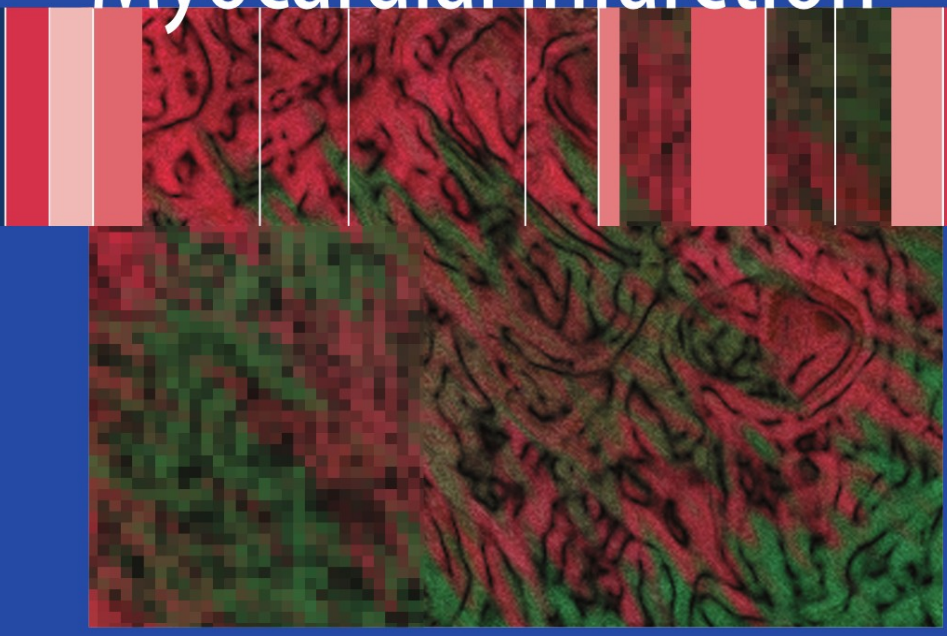
James E. Tcheng *Editor*

Primary Angioplasty in Acute Myocardial Infarction



Second Edition

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Primary Angioplasty in Acute Myocardial Infarction

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Primary Angioplasty in Acute Myocardial Infarction

Second Edition

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Preface

The past 50 years have witnessed a breathtaking evolution in the approaches to the patient with an acute ST elevation myocardial infarction. In the 1960s, the now commonplace cardiac intensive care unit was but a nascent idea. Without much to offer the patient but weeks of absolute bedrest, substantial morbidity and high rates of mortality were the norm. Just 30 years ago, seminal discoveries by DeWood and colleagues suggested that the culprit was plaque rupture with thrombosis, not progressive luminal compromise. Subsequent fibrinolytic-based strategies resulted in a halving of the mortality of acute myocardial infarction. With the introduction of balloon angioplasty in the late 1970s, a few interventional cardiologists braved the question: why not perform emergency angioplasty as a primary reperfusion strategy? Indeed, reports of successful reperfusion via balloon angioplasty appeared (mostly in local newspapers) as early as 1980. Despite being thought of as heretical by mainstream cardiology, these pioneers nonetheless persevered, proving the benefit of "state-of-the-art" balloon angioplasty compared with "state-of-the-art" thrombolytic therapy in a series of landmark trials published in the New England Journal of Medicine in March of 1993.

Publication of the first edition of *Primary Angioplasty in Acute Myocardial Infarction* in 2002 to some extent anticipated the widespread acceptance of primary percutaneous coronary intervention as the standard of care. Since then, in all respects, the evolution of emergency percutaneous revascularization has only accelerated. The universal replacement of balloon angioplasty with stent implantation was clearly one key. But to put this edition in context, it was after the publication of the first edition that the findings of the DANAMI 2 (Danish Multicenter Randomized Study on Fibrinolytic Therapy versus Acute Coronary Angioplasty in Acute Myocardial Infarction) and the PRAGUE 2 (Primary Angioplasty in Acute Myocardial Infarction Patients from General Community Hospitals Transported for Percutaneous Transluminal Coronary Angioplasty Units Versus Emergency Thrombolysis), trials affirmed that emergency intervention still resulted in better outcomes than fibrinolytic therapy, even when transfer was required from a "first responder" hospital to a tertiary referral center. A multitude of additional studies have further refined our knowledge and strategies. Indeed, the question of whether to

implant a stent during acute coronary intervention seems like ancient history; even the moniker "angioplasty" feels dated.

It is both an honor and a pleasure to bring together in this edition the latest concepts and information about this lifesaving approach. The evidence for primary coronary intervention as the standard of care of the patient sustaining an acute myocardial infarction, along with technical and system-related considerations for successfully accomplishing this procedure, is detailed in the first four chapters. These chapters describe requisite fundamentals for any primary angioplasty program. Chapters 5 and 6 tackle the complexities of reducing door to balloon time, covering options available to primary care hospitals without surgical backup and addressing local and regional system and process-related barriers to reperfusion. Chapters 7–10 survey the strategies frequently considered in contemporary practice and include both beneficial findings and negative results that may potentially challenge old habits. A glimpse of the future is provided in Chapter 11, an overview of cell therapies targeting the regeneration of myocardium following cell death secondary to acute myocardial infarction. The final chapter reviews the economics of this approach, particularly critical in our resource-constrained health care environment.

I am grateful to my colleagues, the authors of the chapters of this edition, for their willingness to share their knowledge, experiences, research, and insights. In an age where free time is ever diminishing, it is a tribute to their dedication to the highest quality clinical care that they were willing to spend so much time putting pen to paper (or fingers to keyboard) so that we could all benefit. I would also like to extend a special note of thanks to Joyce Sizemore for her skillful administrative assistance. Most importantly, I dedicate this book to my forever sweetheart, Marianne Powers, without whose patience, understanding, and love this project could not have been accomplished.

Durham, NC James E. Tcheng

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Chapter 1
Overview, Rationale, and Lexicon: Primary Percutaneous Coronary Intervention in Acute Myocardial Infarction

Warren J. Cantor

Angiographic and pathologic studies have contributed greatly to our understanding of the pathogenesis of acute coronary syndromes. "Vulnerable" atherosclerotic plaque, characterized by thin fibrous caps, lipid-rich cores, and infiltration of leukocytes, undergo ulceration, fissure, or rupture [1–3]. Exposure of subendothelial collagen leads to adhesion and activation of platelets. The coagulation cascade is initiated by subendothelial tissue factor as well as vasoactive substances secreted by activated platelets. These processes result in platelet aggregation, thrombin generation, and fibrin deposition, ultimately leading to coronary thrombosis. In the case of ST-segment elevation acute myocardial infarction (MI), the thrombosis is usually occlusive, resulting in transmural myocardial necrosis [4] Reperfusion therapy, whether catheter-based or pharmacological, is critically needed to restore antegrade flow to the infarct-related artery and thus arrest the propagating wave of necrosis [5]. In order to preserve myocardium and reduce morbidity and mortality, reperfusion must be rapid, complete, and sustained.

Traditionally, pharmacologic and catheter-based reperfusion therapies have been considered distinct and mutually exclusive strategies. Each strategy has its own advantages and shortcomings. Fibrinolytic therapy is widely available and can be given rapidly in emergency departments. Even with the most efficacious fibrinolytic agents, however, normal (TIMI-3) flow at 90 minutes is achieved in only 50–60% of patients [6–8] Intracranial hemorrhage occurs in approximately 1% of patients treated with fibrinolytic therapy and is fatal in 60% of cases [9].

In contrast, primary percutaneous coronary intervention (PCI) results in TIMI-3 flow in over 70% of patients and patency (TIMI-2 or -3 flow) in over 90% of patients, without the hemorrhagic risks of fibrinolytic therapy [10–12]. However, emergency PCI facilities are available in only a minority of hospitals. Even in hospitals equipped to perform PCI, the time required to deliver patients to the catheterization laboratory results in an average delay of two hours from

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hospital arrival to the first balloon inflation [13]. Primary PCI performed within 90–120 minutes of hospital arrival is associated with improved survival compared with PCI performed beyond 120 minutes [13–15].

PCI not only restores brisk antegrade flow but also treats the underlying stenosis. Almost 90% of patients with patent infarct-related arteries at 90 minutes after fibrinolytic therapy have a residual stenosis $\geq$50% at the culprit lesion [16]. Successful PCI of hemodynamically significant stenoses should therefore, at least in theory, reduce the risk of recurrent ischemia and reinfarction. Meta-analyses of trials comparing fibrinolytic therapy with primary PCI have found lower rates of reinfarction and recurrent ischemia with primary PCI [17, 18]. In the GUSTO-IIb study, the difference in reinfarction did not become apparent until after five days, lending further credence that the benefits of primary PCI extend beyond early restoration of TIMI-3 flow [12].

There are various contexts in which PCI can be performed in the setting of acute MI (Table 1.1). Primary PCI (also referred to as direct PCI) refers to percutaneous coronary revascularization applied as the initial reperfusion strategy. Primary PCI has been compared with fibrinolytic therapy in over 20 randomized trials and summarized in at least 7 meta-analyses [17–23]. Primary PCI is associated with lower rates of death, reinfarction, recurrent ischemia, and stroke but higher rates of major bleeding [18]. Five trials compared transfer for primary PCI with on-site fibrinolytic therapy for STEMI patients presenting to centers without PCI facilities. A meta-analysis of these trials showed significant reductions in reinfarction and stroke with primary PCI [19]. However, the transfer times in these trials were relatively short, with an average time from randomization to PCI of approximately 90 minutes [24]. Four of the five trials were carried out in European countries with well developed infrastructures for providing rapid interhospital transfers. In contrast, the median time from initial hospital arrival to first balloon inflation was 180 minutes in the National Registry of Myocardial Infarction (NRMI) 3/4 registries carried out in the United States [24].

PCI can also be used for patients who have already received fibrinolytic therapy. The latter category includes rescue PCI for patients who have failed to

Table 1.1 Varieties of Percutaneous Coronary Intervention (PCI) following Acute Myocardial Infarction

	Thrombolytic Therapy Prior to PCI?	Successful Reperfusion after thrombolysis	Timing of PCI after thrombolysis
Direct (Primary, Emergency)	No	N/A	N/A
Rescue (Salvage)	Yes	No	1.5–12 hours
Immediate (Facilitated)	Yes	+/–	Immediate
Early	Yes	Yes	12–48 hours
Deferred (Elective)	Yes	Yes	> 48 hours

N/A = not applicable.

reperfuse [25, 26] and adjunctive PCI, in which all patients routinely undergo catheterization after thrombolysis with PCI performed whenever technically feasible, irrespective of the patency status of the culprit vessel. Adjunctive PCI has been studied at three time-points: immediate (PCI within two hours after thrombolysis), early (2–24 hours after thrombolysis), and deferred (> 24 hours after thrombolysis) (Table 1.1).

Three large randomized trials of immediate and early adjunctive PCI were carried out in the 1980s and showed no benefit with PCI, with increased rates of bleeding complications and a trend towards increased mortality [27–29]. However, these trials were carried out prior to the widespread use of coronary stents, thienopyridines, and glycoprotein (GP) IIb/IIIa receptor antagonists. Patients with acute MI treated with fibrinolytic therapy have increased levels of platelet activation and aggregation [30, 31] and may be predisposed toward thrombotic complications during percutaneous coronary intervention. The GP IIb/IIIa antagonists appear to counteract this prothrombotic state [30]. More recent trials using coronary stents and contemporary pharmacotherapy have shown improved outcomes with routine early PCI after thrombolysis [32, 33]. Facilitated PCI has been proposed as a strategy in which pharmacologic agents (fibrinolytics and/or GP IIb/IIIa antagonists) are administered, followed immediately by PCI [34]. The rationale behind this strategy is that reperfusion will occur in a higher proportion of patients prior to PCI, which may help preserve myocardium during the delay from presentation to the first balloon inflation. Despite encouraging findings of observational studies and small trials [35–38], facilitated PCI with thrombolytic therapy was associated with worse clinical outcomes in the large ASSENT-4 randomized trial and a subsequent meta-analysis [39, 40]. The FINESSE trial showed no benefit and higher bleeding rates for facilitated PCI using a combination of fibrinolytic therapy and GP IIb/IIIa antagonists, or GP IIb/IIIa antagonists alone [41].

Following successful PCI, long-term patency of the infarct vessel may be compromised by restenosis or reocclusion. Nakagawa and colleagues performed serial angiography on 137 patients after successful primary PCI at three weeks, four months, one year, and three years [42]. The cumulative restenosis rates (including reocclusion) were 20%, 43%, 47%, and 49%, respectively. By three weeks, 16 patients (12%) had reocclusion of the infarct vessel, and only three patients developed reocclusion beyond three weeks. The use of coronary stents and GP IIb/IIIa antagonists would be expected to help prevent restenosis and reocclusion. The Stent-PAMI and CADILLAC trials confirmed that stenting reduces the incidence of restenosis and repeat target vessel revascularization after primary PCI [43, 44].

Drug-eluting stents significantly reduce restenosis and target lesion revascularization rates compared with bare metal stents [45]. Initial reports from observational studies, trials, and meta-analyses without patient-level data raised concerns about the potential for increased risk of stent thrombosis, myocardial infarction, and death after implantation of drug-eluting stents [46–48]. Subsequent meta-analyses of actual clinical data applying standardized definitions of stent thrombosis did not show any significant difference in death,

myocardial infarction, or overall stent thrombosis rates at four years follow-up [45, 49–51]. However, there appears to be a small but significant increase in the rate of stent thrombosis beyond one year [45, 47, 49]. There have been two randomized trials compared drug-eluting stents with bare metal stents for primary PCI, one using sirolimus-eluting stents (TYPHOON, n = 712) and one using paclitaxel-eluting stents (PASSION, n = 619) [52, 53]. In both trials, there was no difference in the rates of death, reinfarction, or stent thrombosis at one year. Target-vessel revascularization was significantly reduced with sirolimus-eluting stents (5.6% vs. 13.4%; $p<0.001$), but only a trend to lower target-lesion revascularization was seen with paclitaxel-eluting stents (5.3% vs. 7.8%; $p = 0.23$). The different results in these trials may be related to differences in patient and angiographic characteristics, use of routine angiographic follow-up (performed in a subgroup of TYPHOON patients but not in PASSION), true differences in the restenosis rates of the drug-eluting stents, and/or the bare-metal stents used in the control groups or chance. In both trials, the repeat revascularization rates in the control groups were much lower than seen in the elective PCI trials using the same stents. The use of routine angiographic follow-up in the elective PCI trials may have increased repeat revascularization rates and the absolute reduction in repeat revascularization with drug-eluting stents. Alternatively, symptomatic restenosis may occur less often after primary PCI, as less viable myocardium is supplied by the target vessel compared with elective PCI. The HORIZONS AMI trial will randomize 3400 patients undergoing primary PCI to stent implantation with either a paclitaxel-eluting stent or a bare-metal stent, and preliminary results should be available in 2008 [54].

Finally, the platelet GP IIb/IIIa receptor antagonists, particularly abciximab, have been extensively studied as pharmacologic adjuncts in primary PCI. In the ADMIRAL study, patients undergoing primary PCI with stent implantation were randomized to receive abciximab or placebo [55]. The patients treated with abciximab had higher rates of TIMI-3 flow at 24 hours (86% vs. 78%; $p<0.05$) and lower rates of death, MI, or urgent revascularization at 30 days (10% vs. 11%; $p<0.03$). The CADILLAC trial demonstrated that abciximab significantly reduces the incidence of major adverse cardiac events (4.6% vs. 7.0%; $p = 0.01$) and subacute stent thrombosis (0.4% vs. 1.5%; $p = 0.01$) at 30 days [56]. In the STOPAMI trial, patients randomized to primary PCI with stenting and abciximab had improved myocardial salvage compared with thrombolytic therapy [57]. A meta-analysis documented lower rates of death and reinfarction with abciximab [58].

