirin, and clopidogrel early after PCI with stent and even more so when the OAC is a newer, non-vitamin K-antagonist oral anticoagulant (NOAC), such as dabigatran, rivaroxaban, apixaban, or edoxaban. The clinical experience with warfarin, and its hemorrhagic complications, has allowed the development of common strategies, which may include the administration of the specific reversal agent vitamin K, as well as of nonspecific, prothrombotic agents, including prothrombin complex concentrates, fresh frozen plasma, and recombinant factor VII [11] (Table 12.4). Whereas only very limited data are available regarding the management and outcome of major bleeding complications in patients on OAC with warfarin who have undergone PCI with stent [12], no evidence is currently available regarding NOACs.

As relates to bleeding, NOACs have a more favorable pharmacological profile than warfarin. In particular, the elimination half-life is much shorter than warfarin (12 h on average vs. 36–42 h), thereby allowing for a rapid decline of the anticoagulant effect upon drug discontinuation (Fig. 12.1). Of note, restoration of (at least partially) effective coagulation is expected to be obtained by approximately 24 h from drug discontinuation, a time lapse similar to that observed after oral administration of vitamin K in patients on OAC with warfarin [11] (Tables 12.4 and 12.5). With the exception of life-threatening bleeding, either because of the severity (i.e., leading to hemodynamic impairment) or the location (e.g., intracranial, intrapericardial, retroperitoneal), discontinuation of the NOAC should be the necessary strategy. Available data show that conservative treatment (i.e., drug discontinuation with or without transfusion of red blood cells and/or plasma) of major bleeding

**Table 12.4** Characteristics of therapies for warfarin reversal [11]

| | Time to effect (after administration) | Duration of effect | Evidence of efficacy for warfarin reversal | Risk of thrombosis |
|---|---|---|---|---|
| Oral vitamin K | 24 h | Days | ++++ | Not significant |
| Intravenous vitamin K | 8–12 h | Days | ++++ | Not significant |
| Fresh frozen plasma | Immediate | 12–24 h | ++ | Not significant |
| Prothrombin complex concentrates | Immediate | 12–24 h | +++ | +[a] |
| Recombinant factor VII | Immediate | 2–6 h | + | ++ |

[a]Higher with activated prothrombin complex concentrates

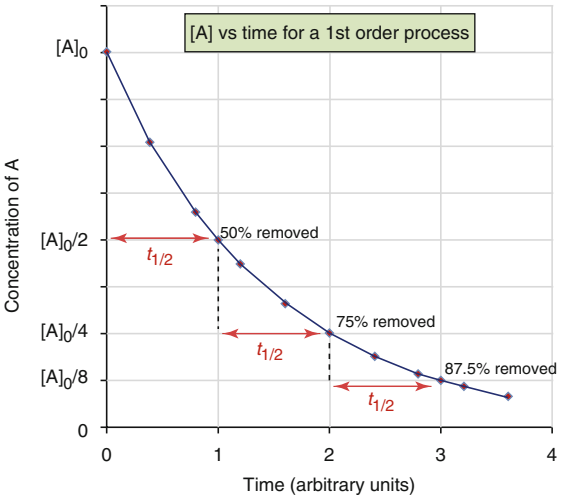


**Fig. 12.1** Decrease of plasma concentration of a given drug A as a function of time (first order kinetic)

**Table 12.5** Main pharmacological properties of warfarin and non-vitamin K-antagonist oral anticoagulants [4]

| | Warfarin | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|---|
| Target | Factors II, VII, IX, X | Factor IIa (thrombin) | Factor Xa | | |
| Prodrug | No | Yes | No | No | No |
| Bioavailability | 100 % | 6 % | 66[a]/100 %[b] | 50 % | 62 % |
| Plasma protein binding | 97 % | 35 % | 93 % | 87 % | 50 % |
| Time to peak | 4–5 days | 1.5–2 h | 2–3 h | 2–3 h | 1–2 h |
| Elimination half-life | 36–42 h | 12–17 h | 5–9[c]/11–13[d] hours | 12 h | 10–14 h |
| Route of clearance | Multiple | 80 % renal | 35 % renal | 27 % renal | 50 % renal |

[a]Without food
[b]With food
[c]In the young
[d]In the elderly

events on NOACs is generally associated with a favorable outcome [13–15]. Also, overall outcome and also mortality appear not different from that with warfarin [13–15].