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Chapter 2
Comparison of Reperfusion Strategies for ST Elevation Acute Myocardial Infarction: Primary Coronary Intervention Versus Fibrinolysis

Bruce R. Brodie

Historical Background

The reperfusion era for acute myocardial infarction was heralded by the demonstration of Rentrop and colleagues in 1979 that an acutely occluded coronary artery could be successfully recanalized with the combination of *pharmacologic intervention* with the infusion of intracoronary streptokinase and *mechanical intervention* with a guidewire [1]. Multiple clinical trials subsequently demonstrated the effectiveness and survival benefit of intravenous streptokinase, and thrombolytic therapy became the standard of care as reperfusion therapy for ST-segment elevation acute myocardial infarction (STEMI) in the late 1980s and 1990s [2–4]. During the same time period, Hartzler and others demonstrated that mechanical reperfusion with primary angioplasty was also a highly effective reperfusion strategy [5–7]. While it was clear that primary angioplasty had certain advantages over thrombolytic therapy in achieving greater patency rates and avoiding the life-threatening complication of intracranial hemorrhage, primary angioplasty did not become a competitive reperfusion strategy until the early 1990s with the publication of the PAMI (Primary Angioplasty in Myocardial Infarction) and Zwolle Trials [8–9]. Subsequently, there have been a number of randomized trials comparing primary PCI with fibrinolysis which have established the role of primary PCI as the preferred reperfusion strategy for STEMI when delivered by experienced operators in a timely fashion. The purpose of this chapter is to review the cumulative data regarding the primary PCI approach.

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Comparison of Clinical Outcomes

Clinical Outcomes from Randomized Trials

Following the initial publication of the PAMI and Zwolle Trials comparing balloon angioplasty to first and second generation fibinolytic agents, there have been a large number of subsequent randomized trials comparing the two strategies. Keeley and Grines have performed a meta-analysis of 23 of these trials, studies which enrolled a total of 7739 patients in comparisons of primary PCI with fibrinolytic therapy [10]. Primary PCI was superior to fibrinolytic therapy in reducing short-term mortality (5.3% vs. 7.4%, $p = 0.0003$), nonfatal re-infarction (2.5% vs. 6.8%, $p < 0.0001$), stroke (1.0% vs. 2.0%, $p = 0.0004$), and the composite endpoint of death, nonfatal re-infarction, and stroke (8.2% vs. 14.3%, $p = 0.0001$) (Fig. 2.1). These favorable results were maintained at long-term follow-up and were independent of the type of thrombolytic agent used (streptokinase vs. fibrin-specific thrombolytics) and whether patients were enrolled at the primary PCI hospital or were an emergency transfer for primary PCI from non-PCI hospitals. The incidence of intracranial hemorrhage was significantly less with primary PCI (0.05% vs. 1.1%, $p < 0.0001$), but the overall risk of major bleeding (mostly related to access-site bleeding) was higher with primary PCI (6.8% vs. 5.3%, $p = 0.03$). The risk of access-site bleeding with primary PCI appears to be less in more recent trials with better management of anticoagulation and earlier femoral artery sheath removal.

The survival benefit of primary PCI compared with fibrinolytic therapy reported in this meta-analysis was substantial (21 lives saved per 1000 patients treated) and is of similar magnitude to the survival benefit of fibrinolytic therapy compared with placebo reported by the Fibrinolytic Therapy Trialists' (FTT) Collaborative Group (19 lives saved per 1000 patients treated) (Fig. 2.2) [4]. The relative reduction in death and nonfatal re-infarction is similar across

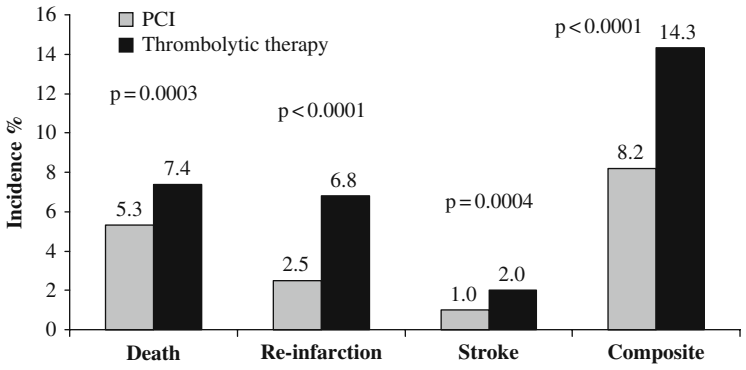

Fig. 2.1 Meta-analysis of 23 randomized trials comparing short term outcomes with primary PCI versus thrombolytic therapy for STEMI. Adapted from Keeley et al. with permission [10]

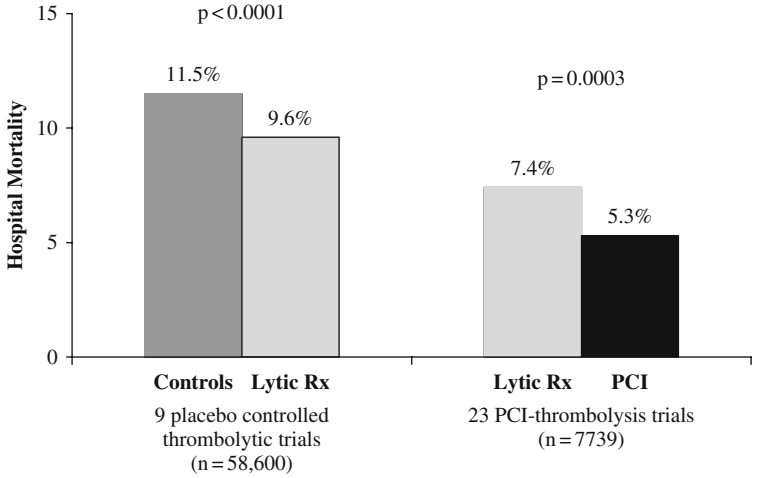

Fig. 2.2 Comparison of mortality reduction with thrombolytic therapy versus placebo[4] and primary PCI versus thrombolytic therapy [10]

all subgroups of patients treated, including elderly patients, women, diabetics, patients with anterior or non-anterior infarction, patients with prior infarction, and patients classified as at low risk or not at low risk.

Of importance, the greatest absolute benefit of primary PCI in AMI has been seen in patients at highest risk, and several randomized trials have specifically evaluated these high-risk subgroups. The SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) Trial, which randomized 302 patients with cardiogenic shock to emergency revascularization versus medical stabilization, found a lower 6-month mortality with emergency revascularization (50 vs. 63%, $p = 0.03$) [11]. The survival benefit was especially pronounced in patients treated within 6 hours of symptom onset but was seen only in patients under the age of 75 years. Garcia and colleagues randomized 220 patients with anterior infarction to primary PCI versus alteplase and found substantially lower mortality with primary PCI (2.8% vs. 10.8%, $p = 0.02$) [12]. Recently, Grines and colleagues reported results from SENIOR PAMI, a study that randomized 481 elderly patients (>70 years old) to fibrinolytic therapy versus primary PCI [13]. The difference in the primary endpoint of death or stroke between groups did not reach statistical significance (11.3% vs. 13.1%, p = NS), but patients treated with PCI had a lower incidence of combined major adverse cardiac events (MACE) at 30 days (death, re-infarction, or stroke) (11.6% vs. 18%, p = 0.05). Thus, although event rates are high with both strategies, elderly patients do appear to do better with primary PCI. An exception is the very elderly patient ($\geq$ 80 years), who did not appear to benefit.

The initial clinical benefit of primary PCI over fibrinolytic therapy in reducing death and re-infarction appears to be maintained at late follow-up. The

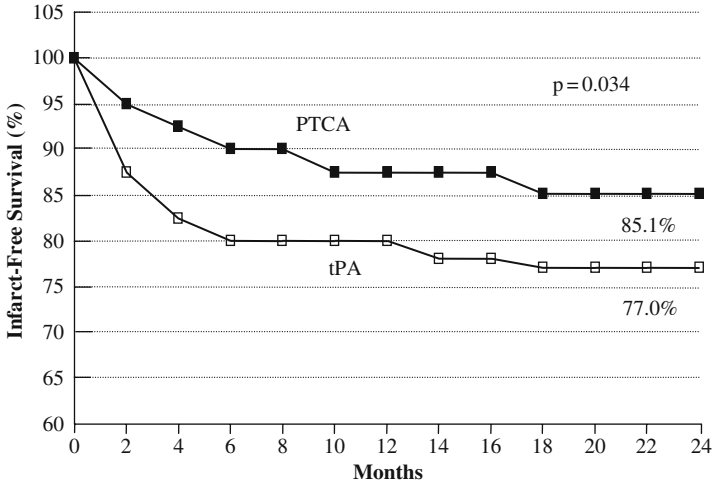

Fig. 2.3 Actuarial infarction-free survival curves for patients with acute myocardial infarction treated with primary angioplasty (PTCA) (*solid boxes*) versus tissue plasminogen activator (tPA) (*open boxes*). Reproduced with permission from Nunn, et al. [14]

PAMI investigators found that death or re-infarction was lower at 2 years with primary PCI versus fibrinolytic therapy (14.9% vs. 23.0%, $p = 0.03$) (Fig. 2.3) [14]. Similarly, the Zwolle investigators found lower mortality (13.4% vs. 23.9%, $p = 0.01$) and less re-infarction (6.2% vs. 21.9%, $p < 0.0001$) with primary PCI compared with streptokinase at 5 years [15]. Both studies found a lower frequency of hospital readmissions with primary PCI. Keeley's recent meta-analysis also showed that the initial benefit with primary PCI was maintained at late follow-up of 6 to 18 months [10].

Clinical Outcomes from Registries

Most randomized trials comparing mechanical reperfusion with primary PCI were performed before the most recent advances in both of these reperfusion strategies. Outcomes with *mechanical reperfusion* have improved considerably with increased operator experience, better imaging, better wires, smaller balloons, the introduction of stents, and better adjunctive pharmacology. Coronary stenting has substantially decreased target vessel revascularization and infarct artery re-occlusion [16,17]. Since stents were available as a "bail-out" strategy in the balloon arms of randomized trials (Stent PAMI and CADILLAC [Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications]), differences in mortality and re-infarction rates appear to have been effectively mitigated [16,17]. Thus the availability of "bail-out" stenting has reduced the need for emergency surgery and is likely at least partly

responsible for trends for decreased rates of re-infarction. The addition of platelet glycoprotein IIb/IIIa inhibitors has decreased ischemic complications and meta-analyses have shown that abciximab may also reduce mortality [18].

Improvements with *pharmacologic reperfusion strategies* have been less impressive. Initial encouraging results of pilot studies showing improved patency rates with combination therapy using half dose lytic therapy plus glycoprotein IIb/IIIa inhibitors have not translated into clinical benefit in major randomized trials. Both GUSTO V (Global Use of Strategies to Open Occluded Coronary Arteries) and ASSENT-3 (Assessment of the Safety and Efficacy of a New Thrombolytic Regimen) found some improvement with combination therapy in reducing ischemic events but this was offset by increased bleeding risk such that there was no overall net benefit [19,20]. It appears that reperfusion rates may have reached a plateau with thrombolytic therapy and that more aggressive strategies result in unacceptable bleeding rates.

Clopidogrel appears to improve outcomes with both strategies. The use of adjunctive clopidogrel given up front at the time of thrombolytic administration has reduced infarct artery re-occlusion and has reduced ischemic events as documented in the recent CLARITY (Clopidogrel as Adjunctive Reperfusion Therapy) Trial [21]. Clopidogrel has been shown to reduce ischemic events in patients with non-ST elevation acute coronary syndromes in the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) Trial and with PCI following thrombolysis in PCI-CLARITY [22,23]. Although it has not been studied directly with primary PCI, it is now widely used with all PCI procedures.

The relative improvements in mechanical reperfusion and pharmacologic reperfusion have not been compared in randomized trials, but registry data have shown greater improvement with mechanical reperfusion than with fibrinolytic therapy over the past number of years. The German MIR (Myocardial Infarction Registry) and MITRA (Maximal Individual Therapy in Acute Myocardial Infarction) Registries have shown significant trends for reduced mortality from 1994–1998 with primary PCI (13.9% to 3.8%, $p = 0.003$) but not with fibrinolytic therapy (10.2% to 12.7%, p = NS) [24]. Data from the National Registry of Myocardial Infarction (NRMI) have shown greater improvement in unadjusted in-hospital mortality from 1990 to 2005 with primary PCI (8.6% to 3.7%) compared with fibrinolytic therapy (5.5%–3.8%) [25]. The RIKS-HIA Registry (Register of Information and Knowledge about Swedish Heart Intensive Care Admissions) evaluated all patients admitted to Swedish hospitals with STEMI who were treated with reperfusion therapy at <15 hours ($n = 26{,}205$) and found a significant mortality advantage at one year with primary PCI over pre-hospital thrombolysis (PHT) and in-hospital thrombolysis (IHT) (7.6% vs. 10.3% vs. 15.9%) (adjusted hazard ratio PCI vs. PHT 0.81 [95% CI 0.69-0.94]; adjusted hazard ratio PCI vs. IHT 0.68 [95% CI 0.60-0.76]) (Fig. 2.4) [26]. The hazard ratio for one year mortality comparing primary PCI with in-hospital fibrinolytic therapy in this registry improved substantially from 1999 to 2004 (1.1[95% CI 0.8-1.5] to 0.4 [95% CI 0.3-0.5]), most likely attributable to the combination of advances described above.

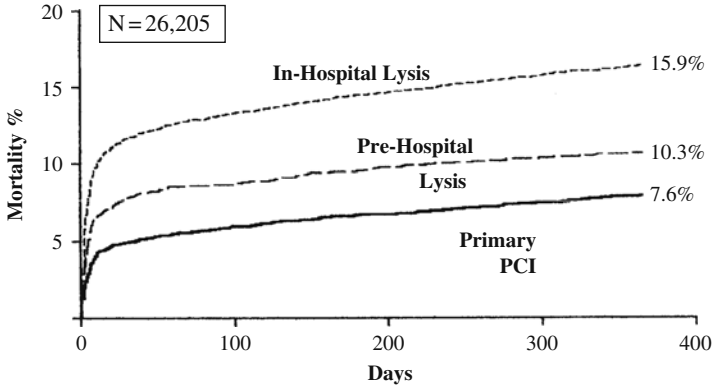

Fig. 2.4 Unadjusted Kaplan-Meier cumulative mortality curves comparing pre-hospital fibrinolysis (PHL) versus in-hospital fibrinolysis (IHL) versus primary PCI from the RIKS-HIA Registry (1999–2004) [26]

Comparison of Angiographic Outcomes and Myocardial Salvage

Angiographic Outcomes

Primary PCI can achieve Thrombolysis in Myocardial Infarction (TIMI)-3 flow in the infarct artery in >90% of patients [17,27] and has a clear advantage over thrombolytic therapy, which can achieve TIMI-3 flow in only about 54% of patients [28,29]. Achieving TIMI-3 flow has a major impact on short and long term mortality [28] and the advantage of primary PCI in achieving high rates of TIMI-3 flow is likely responsible for much of the mortality advantage over fibrinolytic therapy. Indeed, there appears to be a tight inverse relationship between short-term mortality and the ability to achieve TIMI-3 flow with various thrombolytic regimens and with primary PCI (Fig. 2.5) [8,16,17,28,30–33]. Newer fibrinolytic strategies using combination therapy with low-dose thrombolytics and platelet glycoprotein IIb/IIIa inhibitors have shown improved TIMI-3 flow rates in small pilot trials [29], but these rates are well below the TIMI-3 flow rates achieved with primary PCI, and they have not shown any mortality advantage in the large GUSTO V and ASSENT-3 trials [19,20].

While achieving TIMI-3 flow in the *epicardial* coronary artery is important, optimal outcomes with reperfusion therapy also require optimum reperfusion of the microvasculature or optimal *myocardial* reperfusion. Myocardial reperfusion is usually measured with surrogate endpoints such as electrocardiographic ST-segment resolution and angiographic measurement of myocardial blush. Achieving optimal myocardial reperfusion is a major focus of ongoing clinical research with primary PCI and is discussed in later chapters.

Late angiographic outcomes with primary PCI have been substantially improved with the use of stents [16,17]. The need for target vessel revascularization

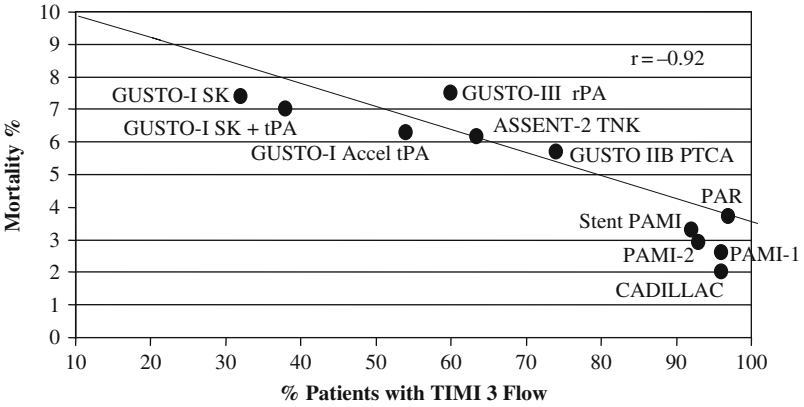

Fig. 2.5 Relationship between short term mortality and the frequency of achieving TIMI-3 flow measured acutely in the infarct artery with thrombolytic therapy from the GUSTO-I,[28] GUSTO-III,[31] and ASSENT-2 [32] Trials and several primary angioplasty (PTCA) trials [8,16,17,30,33]

at 6–9 months following primary PCI has been reduced from 15–17% with balloon angioplasty to 7–8% with stenting and re-occlusion of the infarct artery has been reduced from 10–13% to 5–6%. Target vessel revascularization is lower when stenting is used with primary PCI than with elective PCI, probably related to the lesser plaque burden in infarct artery lesions and to the fact that the infarct artery territory is often only partially viable. Whether drug-eluting stents with primary PCI will further reduce TVR enough to offset the expected small increase in late stent thrombosis is not yet known and is currently being evaluated in the HORIZONS (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) Trial.

Following fibrinolytic therapy, there is usually a significant residual stenosis in the infarct artery and late re-occlusion is frequent (20–28%) when adjunctive PCI is not employed [34,35]. Clopidogrel with aspirin has been shown to improve early infarct artery patency after thrombolytic therapy [21], but its effect on long term patency is unknown.

Myocardial Salvage

Myocardial salvage following primary PCI and fibrinolytic therapy have been evaluated in direct comparisons in several randomized trials using paired technetium-99m sestamibi scintigraphy, and all have shown better salvage with primary PCI [36–38]. Schomig and colleagues found smaller infarct size and better myocardial salvage at all tertiles of time to treatment with primary stenting versus fibrinolytic therapy (tertile 1: 0.56 vs. 0.45, $p = 0.09$, tertile 2: 0.58 vs. 0.29, $p = 0.0003$, tertile 3: 0.57 vs. 0.20, $p = 0.0005$) [38]. The greater

myocardial salvage with primary PCI is probably related to higher frequency of TIMI-3 flow in the infarct artery, less re-occlusion, and possibly better *myocardial* reperfusion.

ACC/AHA and ESC Guidelines for Reperfusion in STEMI

Guidelines for use of primary PCI and fibrinolytic therapy for STEMI from the American Heart Association and the American College of Cardiology (AHA/ACC) were published in 2004 [39]. Primary PCI is indicated (Class I indication) for STEMI (including LBBB) of <12 hours duration, if the procedure can be performed in a timely fashion (balloon inflation within 90 minutes of presentation) by an experienced interventionalist with experienced catheterization laboratory personnel. Fibrinolysis (unless contraindicated) should be administered to STEMI patients (Class I indication) when primary PCI is not available or cannot be performed within 90 minutes of presentation. The authors of the guidelines stressed that the choice of reperfusion strategy should be influenced by several factors:

1. Time from the onset of symptoms to presentation
2. STEMI risk stratification (e.g., cardiogenic shock, advanced age)
3. Risk of bleeding
4. Time required for transport for PCI

In patients presenting early after the onset of symptoms, incremental time delays significantly impact mortality. Consequently, if delays to primary PCI are long, fibrinolytic therapy should be given. In patients presenting late after the onset of symptoms, incremental time delays have less impact on mortality and transfer for primary PCI may be the preferred choice, even with longer delays to PCI. When the estimated mortality risk with STEMI is very high, such as cardiogenic shock, compelling evidence exists that favors a PCI strategy. When the risk of bleeding with fibrinolytic therapy is high, primary PCI may be the preferred reperfusion strategy, even with longer delays to PCI. Finally, when the time required to transport for PCI is very long, fibrinolysis is usually the preferred treatment.

Guidelines for reperfusion for STEMI from the European Society of Cardiology (ESC) were published in 2003 and are very similar to the AHA/ACC Guidelines [40]. Primary PCI is the preferred reperfusion strategy for patients with STEMI when it can be performed within 90 minutes of first medical contact by an experienced interventional team.

These guidelines have resulted in worldwide efforts to shorten door-to-balloon times with primary PCI in order to meet the 90 minute standard. But the guidelines have also been very controversial because of the requirement that primary PCI be performed within 90 minutes of first medical contact or else fibrinolytic therapy should be given. More data are needed to determine the

time delay where outcomes become worse with primary PCI compared with fibrinolytic therapy. These issues will be discussed further in the section below on transferring patients for primary PCI.

Fibrinolysis Versus Transfer for Primary PCI in Patients Presenting to Non-PCI Hospitals

Most primary PCI hospitals are able to meet the 90 minute door-to-balloon guidelines in patients presenting to their institution, but have difficulty meeting these guidelines in patients who present at non-PCI hospitals and require transfer to the PCI facility. This has created a great deal of controversy regarding the management of patients with STEMI presenting at non-PCI hospitals.

It had been hoped that *facilitated PCI* (the use of fibrinolytic therapy as soon as possible after the onset of symptoms to establish early reperfusion followed by transfer for emergency PCI to optimize TIMI-3 flow and stabilize the ruptured plaque with stenting) might prove to be an attractive option in these patients. Unfortunately, facilitated PCI has not been shown to be beneficial, and the recent ASSENT 4-PCI Trial found worse outcomes with facilitated PCI [41].

There have been several randomized trials which have compared fibrinolytic therapy given at the non-PCI hospital versus transfer to a PCI hospital for primary PCI. The largest of these trials are the DANAMI 2 Trial (Danish Multicenter Randomized Study on Fibrinolytic Therapy versus Acute Coronary Angioplasty in Acute Myocardial Infarction) and the PRAGUE 2 Trial (Primary Angioplasty in Acute Myocardial Infarction Patients from General Community Hospitals Transported for Percutaneous Transluminal Coronary Angioplasty Units Versus Emergency Thrombolysis) [42,43]. The DANAMI 2 Trial randomized 1,129 patients with STEMI presenting at 24 referral hospitals in Denmark to fibrinolysis with accelerated tPA versus transfer for primary PCI [42]. Patients treated with primary PCI experienced lower mortality rates (6.5% vs. 8.5%, $p = 0.20$), less re-infarction (1.9% vs. 6.2%, $p > 0.001$), and fewer MACE events (death, re-infarction, or stroke) (8.5% vs. 14.2%, $p = 0.002$). Similarly, the PRAGUE 2 Trial randomized 850 patients with STEMI presenting at 41 non-PCI hospitals to streptokinase versus transfer for primary PCI [43]. Primary PCI was associated with lower 30 day mortality (6.8% vs. 10.0%, $p = 0.12$) and significantly lower 30 day MACE (death, re-infarction, or stroke) (8.4% vs. 15.2%, $p < 0.003$). Mortality was significantly lower in patients actually treated with primary PCI versus fibrinolytic therapy (6.0% vs. 10.4%, $p < 0.05$). Dalby performed a meta-analysis of all randomized trials comparing transfer for primary PCI versus local fibrinolytic therapy and found trends for lower mortality (6.3% vs. 7.7%, $p = 0.09$) and a significant reduction in the combined endpoint of death, re-infarction, or stroke with primary PCI (RR 0.58 95% CI 0.47-0.71, $p < 0.001$) (Fig. 2.6) [44]. When the CAPTIM (Comparison of Angioplasty and Prehospital Thrombolysis In acute

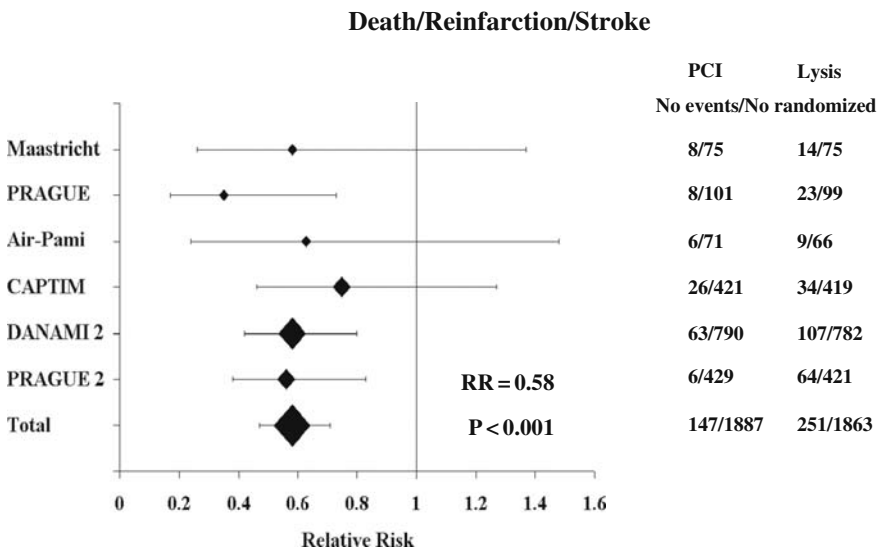

Fig. 2.6 Relative risks for the composite of death/reinfarction/stroke comparing fibrinolytic therapy at non-interventional hospitals versus transfer for primary PCI from several randomized trials. Reproduced with permission from Dalby et al. [44]

Myocardial infarction) Trial, which compared pre-hospital fibrinolyis with PCI, was excluded, mortality was less with primary PCI (RR 0.76 95% CI 0.59-0.98, $p = 0.035$) [44]. The door-to-balloon times in transferred patients in these trials ranged from 105 to 151 minutes.

Unfortunately, in the United States, transfer delays are much longer than this. Data from the NRMI found median delays of 180 minutes from arrival at the non-interventional hospital to balloon inflation at the primary PCI hospital, with only 4.2% of transferred patients achieving door-to-balloon times < 90 minutes [45]. Consequently, many patients presenting to non-primary PCI hospitals in the United States may not currently be eligible for primary PCI because of the long potential treatment delays. There are now extensive nationwide efforts to reduce door-to-balloon times with primary PCI, especially in patients transferred from non-PCI hospitals, in order to increase the utilization of primary PCI for patients with STEMI. Despite these efforts, achieving door-to-balloon times < 90 minutes may not be possible in some situations at non-PCI hospitals, and recommendations regarding triage of patients with STEMI for fibrinolytic therapy versus transfer for primary PCI in these situations remain controversial.

The meta-analysis of Boersma and colleagues of randomized trials comparing fibrinolytic therapy versus primary PCI suggested that primary PCI has a mortality advantage over fibrinolytic therapy even with additional delays to PCI (door-to-balloon minus door-to-needle time) of up to two hours (Fig. 2.7)

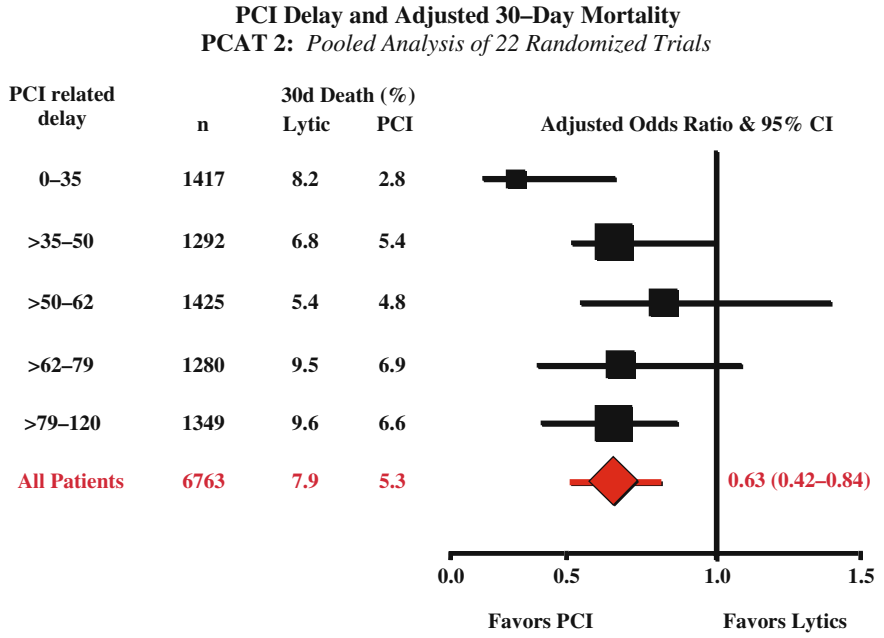

Fig. 2.7 Adjusted odds ratio (95% CI) comparing primary PCI with fibrinolytic therapy from 25 randomized trials according to the additional time delay to primary PCI. Reproduced with permission from Boersma [46]

[46]. Data evaluating the impact of treatment delays with primary PCI on mortality suggest that treatment delays impact mortality in patients presenting early after the onset of symptoms but have much less impact in patients presenting late after the onset of symptoms [47–49]. Currently, ACC/AHA guidelines recommend that patients with cardiogenic shock and patients who are ineligible for fibrinolytic therapy should be transferred for primary PCI [39]. Decisions regarding triage of remaining STEMI patients should depend on an assessment of time and risk – time to presentation, time delay to PCI, risk of bleeding from fibrinolytic therapy, and risk of the STEMI. High risk patients presenting early with long delays to primary PCI should preferentially be treated with fibrinolytic therapy and transferred to PCI hospitals for rescue PCI if needed. In patients presenting later, transfer for primary PCI may be the preferred strategy, even with longer delays to PCI.

Primary PCI as a Reperfusion Strategy

Primary PCI differs from thrombolytic therapy in that primary PCI is a strategy with several treatment options, and not all patients selected for this strategy undergo primary PCI. Following emergency cardiac catheterization,

approximately 10% of patients are triaged to either medical treatment or are treated with coronary bypass surgery as the primary reperfusion strategy [30]. Patients may be selected for coronary bypass surgery when there is severe left main disease or severe three vessel coronary artery disease with unfavorable anatomy for PCI, especially if there is preserved flow in the infarct artery. These patients may undergo emergency or urgent bypass surgery and comprise about 4% of patients brought to the laboratory for "primary PCI." About 6% of patients brought to the laboratory for primary PCI do not undergo revascularization and are treated medically. These include patients with no myocardial infarction (mistaken diagnosis), patients with no significant stenosis in the infarct artery (resolution of spasm or thrombus), patients in whom there is an inability to identify the infarct artery, and occasionally, patients with unsuitable anatomy or a very small infarct artery.

Bypass surgery is also performed on an emergency basis after failed angioplasty, urgently for re-infarction or recurrent ischemia, and electively for definitive treatment of left main or severe multi-vessel disease. With the availability of stents and improved adjunctive pharmacology, emergency and urgent bypass surgery for failed PCI or recurrent ischemia are rare. Elective bypass surgery for treatment of residual coronary artery disease after initial successful primary PCI has been used in about 4–5% of patients. Considering the severity of illness of these patients, surgical mortality has been very acceptable (2.0% with elective bypass surgery in the PAMI-2 Trial) [50].

In summary, the primary PCI strategy of performing diagnostic cardiac catheterization prior to deciding the most appropriate treatment has potential advantages over fibrinolytic therapy. Patients who have no myocardial infarction can be identified and can avoid the hemorrhagic risk of thrombolytic therapy. Selected high risk patients with left main and severe three vessel coronary artery disease can be triaged to early surgery, and low risk patients can be identified and targeted for early discharge.

Conclusions

Primary PCI has clearly emerged as the preferred reperfusion strategy for STEMI when it can be performed in a timely fashion by experienced operators. The advantage of primary PCI over fibrinolytic therapy shown in the early randomized trials appears to have widened with increased experience with PCI and with the addition of stents and new adjunctive pharmacology. As a result, the use of primary PCI has greatly increased and has surpassed the use of fibrinolytic therapy in the NRMI experience [25].

The major current issues regarding to the use of primary PCI for STEMI are related to the time delays required to achieve reperfusion, especially at hospitals without PCI capability. The AHA and ACC have embarked on major efforts to reduce door-to-balloon times and extend primary PCI to a larger proportion of

the STEMI population. Unfortunately, trials of facilitated PCI have not shown any advantage over primary PCI to date [41]. Finally, more data are needed to precisely determine the duration of delay to primary PCI (and in which patients) that compromises outcomes sufficiently to justify the administration of fibrinolytic therapy instead of direct transfer for primary PCI.

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Chapter 3
Operator and Site Requirements for Primary Coronary Intervention

Mark I. Hainer and Michael H. Sketch

Direct or primary revascularization of an infarct related coronary artery by mechanical rather than chemical means simultaneously addresses both the occlusive thrombus and underlying stenosis, is associated with an early patency rate of over 90%, and has become the standard of care of the patient presenting acutely with a myocardial infarction [1–3]. Despite these inherent benefits, primary percutaneous coronary intervention (PCI) remains a practical therapeutic option in only the minority of facilities where continuous access to an operating catheterization laboratory is available. Only 20% of hospitals in the United States have cardiac catheterization laboratories and even less have the capability of performing emergency PCI [4]. Although transfer of a patient to a facility that can perform PCI is possible, the subsequent time delay in achieving reperfusion may outweigh the benefits.