The availability of specific reversal agents for NOACs, i.e., idarucizumab for dabigatran and eventually andexanet alfa for factor Xa inhibitors (i.e., rivaroxaban, apixaban, and edoxaban) (Table 12.6), which has been shown effective in rapidly and completely reversing the anticoagulant effect of NOACs [16, 17], will further increase the safety of these agents. Both specific and nonspecific (e.g., prothrombin complex concentrates, fresh frozen plasma, recombinant factor VIIa) reversal agents (Table 12.7) are intended to be used only for emergency, life-threatening major bleeding complications [18] (Fig. 12.2). Outside this situation, immediate

**Table 12.6** Specific reversal agents for NOACs that have been tested in clinical studies

| | Idarucizumab | Andexanet alfa |
|---|---|---|
| Target | Dabigatran | Oral direct factor Xa inhibitors, Low-molecular-weight heparins, fondaparinux |
| Structure | Humanized Fab fragment | Human rFXa variant |
| Onset of reversal < 10 min | Yes | Yes |
| Duration of effect | (12 to) 24 h | 2 h |
| Re-administration possible | Yes (>24 h) | Unknown |
| Tested in healthy volunteers | Yes | Yes |
| Tested in patients | Yes[a] | Yes[b] |
| Pro-coagulation signals | No | Decrease of TF inhibitor activity |

*TF* tissue factor, *NOAC* non-vitamin K-antagonist oral anticoagulant
[a]Including elderly and renally impaired
[b]Including elderly

**Table 12.7** Doses of reversal agents for (life-threatening) bleeding on warfarin

| | Warfarin | Vitamin K | PCC | FFP | rFVIIa |
|---|---|---|---|---|---|
| Measures | Stop | 5–10 mg IV | 25–50 IU/kg | 150–300 ml | 10–100 mcg/kg |

Note: Assess patient continuously until INR < 5.0 and bleeding stops
If FFP unavailable, give vitamin K (5–10 mg IV) plus PCC (25–50 IU/kg)
If PCC unavailable, give vitamin K (5–10 mg IV) plus FFP (10–15 ml/kg)
*PCC* prothrombin complex concentrates, *FFP* fresh frozen plasma, *rFVIIa* recombinant factor VII

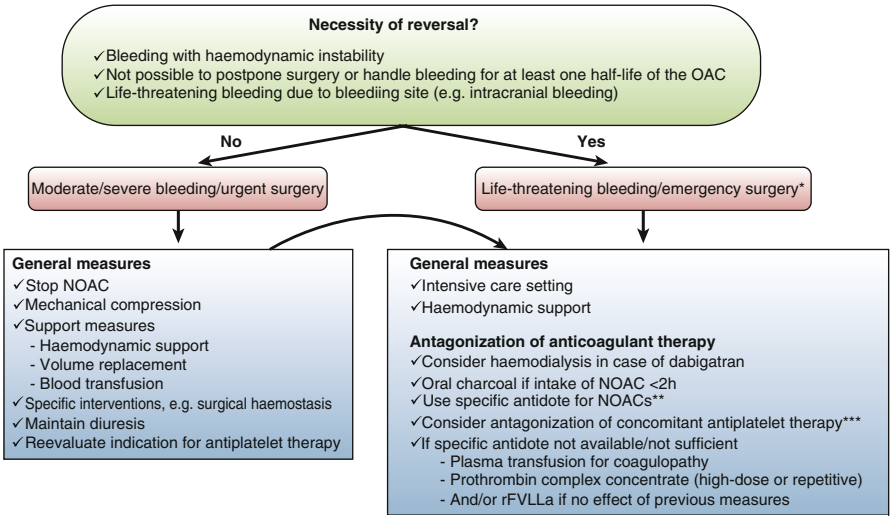


**Fig. 12.2** Algorithm for the management of bleeding during treatment with NOACs. Reproduced with permission from [18]. *NOAC* non-vitamin K-antagonist oral anticoagulant