As has been shown for stable and unstable angina, the results of primary angioplasty are dependent on the setting in which it is performed [5], and therefore, the hospital to hospital outcomes may differ considerably [6]. Establishing a proficient primary angioplasty program takes great institutional will and effort, and even centers with a large experience in coronary angioplasty will encounter a learning curve when embarking on the primary PCI journey [7]. It is axiomatic that centers undertaking primary PCI must be properly equipped and staffed, their operators competent, and the cases selected appropriately. The purpose of this chapter is to describe in detail the operator and site requirements for primary PCI and, where relevant, to discuss the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions 2005 guidelines pertaining to this procedure [8].

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General Considerations

In any catheterization setting, patient safety must be of paramount importance. Patients due to undergo the procedure should have received sound professional advice and their procedure should be undertaken with the outcome and their safety being the central focus of attention for all those involved with their care. Audit of the quality of care delivered should be undertaken, and its implementation and subsequent refinement should be with the wholehearted involvement and cooperation of interventional cardiologists.

A center undertaking primary angioplasty must have a cardiac catheterization laboratory equipped with a physiological measurement system and full facilities for cardiopulmonary resuscitation, including capability for intra-aortic balloon pumping. Sedation is often given during procedures so transcutaneous or an equivalent method of monitoring arterial oxygen saturation must be available. The need for particular items of angioplasty hardware, such as balloons, guiding catheters, stents, and adjunctive pharmacology, often cannot be anticipated until a procedure is in progress; therefore, it is vital that an adequate range of equipment and medication be immediately available at all times. Advances in medical device technology and pharmacotherapy have been very rapid in the field of interventional cardiology, and the need to upgrade and extend the range of available therapies in the light of these advances should be anticipated.

High quality radiographic imaging equipment (preferably digital) capable of imaging the coronary arteries from all directions, including caudal and cranial angulation, must be provided. Image manipulation including freeze frame, zoom, and playback should be immediately available. An adequate system should be in place for the archiving and subsequent retrieval of image data, with images being retained for at least three years or as required by policy or statute. Because excessive use of ionizing radiation may be hazardous, a cardinal principle of diagnostic imaging is to minimize radiation exposure to both the patient and the catheterization laboratory staff. The National Council on Radiation Protection and Measurements has issued recommendations for the proper design and performance of cardiac radiological equipment (NCRP Report No. 49, 1976) and structural shielding systems (NCRP Report No. 102, 1989). An essential element of an effective radiation safety program is consistent monthly monitoring of radiation exposure among the laboratory personnel.

Prehospital Phase

The greatest mortality reduction from acute MI can be achieved by very early treatment after the onset of symptoms [9]. Greater public awareness of the symptoms of acute MI with early recognition and swift response by general

practitioners once the diagnosis is established are of great importance in reducing inherent time delays to treatment. Although the results of primary PCI may be less time-dependent than the results of thrombolysis, the adage that time is muscle during the first few hours of an MI still holds true. Liem and colleagues have shown that an increase in the median time delay from presentation to balloon inflation, from 60 to 103 minutes in patients with anterior infarctions, resulted in a 24% larger enzymatic infarct size and a 4% lower left ventricular ejection fraction measured before hospital discharge [10].

Confirmation of the diagnosis of acute MI by 12-lead electrocardiography (ECG) and the rapid communication of this information to an on-call member of the primary angioplasty team can trim additional minutes off the time from presentation to first device activation by removing the need to visit the emergency and coronary care departments in the hospital. Furthermore, this affords emergency medical personnel the opportunity to initiate pharmacological therapy at the earliest possible stage. If a definitive diagnosis has not been made before hospital arrival, additional delays can be avoided by obtaining a limited history and physical and 12-lead electrocardiogram within 5-10 minutes in all patients with a suspected myocardial infarction [11].

Staffing Issues

A flexible attitude shared by the catheterization staff and interventional cardiologists is a prerequisite for any center providing a primary angioplasty service. The staff must be prepared to change their program at a moment's notice. A backup laboratory (or laboratories) will facilitate this need for flexibility.

In their task force recommendations, the ACC/AHA/SCAI define the performance standard for primary angioplasty as balloon inflation within 90 ($\pm$30) minutes of admission [4,8,12]. Although preferable, on-call laboratory staff does not have to be in-house. All centers should ensure that the intervention laboratory and its staff are fully operational within 60 minutes of being notified of need and each member of the on-call team should arrive at the hospital within 30 minutes. Adequate facilities and staff must be available to provide around the clock 24 hours, 7 days a week service. At a minimum, the on-call team should consist of an appropriately trained and experienced interventional cardiologist and three non-physician personnel, usually a combination of specialized catheterization laboratory nurses and dedicated cardiovascular technicians. The scrub technician/nurse is responsible for ensuring sterile preparation of the catheterization site and for maintaining a sterile field throughout the procedure. Another circulating technician/nurse is responsible for placing and maintaining peripheral intravenous access, administering medications during the procedure and actively monitoring the patient. Finally, a third technician/nurse is responsible for ensuring adequate documentation during the procedure, including verification of the patients' consent, recording the medications

administered, noting both radiation exposure and volume of contrast used, and otherwise maintaining a detailed procedural log. While acknowledging that staffing levels will vary with local circumstances, the Joint Working Group on Coronary Angioplasty of the British Cardiac Society and British Cardiovascular Intervention Society suggests that an on-call coverage frequency of 1 out of 3 nights puts unreasonable and unsustainable demands on the participating staff and interventionalists [13]. The ACC/AHA/SCAI guidelines do not specify an appropriate on-call rotation.

During primary PCI, the catheterization laboratory must function as a critical care unit. Primary PCI is a difficult procedure which may result in a number of potentially fatal complications. Reperfusion arrhythmias must be recognized and treated promptly. Timmis and coworkers have demonstrated more arrhythmias following direct PCI than with thrombolytic therapy [14]. After restoration of flow in the right coronary artery, profound hypotension and bradycardia may develop due to the Bezold-Jarisch reflex, resulting in greater use of inotropic agents, intra-aortic balloon pumping and need for cardiopulmonary resuscitation [15,16]. Recurrent ischemia (10–15%) will occur more frequently than with elective procedures, and the need for emergency coronary artery bypass grafting must be anticipated [3]. Complications such as anaphylaxis, ventricular tachycardia and fibrillation, pulmonary edema, and shock can occur without antecedent warning.

All catheterization laboratory staff must be attentive to patient comfort at all times. Close attention to the patient in the less intensive pre- and post-procedural stages can often reveal early warning signals of impending complications. These include restlessness and agitation indicating hypoxia, somnolence indicating hypoventilation, lower abdominal pain and distention suggesting retroperitoneal hemorrhage and nausea, and itching, hives, and rhinorrhea as precursors to anaphylaxis. In the event of an emergency, all personnel must be able to handle any deterioration in patient status and be able to deliver basic life support. All members of the catheterization team – physicians, nurses, and technologists – should maintain a current course completion card in cardiopulmonary resuscitation. Certification in advanced cardiac life support (ACLS) is desirable.

Pharmacological Requirements

Adequate pain relief and supplemental oxygen are essential. For sedation, a combination of opiates and benzodiazepines are used commonly. Intravenous drugs should be given slowly and the doses titrated according to the patients' clinical status. Naloxone and flumazenil must be immediately available to reverse excess sedation. Aspirin should be given preferably in a dose of 325 mg, chewed or in soluble form. Sublingual and intravenous nitroglycerin, as well as beta-blockers, unless contraindicated, should be given to lower

myocardial oxygen consumption and alleviate myocardial ischemia. Access to a range of additional antiplatelet agents including thienopyridines, glycoprotein IIb/IIIa inhibitors, as well as both direct and indirect anti-thrombin agents should also be available at all times. The appropriate use of these agents will be discussed in more detail in other chapters. Finally, a cardiopulmonary resuscitation cart must be available. This should be checked on a daily basis to ensure that it is adequately stocked.

Operator and Institutional Requirements

The assessment of clinical proficiency in the catheterization laboratory is based on a composite of cognitive skills, procedural conduct and clinical judgment. The assessment of professional competence clearly resides in the domain of the physicians themselves. Within the United States, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has recognized this principle by requiring that the granting of initial or continuing medical staff privileges in any hospital be based on assessments of individual applicants against professional criteria that are specified in medical bylaws. The origin of the current requirements for certification by the Subspeciality Board of Cardiovascular Disease can be traced back to the 17th Bethesda Conference on cardiology training cosponsored by the American College of Cardiology (ACC) and the American Heart Association (AHA) in November 1985 [17]. The Task Force on training in cardiac catheterization established at the conference stipulated that a trainee should perform a minimum of 300 diagnostic cardiac catheterizations, including 200 as primary operator over a 12-month period [18]. Trainees planning to perform coronary angioplasty are required to complete a fourth year of training. During this additional year, a minimum of 250 coronary interventional procedures must be performed. In 1996, the American Board of Medical Specialties approved a Certificate of Added Qualification in Interventional Cardiology. This certification in interventional cardiology was offered for the first time in November 1999 and has become the benchmark by which interventional cardiologists are judged and credentialed.

According to the current ACC/AHA/SCAI updated guidelines for PCI, primary PCI for STEMI remains a class I recommendation. Primary PCI should be performed by experienced operators who perform more than 75 elective PCI procedures per year and with at least 11 PCI procedures for ST-elevation myocardial infarction (STEMI) per year. Ideally, these procedures should be performed at institutions which perform more than 400 elective PCIs per year and more than 36 primary PCI procedures for STEMI annually. The performance of primary PCI by operators performing fewer than 75 elective or fewer than 11 PCIs for STEMI annually is now a class IIb recommendation [8].

Table 3.1 Operator and institutional volume requirements for primary PCI

2001 Recommendation	2005 New or revised recommendation	Comments
Class I	Class I	
PCI done by operators with acceptable volume (greater than or equal to 75) at high-volume centers (greater than 400). (Level of Evidence: B)	Primary PCI for STEMI should be performed by experienced operators who perform more than 75 elective PCI procedures per year and, ideally, at least 11 PCI procedures for STEMI per year. Ideally, these procedures should be performed in institutions that perform more than 400 elective PCIs per year and more than 36 primary PCI procedures for STEMI per year. (Level of Evidence: B)	This recommendation is expanded based on data from the New York State registry indicating that physicians performing more than 10 primary PCI procedures per year have lower mortality rates.
Class IIb	Class IIb	
None	The benefit of primary PCI for STEMI patients eligible for fibrinolysis when performed by an operator who performs fewer than 75 procedures per year (or fewer than 11 PCIs for STEMI per year) is not well established. (Level of Evidence: C).	This recommendation has been added to address the issue of low-volume operators performing primary PCI. It reflects the relative lack of evidence supporting a benefit of primary PCI for low-volume operators.

The current ACC/AHA/SCAI recommendations regarding operator and institutional volumes for the performance of primary PCI for STEMI are listed in Table 3.1 [8].

It must be stressed however that these values all represent minimum, and not optimum, levels of experience. While experience is the sine qua non of proficiency, the myriad of techniques and technologies preclude rigid delineation of "the right way". There is one incontrovertible bottom line, however: patient outcomes. Many studies have documented an inverse relationship between the incidence of major complications of several procedures and the number of these procedures performed by individual operators or hospitals. Lower mortality rates have been associated with higher volumes of elective procedures in studies of PTCA [5,19–21], coronary stenting [22], and coronary artery bypass graft surgery [23,24].

Several studies have examined the impact of operator and hospital PCI volumes and outcomes for procedures performed during a myocardial infarction. In 1995, Vakili et al. [25] queried the New York State Coronary Angioplasty Reporting System Registry (CARS) database and observed that both operator

and hospital PCI volumes are inversely related to in-hospital mortality as well as same-stay CABG surgery when the PCI procedure was performed in the setting of an acute myocardial infarction. Specifically, they found that the performance of primary PCI by a physician who performed greater than 10 procedures annually resulted in a savings of 33 lives per 1000 patients treated. Likewise, they noted a strong trend toward a relation between hospital primary angioplasty volume and mortality such that 18 lives per 1000 patients treated would be saved by treatment in a high-volume PCI hospital (>57 primary PCI procedures per year). Finally, they concluded that there would be 39 fewer deaths per 1000 patients treated if acute myocardial infarction patients were treated by high-volume primary PCI operators in high-volume centers instead of by low-volume operators at low-volume centers. They later reanalyzed their data after categorizing high and low-volume operators and hospitals according to American College of Cardiology/American Heart Association recommendations (<75 procedures per year as low-volume operator; < 400 PCI cases per year considered low-volume hospital) [8,26]. With these thresholds, they found that individual operator PCI volumes did not predict outcomes of angioplasty in acute myocardial infarction but that patients treated with primary PCI at high-volume hospitals had improved outcomes.

Analyzing the National Registry of Myocardial Infarction (NRMI) database from June 1994 through July 1999, Majid et al. [27] examined the association between hospital-specific volumes and short-term mortality in over 62,000 patients presenting with acute myocardial infarction treated with either primary angioplasty or thrombolytic therapy. Mortality rates were significantly lower among patients who received primary angioplasty compared with those who received thrombolysis at hospitals with intermediate volumes (4.5% vs. 5.9%; P<.001) and high volumes (3.4% vs. 5.4%; P<.001). At low volume centers, defined as performing ≤16 primary angioplasty procedures per year, there was no significant difference in mortality between patients treated with primary angioplasty vs. those treated with thrombolytic therapy (6.2% vs. 5.9%; P = 0.58). These findings were not altered by adjusting for differences in demographic, medical history, clinical presentation, treatment, and hospital characteristics.

A more extensive analysis of the NRMI database was performed by Canto and co-investigators [28] to determine the relationship between the number of patients receiving reperfusion therapy (primary angioplasty or thrombolytic therapy) and subsequent in-hospital mortality. A total of 450 hospitals were divided into quartiles according to their primary PCI volumes, and a total of 516 hospitals were divided into quartiles according to the volume of patients treated with thrombolysis. Over 250,000 patients in each group were studied with multiple logistic-regression models used to determine whether volumes of primary angioplasty or thrombolysis were independent predictors of in-hospital mortality among patients receiving these reperfusion strategies. They found that the higher volume hospitals in both the PCI and thrombolysis groups were more likely to administer these therapies sooner than the lower volume hospitals. In-hospital mortality was 28% lower among patients treated with primary PCI at

hospitals with the highest volume than among those who had PCI at hospitals with the lowest volumes. There was no association between in-hospital mortality and hospital volume in patients treated with thrombolytic therapy (7.0% for patients in highest-volume hospitals vs. 6.9% for those in the lowest-volume hospitals, P = 0. 36). These findings support the recommendation of the ACC/AHA Task Force that primary PCI should be used as an alternative to thrombolytic therapy only if it is performed in a timely fashion at high volume centers by individuals skilled in the procedure and supported by experienced personnel.

Requirement for On-site Surgical Backup

An important safety and quality assurance consideration with regard to the performance of primary PCI is the availability of emergency CABG surgery should the procedure fail and a major complication occur. According to the 2005 ACC/AHA/SCAI guideline update, primary PCI for STEMI in facilities with on-site cardiac surgery remains a class I recommendation [8]. The current ACC/AHA/SCAI recommendations for primary PCI for STEMI with on-site cardiac surgery are listed in Table 3.2 [8]. Nevertheless, experience with the performance of coronary interventions at institutions with and without on-site CABG surgery has been gained in both the early era of balloon angioplasty and the contemporary era of coronary stenting. It has been argued that the conditions in acute myocardial infarction present a special set of circumstances favoring a less rigid application of the need for on-site surgical backup.

Outcomes of patients with primary PCI in acute myocardial infarction at hospitals with no surgery on-site have been prospectively studied and compared with patients transferred for primary angioplasty at centers with cardiac surgery in The PAMI – No SOS Study [29]. In this study, 500 fibrinolytic-eligible patients with acute myocardial infarction underwent primary PCI at 19 centers without cardiac surgery if they had at least one high-risk qualifier (age over 70 years, anterior MI, ECG demonstrating left bundle branch block, heart rate over 100 beats per minute, systolic blood pressure less than 100 mmHg, or Killip

Table 3. 2 Role of on-site cardiac surgical back-up in primary PCI

2001 Recommendation	2005 New or revised recommendation	Comments
Class I	Class I	
Patients undergoing primary PCI in facilities with on-site cardiac surgery. *(Level of Evidence: B)*	Primary PCI for patients with STEMI should be performed in facilities with on-site cardiac surgery. *(Level of Evidence: B)*	Phrasing has been changed to reflect current terminology and to be consistent with the ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction.

class 2 or 3 congestive heart failure). These patients were compared with 71 similar patients from the Air Primary Angioplasty in Myocardial Infarction (Air-PAMI) trial who were randomized to transfer for primary angioplasty at a hospital with cardiac surgery. Primary angioplasty was performed in 88% of patients. Patients transferred for PCI had a longer mean time to treatment (187 vs. 120 minutes; $p<0.0001$). Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 was achieved in 96% for on-site PCI and 86% in the transfer group ($p = 0.004$). The combined primary endpoint of 30-day mortality, re-infarction, and disabling stroke occurred in 27 (5%) of onsite PCI patients and 6 (8.5%) of transfer patients ($p = 0.27$). Unadjusted one-year mortality was improved in on-site PCI patients compared with those transferred (6% vs. 13%, $p = 0.043$), but after adjustment for differences in baseline variables, this difference was not significant. In the on-site PCI group, only two patients (0.4%) required surgery due to failed primary PCI; another 5% required emergency surgery because of critical coronary anatomy discovered during diagnostic angiography. Of the transfer group, 5.6% underwent emergency surgery; none of these were transferred for failed primary PCI.

Despite these findings, the performance of PCI without on-site surgical back-up is controversial and the subject of contentious debate [30]. Proponents of PCI without on-site surgery believe that personal, financial, and market-driven motives exist at PCI centers with on-site surgery where fears of increased competition and loss of market share have promoted unnecessarily restrictive standards and state regulations against a practice that facilitates access to early and convenient PCI services in local communities. Opponents of PCI without on-site surgery contend that personal, financial, and market-driven motives have eclipsed quality of care issues and fostered the increased and unregulated growth of PCI. Despite these divergent views, one point is certain; the performance of PCI without on-site cardiac surgical backup is on the rise. Dehmer et al. [31]. reported that in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR) from 2001 to 2005, a significant increase in elective PCI procedures performed at facilities without on-site surgical back-up occurred despite national guidelines indicating that elective PCI should not be performed in centers without on-site cardiac surgery.

The recent ACC/AHA/SCAI guideline update for percutaneous coronary interventions has kept primary PCI for ST-segment elevation myocardial infarction (STEMI) without on-site cardiac surgery as a class IIb recommendation, with the stipulations that the procedure be performed by an experienced operator having an individual procedure volume of more than 75 total PCIs and, ideally at least 11 primary PCIs per year for STEMI, at an institution which performs a minimum of 36 primary PCIs per year. In addition, the recommendation specifies that the catheterization team be experienced and available 24 hours per day, 7 days a week in a well-equipped laboratory with a proven plan and equipment necessary for rapid transfer to a nearby cardiac surgical theater when necessary. Furthermore, primary PCI in facilities without on-site cardiac surgery without a proven plan for rapid transfer to a hospital

offering cardiac surgery remains a class III recommendation. The current ACC/AHA/SCAI recommendations for primary PCI for STEMI without on-site cardiac surgery are listed in Table 3.3 [8].

Interestingly, it has been estimated that in 2000, nearly 80% of the adult population in the United States lived within 60 minutes of a PCI hospital [32]

Table 3.3 Primary PCI for STEMI without on-site cardiac surgery

2001 Recommendation	2005 New or revised recommendation	Comments
Class IIb	Class IIb	
Patients undergoing primary PCI in facilities without on-site cardiac surgery, but with a proven plan for rapid access (within 1 h) to a cardiac surgery operating room in a nearby facility with appropriate hemodynamic support capability for transfer. The procedure should be limited to patients with ST-segment elevation MI or new LBBB on ECG, and done in a timely fashion (balloon inflation within 90 plus or minus 30 min of admission) by persons skilled in the procedure (at least 75 PCIs/year) and only at facilities performing a minimum of 36 primary PCI procedures per year. *(Level of Evidence: B)*	Primary PCI for patients with STEMI might be considered in hospitals without on-site cardiac surgery, provided that appropriate planning for program development has been accomplished, including appropriately experienced physician operators (more than 75 total PCIs and ideally, at least 11 primary PCIs per year for STEMI), an experienced catheterization team on a 24 hours per day, 7 days per week call schedule, and a well-equipped catheterization laboratory with digital imaging equipment, a full array of interventional equipment, and intra-aortic balloon pump capability, and provided that there is a proven plan for rapid transport to a cardiac surgery operating room in a nearby hospital with appropriate hemodynamic support capability for transfer. The procedure should be limited to patients with STEMI or MI with new or presumably new LBBB on ECG and should be performed in a timely fashion (goal of balloon inflation within 90	Phrasing has been changed to reflect current terminology. Recommendations have been added that 1) physicians perform at least 11 primary PCIs per year for STEMI, 2) a 24 hours per day, 7 days per week call schedule be maintained, and 3) the catheterization laboratory be well equipped with digital imaging equipment, a full array of interventional equipment, and intra-aortic balloon pump capability. The intent is to ensure optimal experience availability and capability to perform primary PCI in patients with STEMI.

Table 3.3 (continued)

2001 Recommendation	2005 New or revised recommendation	Comments
	minutes of presentation) by persons skilled in the procedure (at least 75 PCIs per year) and at hospitals that perform a minimum of 36 primary PCI procedures per year. *(Level of Evidence: B)*	
Class III	Class III	
Patients undergoing primary PCI in facilities without on-site cardiac surgery and without a proven plan for rapid access (within 1 h) to a cardiac surgery operating room in a nearby facility with appropriate hemodynamic support capability for transfer or when performed by lower-skilled operators (fewer than 75 PCIs per year) in a facility performing fewer than 36 primary PCI procedures per year. *(Level of Evidence: C)*	Primary PCI should not be performed in hospitals without on-site cardiac surgery and without a proven plan for rapid transport to a cardiac surgery operating room in a nearby hospital or without appropriate hemodynamic support capability for transfer. *(Level of Evidence: C)*	Phrasing has been changed to reflect current terminology and to place emphasis on need for inter-institutional planning and support.

and that regionalization of PCI would not increase travel distance for most patients [33]. Given that the transfer of patients for primary or elective PCI is feasible for the majority of patients, losses of PCI and other cardiovascular care services due to regionalization of PCI could have a direct and substantial impact on both community and system affiliated hospitals. These changes could drastically challenge a hospital's financial viability and ultimately limit access to healthcare services in general [34]. Until more is known about the role of PCI performed at centers without cardiac surgical backup, a recently released expert consensus document from the Society for Cardiovascular Angiography and Interventions regarding this issue offers recommendations addressing both access to care and patient safety concerns and as such, provides guidance and direction for the future. In summary, these recommendations include [30]:

1) Acknowledgement that PCI without on-site surgery may be appropriate in some circumstances.
2) The decision to begin a PCI program without on-site surgery should be based on the health needs of the area served.

3) PCI programs both with and without on-site surgical backup must evaluate their outcomes against acceptable standard benchmarks.
4) Operators performing PCI without on-site surgery should perform $\geq$100 total PCI procedures per year, including $\geq$18 primary PCI procedures per year. In addition, the initial operators at a facility without on-site backup should not begin performing PCI in such facilities until they have a lifetime experience of >500 PCI procedures as primary operator after completing fellowship. Only operators with complication rates and outcomes equivalent or superior to national benchmarks should perform PCI. Note that these requirements exceed those required for the performance of PCI procedures under current ACC/AHA/SCAI 2005 guidelines [8].
5) Independent program oversight should occur and any program failing to perform adequately should close.
6) Further data collection and analysis is needed to define the role of PCI without on-site surgical backup as a strategy for the delivery of cardiovascular care.

Primary PCI: Community Versus Tertiary Care Hospital

The question as to whether patients with acute myocardial infarction should be transferred to a tertiary care center for primary PCI or should receive it at qualified community hospital remains unanswered. This controversial question has been recently debated [30], and the solution will require consideration of the complex interplay of many factors influencing patient access to critical care, patient safety, individual and institutional quality of care, effective use of medical resources, and the competition between hospitals for patients. Key points to support each position in this debate are presented below.

The Case for Community Hospital Primary PCI

There is clearly a need to improve access to primary PCI as the preferred reperfusion strategy in acute myocardial infarction since only 20% of patients with STEMI are treated with primary PCI, a therapy proven superior to thrombolytic therapy [35]. Transferring patients delays treatment; only 4% of patients transferred for primary PCI in the NRMI registry received treatment within 90 minutes of initial presentation, and only 15% received it within 180 minutes. In fact, even where a streamlined, interhospital transfer system is established, transfer may be unreliable or even hazardous to both patient and members of the transport team. Helicopter & ground transport may be limited by severe weather or congested traffic conditions. Patients may be too unstable for transfer, thus creating a substantial liability risk associated with their transfer. Finally, hospital-to-hospital transfer of patients is the lowest priority in the current emergency

medical system and may strain an already limited resource. By eliminating transport delays, primary PCI at point of initial presentation within a community hospital qualified and committed to perform this service could be lifesaving in both stable STEMI patients and those too unstable for air or ground transport to a tertiary care PCI center. Secondly, less than 1% of patients treated with primary PCI require emergency CABG. In the C-PORT trial, Avesano et al. [36] have demonstrated that primary PCI can be safely performed at centers without cardiac surgery and is superior to thrombolytic therapy. Additionally, outcomes following emergency CABG after failed PCI are similar whether the procedure was performed at the institution where the surgery was performed or whether the patient required transfer for the surgery. Lastly, in-hospital mortality and other quality-of-care indicators are comparable between hospitals with and without onsite cardiac surgery, while centers without cardiac surgery capability had shorter door-to-balloon times and greater use of evidence-based medical therapies including aspirin and beta-blockers [37].

The Case for Transfer to a Tertiary Care Hospital for Primary PCI

At present, many community hospitals do not have the annual PCI volumes needed to maintain the skills of both the interventionalist and the cardiac catheterization laboratory staff. Several studies have established decreased mortality and need for emergency CABG in patients treated in high-volume centers. This fact raises both safety and quality of care concerns.

During the thrombolytic era, the transfer of critically ill STEMI patients for primary PCI was shown to be safe and preferable to treatment at a community hospital because it avoided the risk of rescue PCI in patients treated with thrombolytic therapy. Furthermore, the Primary Coronary Angioplasty versus Thrombolysis (PCAT)-2 investigators found that even with PCI-related delays up to two hours, STEMI patients treated with primary PCI had a significantly decreased risk of death compared with those treated with thrombolytic therapy [38].

Currently, it is felt that the inherent delay from a community hospital to a tertiary PCI center should not negatively impact clinical outcome as long as the patient is transferred to a "ready and waiting" cardiac catheterization laboratory in $\leq$2 hours. As seen in Europe [39], delays in the field can be limited by implementing the use of a pre-hospital EKG to speed the diagnosis of STEMI, thus eliminating the door-to-EKG time delay and allowing for simultaneous activation of a PCI team while the patient is en route to a PCI center. Compared with in-hospital diagnosis of STEMI, a pre-hospital diagnosis of STEMI has been shown to decrease the time from ambulance call to the first balloon inflation by 41 minutes ($p<0.001$) in STEMI patients who initially presented to a non-PCI capable community hospital and then immediately transferred to a primary PCI center and by 81 minutes ($p<0.001$) in STEMI patients who were

transported directly to a primary PCI center from the field. Expanding the use of a prehospital EKG in the diagnosis of STEMI, a class IIa recommendation by current ACC/AHA guidelines, can expedite the process of care required for performing primary PCI in a timely fashion.

Lastly, even patients with delayed presentations during STEMI may still benefit from prompt primary PCI. In the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial [40], the clinical outcomes of 1047 STEMI patients presenting during peak hours (Monday through Friday, 8AM to 8PM) were compared with 989 STEMI patients presenting during off-peak hours (weeknights 8PM to 8AM, and weekends). Despite an additional 21-minute delay to balloon inflation in STEMI patients who underwent primary PCI during off-peak hours, there was no significant difference in mortality, achievement of TIMI grade 3 flow, or myocardial function compared with patients treated during peak hours.

Performance Improvement: Strategies for Decreasing Door to Balloon Times

Prompt reperfusion is essential to enhancing outcomes of patients presenting with acute STEMI. Current ACC/AHA/SCAI guidelines recommend that the interval between arrival at a hospital and the inflation of a balloon within the infarct-related artery during primary PCI (door-to-balloon time) should be 90 minutes or less [8]. Despite this recommendation, few hospitals have been able to achieve this performance goal. In evaluating data from the National Registry of Myocardial Infarction-4, Curtis et al. [41] have found that despite national guidelines recommending the use of a pre-hospital ECG to diagnose and facilitate treatment of STEMI in the United States, use remains low (<10%). When used, however, a pre-hospital ECG decreased mean door-to-balloon times by nearly 15 minutes. In a cross-sectional study of 365 acute care hospitals, Bradley et al. [42] have recently identified 6 key strategies for reducing door-to-balloon times from a total of 28 strategies studied. These include:

1. Activation of the catheterization laboratory by an emergency room physician.
2. Activation of the laboratory by a single call to a central operator.
3. Activation of the catheterization laboratory while patient is en route to hospital.
4. Expectation that the staff will arrive within 30 minutes after being paged.
5. Attending cardiologist always on site.
6. Hospital provides real-time feedback to ER and catheterization laboratory staff.

Hospitals employing two or more of these strategies had average door to balloon times of 88 minutes or less, thus achieving the goal quality core measure collected and reported by the Centers for Medicare and Medicaid Services (CMS) and the JCAHO.

To ensure that all patients with STEMI receive reperfusion promptly, the American College of Cardiology, the American Heart Association and other partnering organizations have assembled the Alliance for Quality. This alliance provides institutions and physicians with key evidence-based strategies, supporting tools, and educational information intended to facilitate performance improvement and achieve coronary revascularization within 90 minutes of patient presentation. These materials can be obtained at the D2B Alliance for Quality website at www.d2balliance.com.

Quality Assurance: Audit and Peer Review

Audit and peer review of both institutional and operator competency in the performance of coronary interventional procedures is an integral part of providing an interventional cardiology service and should not be regarded as an optional extra. In fact, the recent ACC/AHA/SCAI 2005 guideline update for PCI has made this a new class I recommendation. Furthermore, institutions that perform PCI should participate in a recognized PCI data registry, such as the ACC-National Cardiovascular Data Registry (ACC-NCDR) for the purpose of measuring its outcomes against national benchmarks. These recommendations are listed in Table 3.4 [8].

For the audit process is to work, standards must be defined in all relevant areas that impact on the quality of care. Performance must then be assessed against these standards, and conclusions drawn from these assessments used to implement appropriate changes. The auditing process should be continuous to allow individual operators or units as a whole to recognize early when problems are developing. This also allows ongoing evaluation of changes made to improve patient care.

The AHA/ACC Guidelines for Cardiac Catheterization Laboratories designate the Catheterization Laboratory director as the person responsible for establishing and monitoring internal quality control systems [43]. In the United States, the process of periodic external audit is the responsibility of the JCAHO. With respect to auditing of primary PCI procedures, some additional points are relevant. In reviewing the interventional cardiologist's performance, both the appropriateness of patient selection as well as the quality of the interventional procedure are equally important. Also, in implementing the auditing process, it is important to ensure that patients judged to be at high risk are not denied treatment because an adverse outcome might reflect badly on the operator's ratings. It would indeed be ironic if the audit process, intended to improve the treatment of patients, actually prevented appropriate care. Finally, if individual

Table 3.4 Quality assurance

2001 Recommendation	2005 New or revised recommendation	Comments
Class I	Class I	
None	An institution that performs PCI should establish an ongoing mechanism for valid peer review of its quality and outcomes. Review should be conducted both at the level of the entire program and at the level of the individual practitioner. Quality-assessment reviews should take risk adjustment, statistical power, and national benchmark statistics into consideration. Quality-assessment reviews should include both tabulation of adverse event rates for comparison with benchmark values and case review of complicated procedures and some uncomplicated procedures. *(Level of Evidence: C)*	Quality assurance is an important responsibility for all institutions in which PCI is performed. Institutions must monitor the PCI program with respect to process, appropriateness, and outcomes and correct any circumstances in which quality falls below accepted norms. The quality assessment should be conducted at the level of both the entire program and the individual practitioner.
	An institution that performs PCI should participate in a recognized PCI data registry for the purpose of benchmarking its outcomes against current national norms. *(Level of Evidence: C)*	Participation in a recognized PCI registry for benchmarking outcomes against current national norms is an important part of the quality-improvement process. The ACC–National Cardiovascular Data Registry® or other databases may serve as a valuable resource in this regard.

operators and centers are to be assessed, and occasionally judged to be failing, such failings should be the result of their own short-comings and not those of a system with wider inadequacies, for which others may more appropriately bear responsibility.