**Table 12.8** Coagulation tests in patients on NOACs

| | Dabigatran | Apixaban | Edoxaban | Rivaroxaban |
|---|---|---|---|---|
| | | | | As reagent; local calibration required |
| INR | Cannot be used | Cannot be used | Cannot be used | Cannot be used |
| aPTT | Range at trough D150: 40.3–76.4 s | Cannot be used | Prolonged but no known relation with bleeding risk | Cannot be used |
| | Range at trough D110: 37.5–60.9 s | | | |
| | At trough: >2×ULN may be associated with excess bleeding risk | | | |
| dTT | No data from RE-LY trial on range of values | Cannot be used | Cannot be used | Cannot be used |
| | At trough: >200 ng/mL ≥ 65 s: may be associated with excess bleeding risk | | | |
| Anti-FXa chromogenic assays | Not applicable | Quantitative; no data on threshold values for bleeding or thrombosis | Quantitative; no data on threshold values for bleeding or thrombosis | Quantitative; no data on threshold values for bleeding or thrombosis |
| | | Range at trough: 1.4–4.8 IU/mL | Range at trough: 0.05–3.57 IU/mL | Range at trough: 6–239 μg/L |
| ECT | Range at trough D 150: 44.3–103 | Not affected | Not affected | Not affected |
| | Range at trough D110: 40.4–84.6 | | | |
| | At trough: ≥3×ULN: exces beeding risk | | | |
| ACT | Rather flat dose response. No investigation on its use. | No data. Cannot be used | No data. Cannot be used | Minor effect. Cannot be used |
| | Limited utility | | | |

Modified from [19]
*S* seconds, *ULN* upper limit of normality, *IU* international unit

NOAC discontinuation associated with general measures should generally be sufficient [18].

In the management of life-threatening major bleeding, indications may also come from coagulation tests (Table 12.8) [19], although clinical experience is lacking.

### 12.2.1 Initial Management

- Owing to the absence of life-threatening features of the bleeding event, a conservative approach was selected.
- The risk of stroke as estimated by a CHA2DS2-VASc score of 3 was considered sufficiently low to allow for a short interruption of OAC.
- Dabigatran 110 mg twice daily (last dose taken 8 h before) was therefore immediately withdrawn.
- Urgent gastroscopy was also scheduled for the search of the bleeding source.

## 12.3 Further Management Issues

While NOAC interruption should be regarded as the initial, mandatory measure to treat bleeding, in a patient on TT early after PCI with stent, consideration should also be given to how to manage antiplatelet therapy. Every effort should be made not to interrupt both aspirin and clopidogrel at the same time. Withdrawal of one antiplatelet (generally aspirin) may be performed, provided that at least 1 and 3–6 months have elapsed from bare-metal and new-generation drug-eluting stent implantation. Within those time periods, the management should be individualized based on the actual risk of adverse events with antiplatelet interruption compared to no interruption. While there are no data available, consideration of platelet transfusions appears largely unfeasible due to the possible increase in adverse thrombotic events [20].

Withdrawal of antiplatelet therapy is likely of greater importance as regard to the risk of stent thrombosis rather than that of recurrent cardiac events, which is hardly affected by a short (days to weeks) interruption of secondary prevention with antiplatelet therapy. Albeit nonspecific data are available, the risk of thrombosis associated with the (temporary) withdrawal of one antiplatelet agent when 6 months have elapsed from BVS implantation should generally be regarded as low. It should nonetheless go overlooked that BVS may be associated to an increase in device thrombosis as compared to new-generation drug-eluting stents [21, 22].

### 12.3.1 Further Management

- Aspirin was discontinued, while clopidogrel was continued.
- Gastroscopy was performed, and a hemorrhagic gastritis was detected.
- Gastric protection with pantoprazole 40 mg once daily was started.

- Coronary angiography was then planned with the aim of assessing whether angina was related to in-stent restenosis or to myocardial ischemia secondary to the anemia.
- Upon coronary angiography, which was performed at day 5 from the hospital admission, in the LAD was widely patent, with TIMI 3 flow (Fig. 12.3) An optical coherence tomography (OCT) pullback was performed in both the LAD and the diagonal. Axial frames (Fig. 12.4a) and longitudinal reconstructions (Fig. 12.4b) obtained from the LAD pullback showed a fully deployed scaffold in the LAD, with partial reabsorption and complete endothelialization at the distal edge (Fig. 12.4c), complete endothelialization and protrusion of two struts into the ostium of the diagonal at the bifurcation (Fig. 12.4d), and partial reabsorption with incomplete endothelial coverage of the scaffold at the proximal edge (Fig. 12.4e). OCT views of the diagonal showed a thick cap fibroatheroma distal to the bifurcation (Fig. 12.4f) and a strut protruding into the ostium (*arrowhead*), but leaving a good ostium opening at the bifurcation site (Fig. 12.4 g).