Conclusions

Primary percutaneous coronary intervention has emerged as the preferred reperfusion strategy for patients with acute myocardial infarction if it can be provided in a timely manner. Coronary artery stenting and adjunctive pharmacotherapy have improved the procedural success and clinical outcomes of patients undergoing coronary interventions in both elective and emergency

care settings. Optimal delivery of these complementary technologies to patients with acute myocardial infarction involves a complex interplay of many factors. These include patient specific characteristics, the performing interventional cardiologists' annual PCI volumes, career experience, technical expertise and clinical judgment, as well as an the commitment of the institution to provide 24 hours, 7 days a week, 365 days a year service with an experienced support staff. Furthermore, institutions offering this service must have sufficient procedural volume and streamlined processes of care geared toward achieving reperfusion within 90 minutes of patient presentation regardless of time from symptom onset. Refinements in interventional techniques have enhanced procedural success and safety to a point where emergency coronary artery bypass graft surgery for failed PCI is rarely needed. This has led to a growing number of PCI procedures being performed in the United States and worldwide in community hospitals without on-site surgical backup. Central to resolving this issue will be striking a balance between early access to PCI (favoring primary PCI at the community hospital) and the case volumes and clinical processes typical of the tertiary referral center with on-site surgical backup. Until this balance is achieved, the recently published Society for Cardiovascular Angiography and Interventions consensus statement regarding primary PCI at centers without on-site surgery provides guidance and direction for the future by addressing both early access to care and patient safety concerns. Their recommendations provide centers without on-site cardiac surgery with stringent guidelines for developing a primary PCI program. This practice may achieve a desirable balance between early access to care and patient safety.

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Chapter 4
Primary Coronary Intervention: The Technical Approach

James E. Tcheng and David A. Cox

Introduction

The performance of primary percutaneous coronary intervention (PCI) during acute ST elevation myocardial infarction (STEMI) has emerged as the preferred standard of care for the patient presenting to a PCI-capable facility [1,2]. Compared with thrombolytic therapy, emergency PCI reduces mortality, recurrent myocardial infarction and recurrent ischemia, and is associated with lower rates of stroke including a near-elimination of hemorrhagic stroke [3–8]. Performing primary PCI is taxing and stressful, requiring a highly skilled operator and cardiac catheterization team along with ancillary acute care support. The tenuous patient demands full attention to detail, and decisions in the catheterization suite can have both immediate and long-lasting consequences. Unfortunately, opportunities to participate in primary PCI cases during fellowship are typically limited. The aim of this chapter is therefore to provide a timeline oriented, step by step guidance regarding the technical aspects of primary PCI to facilitate the replication of outcomes observed in clinical trials of this approach.

Initial Contact

Hospitals performing primary PCI should have set protocols for the rapid recognition of the acute STEMI patient. Once the diagnosis is established, several processes should be activated simultaneously [9,10]. Since rapid transfer to the catheterization suite is an immediate goal, mobilization of catheterization laboratory personnel should be initiated as the interventional cardiologist is being called, rather than waiting for the cardiologist to activate the staff. If elective cases are ongoing, a catheterization suite must be opened urgently.

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While the catheterization laboratory is being readied, a cocktail of anticoagulant and antiplatelet therapies should be started. Our approach includes 325 mg of chewable aspirin, a 50 unit/kilogram bolus of heparin, beta-blocker (absent contraindication), and 600 mg of clopidogrel. Specific notes about this approach include the following. The investigators of the PAMI-No SOS (Primary Angioplasty in Acute Myocardial Infarction at Hospitals with No Surgery On-Site) trial demonstrated remarkably rapid door-to-balloon times partly by abandoning intravenous nitroglycerin and heparin drips as sources of time delay [11,12].

Additional heparin can be administered in the catheterization laboratory once an activated clotting time has been obtained. Regarding clopidogrel, no clinical trials have directly evaluated the efficacy of a 600 mg load of this agent as an adjunct to primary PCI; instead, only a 300 mg load has been systematically evaluated in STEMI, and even then primarily as an adjunct to thrombolysis rather than PCI [13,14]. Nonetheless, since evidence overall favors stent implantation over balloon angioplasty alone in primary PCI [15–18], and since emergency referral for surgery is unusual in this setting [11,12] loading with clopidogrel would seem in order. Finally, platelet glycoprotein IIb/IIIa inhibitors should be considered early in the care timeline, particularly when there are long delays to arrival in the catheterization suite, as these agents independently promote reperfusion and are associated with improvements in coronary flow and left ventricular function and reductions in stent thrombosis and recurrent ischemia when given prior to angiography [19–22].

Pre-Procedure Evaluation

Performing PCI in acute STEMI is quite different than the elective situation. Patients with acute STEMI present in pain, have high catecholoamine and stress levels, are electrophysiologically unstable, and can deteriorate rapidly into heart failure or shock. In particular, patients in cardiogenic shock represent a true emergency in which clinical stabilization and time-to-treatment critically affects outcomes [23–25]

Interventional cardiologists treating patients with AMI must therefore be skilled in critical care medicine. Proper initial assessment of the critically ill patient can make a tangible difference, particularly in the unstable patient. While the acute STEMI patient needs to be transported to the catheterization laboratory with all due haste, a brief history and physical exam by the interventionalist focusing on vital signs, presence of rales, presence of murmurs suggesting a ventricular septal defect or severe mitral regurgitation, and peripheral pulses should always be performed. Furthermore, evaluating the patient for sedation administration, determining whether a true aspirin or clopidogrel allergy exists, and reviewing the history for contraindications to anticoagulant and platelet glycoprotein IIb/IIIa inhibitor therapy can all be

done without delaying cardiac catheterization and should be incorporated into the consent process.

Entry into the Catheterization Laboratory

Upon arrival in the catheterization suite, the acute STEMI patient should be rapidly assessed again for respiratory and hemodynamic compromise, the need for sedation, and rhythm disturbances. A fully supplied cardiopulmonary resuscitation cart, temporary pacemaker with wires and cables, and an intra-aortic balloon pump should be readily available, and "fast" cutaneous patches placed for defibrillation. Both groins should be prepped in case placement of an intra-aortic balloon pump becomes urgently required.

If the question of respiratory compromise exists, a case can be made for early intubation before coronary intervention. The airway will then be protected from aspiration, and further sedation can be given without concern for excessive respiratory suppression. It should be noted that progressive respiratory compromise can be expressed (and misinterpreted) as an uncooperative patient – and the results can be disastrous, particularly if the patient becomes unstable at a critical juncture. The bleeding risk of traumatic emergency intubation in the presence of high dose anticoagulation and antiplatelet therapies also favors a more controlled intubation prior to the initiation of catheterization.

The initial blood pressure on arrival is a key vital sign: a blood pressure of 80/60 in an anterior STEMI is an ominous sign, regardless of how stable the patient appears. Initial systolic blood pressure has been shown to be a powerful predictor of final ST segment resolution and subsequent mortality [24–25].

Regarding intra-aortic balloon pump (IABP) placement, in a prospective randomized trial of 437 patients meeting high risk criteria out of a cohort of 1,100 acute STEMI patients undergoing emergency primary PCI, routine placement of an IABP was not shown to improve long-term outcomes [26]. However, other studies have demonstrated early benefits when an IABP is placed prior to catheterization in selected patients [27], reflecting current practice of using this adjunct in patients with hypotension or other evidence of hypoperfusion [28]. In particular, patients with hypotension unresponsive to fluids and in frank cardiogenic shock should undergo rapid IABP placement before catheterization is initiated. Because a perfusionist is typically not in-house 24 hours per day, it is critical that the cath laboratory staff and the intensive care unit staff be trained and competent in the management of IABP support. In the SHOCK trial, 86% of patients received IABP support [24]. Use of flexible, low profile 8 Fr IABP systems decreases complications related to peripheral vascular disease with no differences in overall clinical outcomes [29].

Right ventricular infarction should be clinically recognized and hypotension addressed with fluid resuscitation and vasoactive pressors prior to the initiation of catheterization. Right ventricular infarction does carry

increased mortality risk; early hemodynamic improvement and urgent intervention in this context is particularly required [30,31]

Coronary Angiography

As door-to-balloon time has become a standard performance metric due to the high correlation of this parameter with outcomes, moving forward to coronary angiography expeditiously is of paramount importance [1,2] The cardiologist can help the process by assisting with draping and setup. If the infarct-related artery can be determined by electrocardiographic criteria, angiography of the non-infarct related artery should be performed first. A guiding catheter can then be used to perform the initial angiograms of the infarct artery, eliminating the time required to switch catheters. Most operators delay the performance of left ventriculography until after the infarct vessel has been opened, particularly in the "stable" STEMI patient. However, in the unstable patient, particularly when there is a suspicion of a mechanical complication such as ventricular septal defect or papillary muscle rupture, left ventriculography should be performed prior to intervention in case surgical repair is needed. In the presence of surgical lesions, PCI is relatively contraindicated.

Approximately one-third of patients presenting with an acute STEMI will have an open infarct-related artery with TIMI-2 or -3 flow before intervention; outcomes in these patients are better than those with TIMI-0–1 flow on the initial angiogram [32]. Final TIMI flow after PCI, however, remains the most potent predictor of mortality both at 30 days and at 1 year. Regardless of the initial TIMI flow, the goal thus remains the achievement of TIMI-3 flow at the infarct lesion and all of the distal branches. A final result of TIMI-3 flow, along with the "door to TIMI-3 flow" time, are highly correlated with lowered mortality when compared with TIMI-0, -1, or -2 flow on the final angiogram [1,2,33].

Crossing the Lesion

Successful PCI of an occluded infarct artery requires successful wiring of the lesion. As opposed to the elective situation, in primary PCI the pathway to the distal lumen frequently cannot be visualized. Selection of guidewires is predicated by the familiarity, experience, and prefence of the interventionalist with the guidewires available in the laboratory. Most interventionalists use conventional, soft-tipped, non-hydrophilic guidewires to primarily cross the lesion. In general, it is recommended that hydrophilic guidewires *not* be used first, given the increased risk of vessel perforation of downstream vessels when those vessels cannot be visualized. Fortunately, most lesions are fairly soft and, with careful attention to technique, can be crossed with conventional coronary guidewires.

The most common reason for failure to cross with a guidewire is entry of the wire into a false channel. While this typically occurs in a tortuous or distal vessel where wire tip control is not ideal, it can even occur in what otherwise appears to be a straightforward lesion. The most important clue suggesting entry into a false channel is the loss of free movement of the wire tip and wire in the distal vessel. The situation can be compounded if the operator rushes to open the vessel, rather than carefully probing the occlusion and even rewiring the vessel if necessary. Once a false lumen is entered, particularly if there is propagation of the false channel distally, accessing the true lumen can become quite difficult. If a question exists about the coronary anatomy distal to the lesion or about the location of the wire in the distal lumen, an over-the-wire balloon or end-hole infusion catheter should be advanced just past the lesion, the wire withdrawn, and diluted contrast gently injected to document that the distal true lumen has been properly accessed.

Crossing the infarct lesion with the wire will oftentimes re-establish at least partial flow. Particularly in right coronary artery infarcts, and on occasion in left anterior descending infarcts where there is a narrow pulse pressure, severe bradycardia, and / or profound hypotension may occur and should be anticipated. The triad of responses of bradycardia, hypotension, and apnea, termed the Bezold-Jarisch reflex, appears to be vagally mediated [34]. Administration of 0.5 mg of atropine immediately prior to reperfusion of the RCA can partially obviate the response. The response typically resolves in 5–10 minutes; persistent hypotension lasting longer than 10–15 minutes following reperfusion should prompt a search for other etiologies of hypotension. On rare occasions, if significant lesions exist in the left system, the profound hypotension of the Bezold-Jarisch response can lead to closure of a second stenosis in the left anterior descending or left circumflex distributions and result in cardiogenic shock.

Whether to use an over-the-wire balloon preloaded with a wire or a rapid exchange system is largely a matter of experience and preference. If difficulties with the bare-wire technique are encountered, particularly in tortuous vessels that limit control of the distal wire tip, an early switch to an over-the-wire balloon or distal end hole infusion catheter may aid in crossing of the lesion.

As the lesion is being crossed, careful attention should also be independently directed to assessing the status of antithrombotic therapies. In the emergency STEMI setting, instructions regarding the administration of heparin or other anticoagulants can be misinterpreted, misconstrued, or simply not given. Intervention on a clot-laden vessel demands that appropriate anticoagulant and antiplatelet drugs be given to the patient. If the operator chooses not to give a platelet glycoprotein IIb/IIIa inhibitor, the activated clotting time should be in the 300 second range prior to intervention. In patients receiving a glycoprotein IIb/IIIa inhibitor, heparin dosing should be adjusted downward to achieve an activated clotting time in the 200–250 second range. Greater degrees of anticoagulation can lead to major bleeding complications without improvement in efficacy.

Coronary Intervention

Coronary intervention should follow promptly once the wire is appropriately placed in the distal true lumen. A working knowledge of coronary anatomy and the variants thereof is a must – inflating a 3.0 mm balloon over a wire lodged in a 2.0 mm branch vessel can be disastrous.

If the distal vessel is not visualized and only TIMI 0–1 flow exists, balloon angioplasty should be first performed to rapidly re-establish flow and define the distal anatomy. Definitive treatment via balloon inflation is not the goal here, as compression of soft thrombus is often not particularly rewarding and dilation with an oversized balloon increases the propensity for vessel dissection. Instead, dilating with a balloon half a millimeter or so smaller than the nominal vessel diameter should be considered.

Whether to proceed with further definitive balloon inflation or to place a stent once flow is reestablished was once debated [35], but contemporary practice targets stent implantation at the infarct lesion (along with restored myocardial perfusion) as the goal of the procedure. In long-term (5 year) follow-up of the 2,087 patients enrolled in the Primary Angioplasty in Myocardial Infarction (PAMI) trials, the 692 patients receiving a stent experienced lower mortality rates than those treated with balloon angioplasty [36]. In Stent PAMI, the first large-scale trial to randomize patients to balloon versus stent implantation in acute STEMI, patients assigned to the balloon angioplasty arm had a greater incidence of restenosis, target vessel revascularization, and angina at six months than those randomized to stent implantation [15]. Balancing this was an increase in mortality in the stent cohort. Stent PAMI, however, was conducted with early generation devices that used bulky stent delivery stystems, and the use of platelet glycoprotein IIb/IIIa antagonists occurred in only 5.8% of patients, raising the question as to whether the observations were specific to the stent versus balloon question or to the era of the study.

In the CADILLAC trial, a study in which later generation, lower profile stents were used, stent patients with or without adjunctive abciximab had less restenosis compared to balloon angioplasty patients and experienced no differences in death or reinfarction [17]. Stenting with abciximab provided an early (30 day) benefit in terms of lowered rates of subacute stent thrombosis and recurrent myocardial infarction, although there was no benefit in terms of 1-year mortality or target vessel revascularization [21]. In the balloon angioplasty cohort of CADILLAC, treatment with abciximab also provided for less subsequent ischemic events than those not treated with this agent. Nonetheless, given the markedly higher restenosis rates with balloon intervention relative to stent implantation, and given the plethora of additional data supporting the stenting approach [18], stent implantation is now essentially the *de facto*standard in primary PCI.

Marked generalized vasoconstriction usually accompanies acute myocardial infarction. Administration of intracoronary nitroglycerin or nitroprusside after

reestablishing flow often results in a marked increase in vessel size. Even in the hypotensive patient, a small amount of intracoronary nitroglycerin (50 mcg) should be administered to better establish the nominal vessel diameter. As noted above, for the initial dilation, the recommended approach is to select an undersized balloon to restore perfusion and to reduce "door to balloon" time. Given the beta-adrenergic excess of the acute STEMI patient and the consequent coronary vasoconstriction, the opposite is true for stent selection; erring on the side of deploying a slightly oversized stent (0.25 mm or so) that is slightly longer (5–10 mm) than the target lesion is recommended.

In general, post-dilation of a coronary stent (and even second dilation with the stent deployment balloon) should be avoided. The aim should be to deploy the stent to the desired diameter with one and only one inflation of the stent deployment balloon. This "one and done" approach is recommended because of the propensity for secondary dilation to cause further microembolization and resultant "no-reflow". Once flow has been re-established, microcirculatory recovery will then become the primary determinant of ventricular recovery. Every effort should thus be made to avoid further compromise to the microcirculation.

Note that treatment with balloon PCI only remains an acceptable approach. If balloon angioplasty alone is chosen as the preferred technique, every attempt to achieve an optimal result (absence of dissection, residual stenosis $<20\%$, final TIMI-3 flow) should be made. Longer inflation times with appropriately sized balloons usually results in acceptable angiographic results. In patients with non-compliant, calcified vessels with ostial disease, a scenario frequently encountered in the elderly, attempts to force a stent into the coronary can induce dissection. Increased ischemia, sustained hypotension, and markedly larger contrast loads can all combine to result in poor outcomes in this subgroup. Dealing with restenosis at a later date under more elective conditions in selected patients with advanced age or tortuous vessels should be considered an acceptable outcome.

Some enthusiasm for direct stenting in AMI exists, even in patients with occluded vessels where the distal anatomy cannot be assessed following wire placement. By protocol, stent patients in the Stent PAMI and CADILLAC trials underwent predilatation before device placement; on the other hand, direct stenting was permitted in the ISAR-2 and ADMIRAL trials [19,37]. The rationale for direct stent implantation is the potential reduction in distal embolization and the no-reflow phenomenon related to the trapping of thrombus with stent deployment. Direct stenting might also result in lower volumes of contrast, an important consideration in elderly patients. Direct stenting, while technically feasible, remains to be rigorously evaluated in large clinical trials.

Recently, the Zwolle group has forwarded concepts related to the microcirculatory recovery as manifested by myocardial blush score as being critical to patient recovery following acute STEMI [38]. While TIMI-3 flow predicts mortality, final TIMI flow rates focus only on epicardial blood flow. Myocardial blush scores attempt to quantify improvement in microvascular

reperfusion and can further risk stratify even in patients with TIMI 3 epicardial coronary blood flow. In 163 patients undergoing PCI within 24 hours of an acute MI, patients with TIMI-3 flow after acute intervention but only a grade 0-1 myocardial blush score had increased early and late mortality compared to those with those with both TIMI-3 flow and grade 3 blush scores [39], underscoring the importance of approaches to minimizing distal microembolization and the "no reflow" phenomenon. Finally, early ST resolution is another marker of improvement in microvascular reperfusion [40]. Patients with successful acute PCI who do not have >50% resolution of their initial EKG have markedly increased 1-year mortality. The approach of PCI during acute STEMI must therefore focus not just on achieving TIMI-3 flow at the infarct site but also focus on optimal perfusion of the microcirculation with ST segment resolution by ECG.

Multilesion PCI During Primary Angioplasty

Treatment of the infarct lesion during primary PCI is in and of itself one of the most challenging of emergency clinical scenarios. Patients with multivessel disease without shock are best left to recover from the initial platelet activation and hemodynamic insult once the infarct-related artery has been successfully treated. Still, given the availability of platelet glycoprotein IIb/IIIa inhibitor therapy and the ease and confidence that stent placement brings to the treatment of most lesions, some operators have made a case for complete revascularization of all significant stenoses during acute intervention.

Multilesion PCI in addition to primary PCI of an infarct vessel has not been systematically studied. The superb results noted by the PAMI-No SOS investigators were achieved with intervention upon the IRA only, as were the results reported in Stent PAMI and CADILLAC where multivessel intervention was prohibited by protocol [12,15,17].Common sense and clinical judgment should prevail, as subjecting an already compromised infarct patient to additional ischemia and further contrast volume cannot generally be considered reasonable. Even the simplest lesion can have an unpredictable outcome; a new territory of wall motion dysfunction is obviously not a desirable outcome in a patient already sustaining an AMI.

In patients in shock who manifest decreased left ventricular dysfunction in non-infarct related arteries (or if the infarct involves two different epicardial arteries with reduced TIMI flow in both), a case for rapid revascularization of both vessels with balloon pump support can be made. In shock patients with multivessel disease but normal left ventricular function in segments fed by a non-infarct related artery, little is to be gained by intervening upon non-infarct related vessels; potentially disastrous results may result if complications arise related to treatment of the non-infarct vessel.

Arrhythmia Management

For most interventionalists, a working knowledge of cardiac arrhythmias should be second nature when performing primary PCI in acute STEMI. Appropriate treatment of bradyarrhythmias with atropine or temporary pacing is obvious. Particularly in infarction secondary to occlusion of a dominant right coronary artery (or dominant left circumflex), maintenance of atrioventricular synchrony by either the judicious use of atropine or by atrial or atrioventricular sequential pacing can usually resolve hypotension following reperfusion. In this situation, a "stable" infarct patient will suddenly become hypotensive, develop increasing chest pain, and exhibit atrioventricular block or ventricular dysrhythmias (the Bezold-Jarisch reflex) with initial reperfusion with the guidewire passage or balloon dilation [34].

Ventricular arrhythmias are common and defibrillation pads should routinely be placed on infarct patients. Hemodynamic compromise resulting from an untoward delay in defibrillation can turn a relatively stable situation into full-blown shock. Attention to early recognition and prompt defibrillation of ventricular tachycardia and ventricular fibrillation cannot be over-emphasized, particularly in catheterization laboratories just initiating a primary angioplasty program.

Recognizing and differentiating accelerated idioventricular rhythms, true ventricular tachycardia, and atrial fibrillation with aberrancy can be a challenge. Whenever hemodynamic compromise occurs, rapid countershock should be done to improve coronary and systemic perfusion pressures. Ventricular tachycardia can occur suddenly in a stable infarct patient simply with wire passage, initial balloon inflation, and during left ventriculography and should always be anticipated. Treatment with intravenous amiodarone, beta-blockers, or lidocaine should rapidly be instituted. Given the likelihood of automaticity as the cause of ventricular tachycardia, amiodarone should be used as either a first-line drug or rapidly started if lidocaine is ineffective.

Mechanical Complications of Infarction and Intervention

Recognizing mechanical complications can be difficult. Mechanical complications such as ventricular septal defect or papillary muscle rupture should be rapidly diagnosed with either left ventriculography or a prompt transthoracic or transesophageal echo. These complications should be suspected when a patient appears sicker than the coronary anatomy would predict. Rapid diagnosis is necessary as the treatment is often surgical and emergency PCI is thus relatively contraindicated.

An acquired ventricular septal defect should be vigorously searched for, particularly in elderly patients. Often, the clinical presentation of AMI is confusing; as some patients have precedent infarcts 24–48 hours before presentation, develop a ventricular septal defect, and then present to the emergency

room. A loud holosystolic murmur should raise suspicion, but can be relatively easily missed. Because the treatment of ventricular septal defect is surgical rather than interventional, a case can be made for proceeding with left ventriculography before coronary intervention to rule out this complication, particularly in the unstable patient.

Papillary muscle dysfunction with chordal rupture is most easily diagnosed by echocardiography; again the treatment is surgical repair, rather than coronary intervention. Papillary muscle dysfunction without chordal rupture is best managed by completing the coronary intervention and medically treating mitral regurgitation with afterload reduction. On occasion, marked and rapid resolution of ischemic mitral regurgitation will occur after coronary flow is reestablished [41]. Particularly with large circumflex or infarcts involving the distal right coronary artery, a high suspicion for ischemic mitral regurgitation should be maintained. These patients can rapidly develop severe pulmonary edema with the added insult of contrast injections.

Pericardial tamponade is unlikely to exist in patients presenting within 12 hours after the onset of infarction, but a hemorrhagic pericardial effusion can occur after heparin anticoagulation in patients who present late. Thrombolytic therapy also is associated with the possibility of hemorrhagic pericardial effusion and this concern should be considered whenever dealing with a hypotensive patient after rescue PCI. A quick echocardiogram and pericardiocentesis can be life-saving.

Careful attention to distal placement of the guide wire is critical and care should be given to keeping the wire in the main arterial channel. Distal wire perforation, particularly in the setting of treatment with platelet glycoprotein IIb/IIIa inhibitor therapy, may not always be apparent on the final angiogram where the focus is on the infarct lesion. For this reason, pericardial tamponade should be ruled out in any infarct patient who is hypotensive 2–6 hours after an intervention.

Hypotension early after PCI should raise the question of retroperitoneal hemorrhage. Meticulous arterial access is even more important in primary PCI during acute STEMI, and decreased arterial pulses from hypotension secondary to an acute infarction increases the potential for inadvertent puncture of the posterior wall of the femoral artery. Whether to use a groin closure device in infarct patients is a matter of choice, but careful attention to groin bleeding is critical in the first 12 hours after intervention. In an already compromised patient, increasing the workload upon a damaged ventricle because of groin bleeding and hypotension is clearly not desirable and should be promptly managed. The diagnosis can be established in minutes with ultrafast CT without giving further contrast.

Thrombotic Complications

Once flow has been re-established, abrupt vessel closure occurs only rarely. Contemporary techniques of primary stent PCI coupled with adjunctive pharmacotherapy carry little risk of vessel closure—the best treatment for clot is

improved blood flow. The risk of subacute thrombosis is likewise low. In Stent PAMI, where abciximab was used in only 5% of patients, rates of subacute thrombosis in the balloon angioplasty and the stent arms were 0.9% and 1% respectively [15]. In CADILLAC, over 500 stent patients randomized to abciximab were completely free of subacute thrombosis at one month, compared to 1% in stent patients randomized to heparin only [21]. While no differences in definite clinical outcomes resulted, a clear advantage to using abciximab to avoid subacute thrombosis in infarct patients is consistently seen in clinical trials.

Distal embolization occurs frequently while attaining reperfusion and probably occurs to some extent in all patients. Large macroemboli in the distal coronary bed are easily managed with an aspiration catheter and / or low-pressure balloon inflation with an appropriately sized device. Low pressure balloon PCI does not seem to entail a higher restenosis risk at the site of distal embolization and is often required to achieve TIMI-3 flow and higher myocardial blush scores. On occasion the mere action of advancing a stent delivery balloon through an embolus can resolve distal flow issues.

No-reflow presents more of a challenge, as the microscopic capillary beds are the culprit and are not amenable to specific mechanical intervention. Minimizing manipulation of the infarct vessel may help avoid no-reflow, as well as using the same "light touch" techniques seen with saphenous vein graft stenting. Interestingly, larger vessel infarcts may be more prone to this phenomenon than smaller vessels, presumably to the larger volume of lipid-rich material expressed from the plaque with balloon dilation [42]. Treatment of no-reflow requires a rapid response. In general, little is to be gained by using intracoronary nitroglycerin, as this agent has no effect on the distal capillary bed. Treatment with intracoronary calcium channel blockers, adenosine, or nitroprusside with drug delivered directly to the distal epicardial artery beyond the target lesion with an end-hole infusion catheter or through the lumen of an over-the-wire balloon will often immediately resolve the problem. Large doses should be given as long as blood pressure is maintained. Careful maintenance of adequate blood pressure with fluids and/or pressors should be anticipated when using these agents. No-reflow is unlikely to resolve if sustained hypotension is induced by its treatment. In refractory cases of no-reflow and in any case where a large coronary bed has less than TIMI-3 flow, placement of an intra-aortic balloon pump should be considered.

Managing no-reflow is a critical hurdle for interventionalists performing PCI for acute infarction. Clinical studies likely underreport the incidence of transient no-reflow. Sustained no-reflow may have a major influence on clinical course and long-term mortality, as these patients are less likely to have TIMI-3 flow or normal blush scores. Elevation of ST segments immediately after the intervention likely reflects impaired microvascular perfusion and, particularly when resolution does not occur on serial electrocardiograms, is associated with higher mortality.

The continuous electrocardiographic monitoring system used in the cardiac catheterization suite is an underutilized tool. If acute ST elevation on the catheterization laboratory monitor resolves and then recurs after stent deployment or further balloon inflations, further manipulation of the infarct vessel should be done with caution if at all, particularly if transient no-reflow occurred. Managing restenosis electively can be safely performed later, while worsening a no-reflow situation or creating sustained and dramatic ST elevation by further intervention may result in poorer clinical outcomes.

Alternative Devices

Present clinical trials of PCI in AMI document procedural success rates (with TIMI-3 flow rates) of over 90% and 30 day mortality rates of 2–4% along with the virtual elimination of intracranial hemorrhage and other forms of stroke. Furthermore, target vessel revascularization is subsequently required in only 5–10% of patients. Given these excellent outcomes, opportunities for further improvement using alternative devices would appear to be modest. Nonetheless, since TIMI-3 flow and the perfusion at the level of the microcirculation both influence clinical outcomes, several devices directed at reducing thrombus burden or protecting the distal vascular bed have been intensively investigated.

The Possis Medical Angiojet® is a catheter system that uses high pressure jets of saline to create a vacuum to remove loose material such as thrombus from the target site. In a registry trial of 70 patients, the Angiojet system was used prior to stent PCI and outcomes assessed [43]. Final TIMI-3 flow was 88%, in-hospital mortality was 7.1%, and there were six cases of documented distal embolization and two perforations. This was followed by the 480 patient randomized AiMI (AngioJet Rheolytic Thrombectomy In Patients Undergoing Primary Angioplasty for Acute Myocardial Infarction) trial which found that the group receiving adjunctive treatment with the Angiojet had worse outcomes (larger infarcts and less TIMI-3 flow at procedure completion) and no differences in myocardial blush or ST segment resolution [44].

Another novel device, the Endicor XSizer, is a mechanical two-lumen, over the wire system with a helical cutter at the tip for the removal of thrombus and other friable atherosclerotic material. A 216 patient registry demonstrated that the device could be used relatively safely [45]. In a 201 patient randomized trial, improvements in the magnitude of ST resolution, myocardial blush score, and the occurrence of distal embolization were observed, but this did not translate to a difference in clinical outcomes [46].

Studies of distal protection, including an evaluation of the Boston Scientific Filterwire® system and the PercuSurge Guardwire® system have yielded similar (essentially neutral) results [47–49]. Coupled with the lack of evidence demonstrating clinical outcomes improvement with any of these devices, it

would appear that distal protection per se in native vessels has no role in primary PCI in acute STEMI.

However, there is one approach that is frequently used that can provide dramatic results in the appropriate setting – simple aspiration using a dual lumen catheter such as the Export® and Pronto® catheters. Aspiration of material from an acute infarct lesion is technically straightforward and may obviate the opportunity for distal embolization. Whether application of these devices become a standard approach awaits the outcomes of large randomized clinical outcomes trials.

Conclusions

Clinical trials of the past decade have defined the benefits of stenting for primary PCI and clarified the role of platelet glycoprotein IIb/IIIa blockade in this setting. Unanswered questions remain about the role of small molecule glycoprotein IIb/IIIa inhibitors in primary PCI, about "upstream" combination therapy before primary PCI, approaches to improving myocardial perfusion at the level of the microcirculation, avoiding and treating no-reflow, clarifying the role of thrombectomy and distal protection devices, and improving myocardial salvage. All of these issues demand the best of technical expertise of the interventional cardiologists performing PCI for acute STEMI Improvement in patient outcomes begins with the technical skills needed to attain final TIMI-3 flow, ST segment resolution, and optimal myocardial blush scores in patients presenting with this disorder.

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Chapter 5
Primary Coronary Intervention in Community Hospitals with Off-Site Cardiac Surgery Backup: Rationale and Steps to Quality

Thomas P. Wharton and Nancy Sinclair

Primary Coronary Intervention at Hospitals Without Cardiac Surgery: Role and Rationale

Primary percutaneous coronary intervention (PCI) has been demonstrated to be the best strategy for treatment of patients with ST-segment elevation acute myocardial infarction (STEMI) when delivered rapidly and expertly [1]. This approach is associated with lower rates of mortality, stroke, recurrent ischemia, and infarction compared with fibrinolytic therapy, and is more broadly applicable to patients including those with bleeding risks, previous bypass surgery, stent thrombosis, and cardiogenic shock. But the benefits of primary PCI are limited by severe underutilization due to limited availability of hospitals capable of performing emergency primary PCI and even by inconsistent use at centers capable of this strategy but where its application may depend on time of day or weekend or cardiologist on call. Only 20% of patients with STEMI are treated with primary PCI in the US [2,3], and over one-third of patients with STEMI do not receive any type of reperfusion therapy at all. This lack of effective dissemination into the community of this "best" treatment for one of the most common fatal illnesses represents a most vital public health problem.

Primary PCI is seldom available at community hospitals without on-site cardiac surgery, which is where most patients with acute myocardial infarction (AMI) present [4]. Several states prohibit PCI at hospitals without cardiac surgery, even for STEMI. Patients with STEMI that present to hospitals without PCI can receive reperfusion therapy in one of two ways: (1) local treatment with fibrinolytics, an inferior treatment compared with rapid and expert PCI, or (2) rapid transfer to a hospital providing 24-hours, 7-days per week emergency PCI. For patients who are not candidates for fibrinolytic therapy, which may be a majority of those with AMI, ambulance triage, or transfer to a PCI center is obligatory if reperfusion therapy is to be offered.