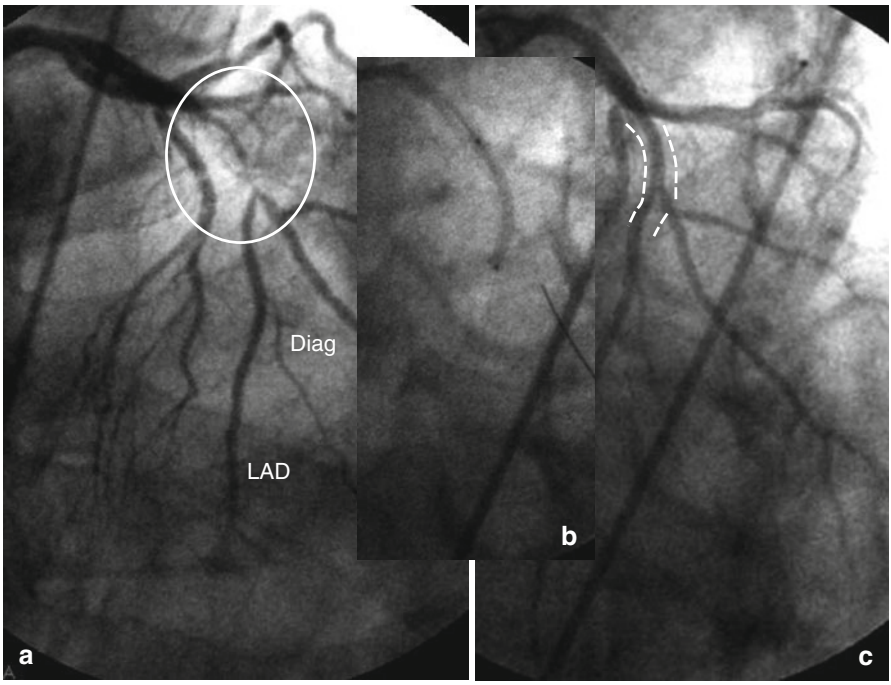


**Fig. 12.3** Baseline (**a**), during (**b**), and after (**c**) stent implantation coronary angiogram of left coronary artery (RAO view cranial). *RAO* right anterior oblique

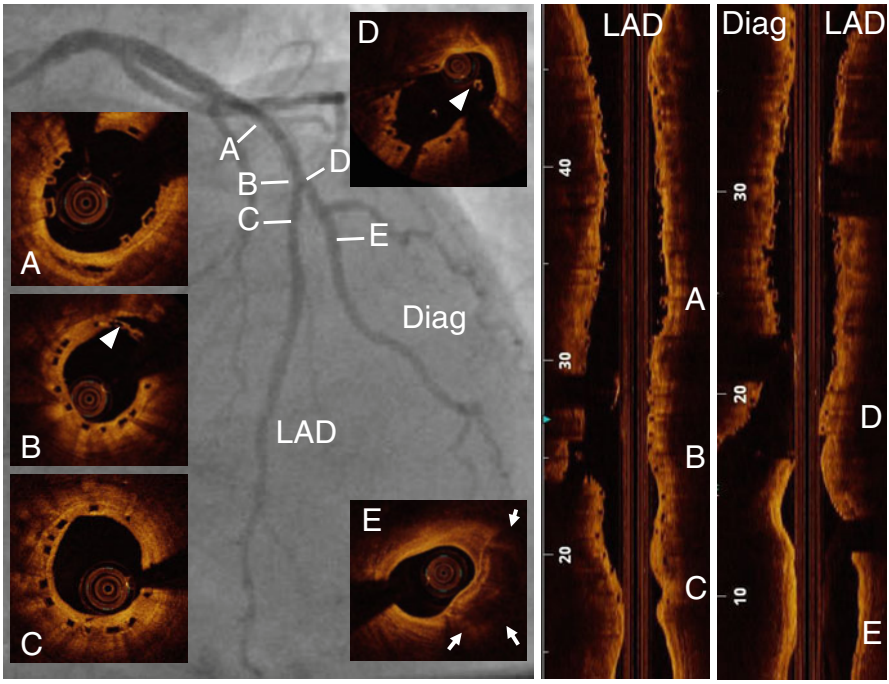


**Fig. 12.4** Optical coherence tomography (OCT) of left anterior descending (LAD) and diagonal branch after stent implantation at different cross sections (See Box 12.3.1)

## 12.4 Post-acute Issues

After controlling bleeding and identifying (and treating) the source of hemorrhage, the key question is whether and how antithrombotic therapy should be modified and when should it be restarted. The risk of (re)bleeding should guide the choice of subsequent antithrombotic therapy together with the residual risk of stent thrombosis and recurrent cardiac events.

Continuation of OAC should generally not be questioned when the stroke risk is increased. It is less certain whether the same NOAC ongoing at the time of bleeding should be continued or another NOAC should be prescribed or warfarin should be prescribed instead. Overall the NOACs generally show similar (and in some cases superior) efficacy and safety, in terms of stroke/systemic embolism prevention and major bleeding, when compared to warfarin (Table 12.9) [23–26]; NOACs are associated overall to an approximately 25 % increase in the incidence of gastrointestinal bleeding [27]. Of the various NOACs, apixaban 5 mg twice daily and dabigatran 110 mg twice daily are the only two agents that show no significant increase in gastrointestinal (GI) bleeding compared to warfarin (Table 12.9). In contrast, the risk of GI bleeding appears significantly increased with dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, and edoxaban 60 mg once daily compared to warfarin (Table 12.9).

**Table 12.9** Efficacy and safety of non-vitamin K-antagonist oral anticoagulants vs. warfarin in clinical trials on shake prevention in AF (hazard ratio; 95 % confidence intervals) [23–26]

| | Dabigatran 110 mg BID | Dabigatran 150 mg BID | Rivaroxaban 20 mg[a] OD | Apixaban 5 mg[b] BID | Edoxaban 30 mg BID | Edoxaban 60 mg BID |
|---|---|---|---|---|---|---|
| Stroke or systemic embolism | 0.91[c] (0.74–1.11) | 0.66[d] (0.53–0.82) | 0.88[c] (0.74–1.03) | 0.79[d] (0.66–0.95) | 1.07[c] (0.87–1.31) | 0.79[c] (0.63–0.99) |
| Major bleeding | 0.80[e] (0.69–0.93) | 0.93 (0.81–1.07) | 1.04 (0.90–1.20) | 0.69[e] (0.60.0.80) | 0.47[e] (0.41–0.55) | 0.80[e] (0.71–0.91) |
| Intracranial bleeding | 0.31[e] (0.20–0.47) | 0.40[e] (0.27–0.60) | 0.67[e] (0.47–0.93) | 0.42[e] (0.30–0.58) | 0.30[e] (0.21–0.43) | 0.47[e] (0.34–0.63) |
| Gastrointestinal bleeding | 1.10 (0.86–1.41) | 1.50[e] (1.19–1.89) | 1.60[e] (1.29–1.98) | 0.89 (0.70–1.15) | 0.67[e] (0.53–0.83) | 1.23[e] (1.02–1.50) |

*BID* twice daily, *OD* once daily, *AF* atrial fibrillation
[a]15 mg OD in patients with creatinine clearance 30–50 ml/min
[b]2.5 mg BID in patients with two of the following three features: age ≥ 80 years, weight ≤ 60 kg, creatinine ≥ 1.5 ml/min
[c]Significant for non-inferiority
[d]Significant for superiority
[e]Statistically significant

Based on the long-lasting experience with warfarin management, as well as with it as the OAC in patients treated with PCI, warfarin might be considered as an alternative to NOACs. However, warfarin is less convenient as oral anticoagulant agent, given the need for several days before being effective and the relevant risk of bleeding upon introducing OAC in naïve patients [28]. Also, available data show that the overall safety profile of NOACs is superior to warfarin and that major bleeding events, even when managed conservatively (i.e., with no specific antidotes), generally have a favorable outcome [13–15]. Thus, ongoing NOAC may be confirmed, with consideration to possibly switching to the "safest" ones, that is, apixaban 5 mg twice daily or dabigatran 110 mg twice daily, or to reduce the dose (when indicated for the specific NOAC and therefore essentially downgrading dabigatran from 150 to 110 mg twice daily).

Whether dual, single, or even no antiplatelet therapy should be given in conjunction with NOAC after a major bleeding event, this essentially depends once again on the time from (and type of) stent implantation, the clinical setting where PCI has been performed, and the individual risk of bleeding. Following a bleeding event occurring within the first 3–6 months from bare-metal or new-generation drug-eluting stent or BVS implantation in the context of ACS, DAPT of aspirin and clopidogrel should generally be given together with warfarin. Upon

stratification of the risk of bleeding by applying the HAS-BLED score (Table 12.2), a shorter duration of 1 month only may be considered when the estimated bleeding risk is high (i.e., HAS-BLED score $\geq 3$) and either a bare-metal or new-generation drug-eluting stent (especially durable polymer zotarolimus-eluting or absorbable polymer everolimus-eluting) (Table 12.10) has been implanted, irrespective of whether PCI has been performed in the setting of stable vs. unstable coronary artery disease.

Beyond the first 3–6 months of stent implantation, continuation of NOAC and single antiplatelet agent (either aspirin or – preferably – clopidogrel) should generally be preferred as the risk of stent thrombosis, and/or recurrent cardiac events have largely decreased compared to the previous period. Should a major bleeding occur after the first 3–6 months of TT, when the patient is on dual therapy with NOAC and single antiplatelet agent (preferably clopidogrel), resumption of both agents should generally be preferred after bleeding control up to 1 year from the index event.

After effective management of bleeding (without interruption of DAPT), a further issue is when to restart NOAC. Because of NOAC pharmacology (Table 12.5), given that only approximately 2–3 h is required before a therapeutic anticoagulation effect is reached, these agents may and should be restarted after effective hemostasis and bleeding control. Clopidogrel should be restarted as soon as possible either with 300–600 mg oral loading depending on the duration of interruption and the required rapidity for an effective antiplatelet effect [29].

Given the persistent increased risk of bleeding from the (upper) gastrointestinal tract, adjunct proton-pump inhibitor gastric protection is advisable throughout combined NOAC and (single or dual) antiplatelet therapy [30].

An overview of the suggested strategies for the management of a major bleeding event in a NOAC patient, who has undergone PCI with stenting, is given in Table 12.11.

**Table 12.10** General classification of coronary stents/scaffolds

| | | |
|---|---|---|
| BMS | | (a) Stainless steel<br>(b) Non-stainless steel, cobalt- or platinum-chrome alloy |
| DES | Early generation | (a) Durable polymer: sirolimus and paclitaxel eluting |
| | New generation | (a) Durable polymer: zotarolimus and everolimus eluting<br>(b) Biodegradable polymer: biolimus A9 and everolimus eluting<br>(c) Polymer-free: biolimus A9 and amphilimus eluting |
| BAS | | (a) Diamond-like carbon coated, titanium nitric oxide coated<br>(b) Endothelial progenitor cell capturing |
| BVS | | (a) Nondrug eluting<br>(b) Everolimus, myolimus, and sirolimus eluting |

*BMS* bare-metal stent, *DES* drug-eluting stent, *BAS* bioactive stent, *BVS* bioresorbable vascular scaffold

**Table 12.11** Strategies for the management of major bleeding at various time points following PCI with stent

| | During TT | During NOAC + SAPT | During NOAC only |
|---|---|---|---|
| NOAC interruption | Recommended | Recommended | Recommended |
| NOAC reversal | To be considered[a] | To be considered[a] | To be considered[a] |
| Withdrawal of both antiplatelets | Not recommended | – | – |
| Withdrawal of one antiplatelet | To be considered | Recommended | – |
| General measures to preserve circulation[b] | Recommended | Recommended | Recommended |
| Endoscopic and/or surgical hemostasis[c] | Recommended | Recommended | Recommended |

*TT* triple therapy, *PCI* percutaneous coronary intervention, *SAPT* single antiplatelet therapy, *NOAC* non-vitamin K-antagonist oral anticoagulant
[a]In life-threatening bleeding
[b]For example, plasma expanders, blood transfusions, inotropic support, etc.
[c]When feasible

### 12.4.1 Long-Term Management

- Because of the moderate risks of stent thrombosis and recurrent coronary events associated with the time elapsed from PCI, the HAS-BLED score of 2, as well as the conservative approach adopted in the management of bleeding, aspirin was permanently stopped, and dual therapy with dabigatran 110 mg twice daily and clopidogrel 75 mg continued up to 12 months.
- Gastric protection with pantoprazole 20 mg once daily was continued for as long as combination therapy of NOAC and clopidogrel was given.
- Remaining therapy with ramipril 5 mg twice daily and atorvastatin 40 mg daily was confirmed.

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