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Trials comparing transfer to a PCI center vs. local fibrinolytic therapy for patients with acute STEMI presenting to hospitals without PCI programs have demonstrated superior outcomes in the transfer group [5,6,7]. Early rapid transfer and pre-hospital ambulance triage to PCI centers have been therefore advocated to meet the need to increase access to primary PCI [8], but these strategies of rapid transfer after either pre- or post-hospital triage are fraught with limitations. These strategies are usually limited to urban areas, where tertiary hospitals are located, since the transport time must be short. The risk, delay, and barrier of transfer are compounded, usually prohibitively, if the nearest PCI center is geographically remote. Air transport is not always a reliable option. Pre-hospital ambulance triage cannot be applied to the 50% of AMI patients that do not arrive by ambulance [9]. The inter-hospital transport or triage of unstable patients with AMI may risk legal liability. Another potential deterrent to transfer includes extraneous pressures such as institutional pride and fear of loss of reimbursement. And some AMI patients are too unstable to travel. In the Denmark and Prague trials, 4% and 1% of patients, respectively, were deemed too unstable to travel; some of these patients died [5,6]. Deaths during transfer also occurred. Patients too unstable to transfer, including many with cardiogenic shock, are among the highest risk of all patients with AMI; these highest risk patients are the very ones that could benefit the most from primary PCI if available on an emergency basis at the presenting hospital. Patients with cardiogenic shock randomized to mechanical revascularization within the first six hours of infarction, likely at the point of first patient contact, had the greatest survival advantage of all subgroups in the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) study [10].

The need for inter-hospital transfer, which may present increased risk and may even be a barrier to the delivery of reperfusion therapy, also carries an intrinsic delay, which is perhaps the most important problem with this approach. Though pilot studies of the strategies of rapid transfer for PCI in Boston MA, Durham, NC, and Minneapolis, MN, have shown promising initial results [11,12,13], and though nearly 80% of the US population lives with 60 minutes of a PCI hospital [14], recent data from the National Registry of Myocardial Infarction (NRMI) document that door-to-balloon (D2B) times in the US are still 71 minutes longer for patients transferred for primary PCI than for those receiving PCI at the point of first presentation [15]. Since the transfer delay in NRMI was approximately one hour greater than that seen the Denmark and Prague studies, the positive findings of these European randomized trials that show superiority of transfer for PCI may not be directly applicable to most hospitals in the US [16]. D2B times of 2.5 to 3 hours, as seen in patients transferred for PCI in the US, are associated with a 60% increase in mortality compared with less than two hours [17]. In fact, 85% of patients transferred for primary PCI in the NRMI registries did not receive it within 120 minutes [18].

In striking contrast, nine published studies of primary PCI at hospitals with off-site backup, which include an aggregate of 5750 patients, indicate that

primary PCI at such centers can be performed within 56–110 minutes of first presentation [19,20,21,22,23,24,25,26,27,28,29,30]. Data from the NRMI Registry demonstrates that hospitals without onsite cardiac surgery have more rapid D2B times [31].

Justification for Primary Coronary Intervention Programs in Hospitals Without Cardiac Surgery

An increasing number of hospitals in the US that have cardiac catheterization laboratories but not on-site cardiac surgery are initiating programs to offer both primary and elective PCI. This effort is growing rapidly: in 2005, 16% of hospitals enrolling PCI procedures in the National Cardiovascular Data Registry for PCI (NCDR) did not have surgery backup on site [32]. Rapid and expert PCI at more acute care hospitals in broader geographic locations can help surmount the major limitations of rapid triage and transfer of patients with STEMI to PCI centers. This growth of PCI at hospitals with off-site cardiac surgery backup is occurring despite the fact that the American College of Cardiology (ACC)/ American Heart Association (AHA) Guidelines for STEMI [33] still designates primary PCI at hospitals with off-site cardiac surgery backup with only a "class IIb" indication (usefulness/efficacy less well established by evidence/opinion). These Guidelines apply a "class III" indication (not useful and in some cases may be harmful) to elective PCI at such hospitals. For those community hospitals that choose to offer primary PCI, a situation not "advocated" by the Guidelines, these same Guidelines recommend that such hospitals perform at least 36 primary PCI procedures per year, that the interventionalists perform at least 75 procedures per year, that procedures are performed within 90 minutes of presentation, and that there is a proven plan for rapid access to a cardiac surgery center.

These STEMI guidelines and the more recent ACC/AHA/Society for Cardiovascular Angiography and Interventions (SCAI) PCI Guidelines [34] also affirm other rigorous operator, institutional, and angiographic selection criteria for institutions that seek to establish primary PCI programs with off-site surgery backup, based on criteria initially proposed by our group (updated in Tables 5.1, 5.2, 5.3) [23]. These recommendations, including clinical criteria for emergency angiography, have been further elaborated in more recent recommendations from the SCAI [35].

Several states that formerly prohibited all PCI at hospitals without cardiac surgery now have changed their regulations to allow primary and/or non-emergency PCI (NH) or have established pilot programs or demonstration or research projects at selected hospitals with off-site backup (GA, KY, MA, MD, MI, MT, NJ, NY, PA, SC, TN, WA, WV). Most if not all of these states have established criteria for non-surgical programs based on the ACC/AHA/SCAI Guidelines [33,34] and the criteria in Tables 5.1, 5.2, 5.3. This remains a very

Table 5.1 Operator and institutional criteria for primary PCI programs at hospitals with off-site cardiac surgery backup

1. Experienced high-volume interventionalists.
2. Experienced nursing and technical CCL staff with training in interventional laboratories.
3. Well-equipped and well-stocked CCL, with full array of interventional equipment, IABP, thrombectomy and distal protection devices, covered stents, pericardiocentesis equipment, femoral closure, and compression devices.
4. Experienced CCU nursing staff, comfortable with invasive hemodynamic monitoring, temporary pacemakers, and IABP management.
5. Formalized protocols and agreements for emergency transfer of patients to the nearest cardiac surgical facility.
6. Full support from hospital administration in fulfilling the preceding institutional requirements.
7. Rigorous clinical and angiographic selection criteria for PCI and for emergency transfer (Tables 5.2 and 5.3).
8. Performance of primary PCI as the treatment of first choice for STEMI to ensure streamlined care paths and increased case volumes.
9. Primary PCI coverage on a 24-hour, 7-day per week basis.
10. Performance of at least 3 to 4 primary PCI procedures per month.
11. Ongoing outcomes analysis and formalized periodic case review, with monitoring of all D2B times and review of all times >90 minutes for quality improvement opportunities.
12. Participation in a national data registry such as the American College of Cardiology National Cardiovascular Data Registry.

CABG = coronary artery bypass graft; CCL = cardiac catheterization laboratory; CCU = cardiac care unit; D2B = door-to-balloon; IABP = intra-aortic balloon pump; PCI = percutaneous coronary intervention; STEMI = ST-segment acute myocardial infarction. Adapted from Wharton et al. (1999). Printed with permission from Wharton, Sinclair, copyright 2004, updated 2007.

Table 5.2 Clinical selection criteria for emergent coronary angiography with PCI when indicated

Clinical Inclusion criteria

- >30 min of ischemic pain not controlled by conventional medications (ASA, NTG, beta-blockers, and heparin)
  and/or
- ECG with $\geq$ 2.0 mV of ischemic ST-segment deviation in two or more contiguous leads (there is no time limit on duration of pain if patient has ongoing chest pain, ST-segment deviation with preserved R waves in two or more infarct leads, or cardiogenic shock)

Clinical exclusion criteria

- Lack of vascular access
- Absolute contraindication to any heparin/antiplatelet/antithrombin agents (i.e., acute cerebral hemorrhage)
- Patient or representative refuses informed consent
- Severe dementia or coma (excepting patients with successful cardioversion of out-of-hospital ventricular fibrillation in the field, regardless of acute mental status)
- Any serious illness with life expectancy of only a few weeks

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Table 5.3 Angiographic selection for primary PCI and emergency aortocoronary bypass surgery at hospitals with off-site cardiac surgery backup

Avoid intervention in:

- Patients with severe left main disease proximal to infarct-related lesion that might be disrupted by interventional catheters.
- Extremely long or angulated target lesions with TIMI grade 3 flow at high-risk for PCI failure.
- Lesions in other than the infarct artery (unless they appeared to be flow-limiting in patients with hemodynamic instability or ongoing symptoms).
- Lesions with TIMI grade 3 flow that are not amenable to stenting in patients with left-main or three-vessel disease that will require coronary bypass surgery.

Transfer emergently for coronary bypass surgery patients with:

- High-grade residual left main or three-vessel coronary disease and clinical or hemodynamic instability after PCI of occluded vessels when appropriate and preferably with intra-aortic balloon pump support.
- Failed or unstable PCI result in major epicardial coronary artery with ongoing ischemia. Intra-aortic balloon pump placement mandatory before transfer.

PCI = percutaneous coronary intervention; TIMI = Thrombolysis in Myocardial Infarction.

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controversial issue [35,36,37]; a recent change in NJ state regulations to allow a research study of elective PCI at selected hospitals with off-site backup has spawned a lawsuit from some NJ tertiary surgery centers.

Primary PCI has been performed at community hospitals in the US with off-site surgery backup since the early 1990s. The continued growth of this approach is supported by improvements in interventional technology and pharmacology that have dramatically reduced the risk of needing emergency surgery for PCI complication.

There are at least nineteen studies and registry reports of primary PCI at hospitals without cardiac surgery programs, all of which indicate that community hospitals can deliver primary PCI safely, effectively, and rapidly, with outcomes that are similar to those reported from cardiac surgery centers [19,20,21,22,23,24,25,26,27,28,29,30,38,39,40,41,42,43,44,45,46]. These studies report on an aggregate of over 9,000 primary PCI procedures. These excellent outcomes should not be surprising, since it is reasonable to expect that the benefits of increasing the speed of delivery and greater access to primary PCI should far outweigh any theoretical risk of not having an operating room on site if the PCI program otherwise meets stringent quality measures.

The inherently lower overall interventional volumes of smaller hospitals may not affect outcomes if primary PCI is performed by high volume interventionalists that regularly perform elective intervention, either locally or at a tertiary center. Community hospitals that perform primary PCI on a 24-hours, 7-days per week, 365-days per year (24/7/365) basis as first-line therapy for all patients with STEMI can easily achieve a primary PCI volume of over 33 to 48

procedures per year, a volume that correlates with improved mortality rates [17,47,48,49,50]. Moreover, such hospitals may be able to deliver primary PCI more rapidly than surgery centers, both during regular working hours and during nights and weekends [31]. Reasons for greater efficiency of smaller hospitals may include more direct communication between the emergency department and the interventional cardiologist, decreased travel times in a smaller community, and greater flexibility in a catheterization laboratory schedule that may not be as congested.

There is a clear potential to continue to increase the availability of primary PCI, since well over 600 community hospitals in the United States have cardiac catheterization laboratories without cardiac surgery [51]. PCI is being performed at hospitals with off-site cardiac surgery backup in approximately 40 states [35]. Many of these programs are also offering non-emergency PCI, which can improve access to PCI for patients with other high-risk acute coronary syndromes [52]. Non-emergency PCI at primary PCI centers with off-site cardiac surgery backup will of course increase interventional volumes at these hospitals and thus should be expected to further improve outcomes.

The ever-growing published data indicates that interventional programs which rigorously follow the highest standards and protocols should be able to achieve optimal outcomes whether or not they have on-site cardiac surgery programs [19,20,21,22,23,24,25,26,27,28,29,30,38,39,40,41,42,43,44,45,46]. Ensuring the highest quality in the delivery of primary PCI at all hours, which is well-reflected in the achievement of rapid D2B times regardless of shift or day of the week at community hospitals [31], is likely to save more lives than having on-site cardiac surgery.

Key Program Elements for Hospitals Considering Primary Pci with Off-Site Cardiac Surgery Backup

Interdisciplinary Acute Myocardial Infarction Quality Improvement Team

Hospitals with cardiac catheterization laboratories (CCL) cath labs but without cardiac surgery that are considering primary PCI must enlist the commitment and collaboration of cardiologists, emergency department (ED) and paramedical staff, CCL staff, primary care physicians, cardiac nurses, cardiac rehabilitation staff, and hospital administrators. These groups need to work together to develop a uniform standard of care for patients with AMI from the point of first patient contact (often in the pre-hospital phase) through the ED management, the CCL, the nursing units, and through discharge planning and follow-up. Rigorous ongoing quality improvement (QI) processes must be implemented ensure a safe and effective program.

Representatives from these groups must join to establish an AMI QI team, whose goal should be to develop the necessary care plans for each phase. The full support of the hospital administration must be engaged early-on to commit the resources to recruit experienced interventionalists and sufficiently well-trained CCL personnel (or to provide for this training at a tertiary center), to establish an on-call system, and to equip the CCL with state-of-the art imaging, interventional, and supportive equipment and supplies. Nursing, technical, and paramedical CCL staff must be trained in handling acutely ill patients and be comfortable with interventional equipment. CCL team members not already experienced in interventional procedures should be sent on rotation by formal arrangement to a PCI center, often the referral surgical hospital, for observation and "hands-on" experience in a busy interventional laboratory. The hospital administration must invest in and commit fully to providing resources necessary to launch and maintain effective, state-of-the-art, 24/7/365 primary PCI coverage. The more limited resources at community hospitals need not impair PCI success rates, complications, or major in-hospital clinical outcomes [31,53,54].

The AMI QI team should review the current literature and standards for the care of patients with AMI and incorporate these into care plans. The team should establish ongoing processes to track and review their institution's outcomes. There should be special emphasis on examining and improving the hospital's compliance with currently established standards of care, including, for example, the percentage of patients offered primary PCI, the D2B times, the rates of PCI success and complications, the percentage of AMI patients given appropriate cardiac medications, antismoking advice, cardiac teaching, and rehabilitation. Nursing and educational care plans should be revised to mirror these objectives.

Cardiologists, credentialing staff, and hospital administration should develop credentialing criteria based on national guidelines [33,34] and regional standards.

Cardiac surgeons from the surgical referral center should be invited to attend cardiac catheterization conferences and to become credentialed locally. This open communication will foster an atmosphere of collaboration and trust to ensure a seamless transition of care from the community hospital to the surgery center. Local credentialing will enable the surgeon to consult on non-emergency in-patients and review treatment options with patients and families. The surgeons should provide feedback on surgical outcomes of transferred patients, participate in discussion of case studies, and discuss and newer cardiac surgical techniques and procedures.

The institution should enroll in a national or regional data registry such as the NCDR. This is particularly important to increase the knowledge base about the safety and efficacy of PCI with off-site surgery backup. This data collection tool much important information for each patient, including demographic information, clinical presentation, initial treatment, time intervals (ED arrival, angiography, first intervention), coronary anatomy, medications, therapies

chosen and reasons, results of PCI, CCL complications, in-hospital complications, in-hospital mortality, and further procedures or cardiac surgery.

Primary PCI Care Plans

Key features of primary PCI care plans should include protocols for the emergency medical services (EMS) paramedics in the field and for the ED physicians that will reduce time-to-reperfusion. Every effort should be made to assure that all EMS services are provided with the capability to perform and transmit the electrocardiogram (ECG) from the field. The prehospital ECG can greatly reduce time-to-diagnosis and thus the time-to-reperfusion, which can be expected to improve survival [55,56,57,58,59,60,61]. Paramedics should be able to apply ACLS protocols in the field and to administer aspirin, intravenous beta blockers, heparin, and narcotic analgesia to patients with STEMI or other evidence of ongoing myocardial necrosis.

When the diagnosis of STEMI is made, the ED physicians should be empowered to page the cath team and interventionalist, even before the patient arrives, by activating a single page number, and without obligation to call another non-interventional cardiologist or primary care physician first. One of the more correctable causes of delay in D2B time is the time that it takes between diagnosis and call to the interventional team. The ED physician must make the call as soon as the ECG diagnosis of STEMI is made, even by transmitted ECG or verbal report from the field paramedic, and should not worry about the potential for a "false alarm."

It is imperative to provide primary PCI on a 24/7/365 basis at any PCI center, with or without on-site cardiac surgery, as a routine standard of care for all patients with acute STEMI [62]. This will increase interventional volumes, streamline care paths, and avoid differing standards of care depending on the time or day. This single strategy for all patients with STEMI will eliminate the "door-to-decision" time, which should in turn result in further decreased times to reperfusion, which in turn reduces mortality [17]. The increase in procedural volumes when all STEMI patients are offered primary PCI will accelerate the learning curve for ED staff and CCL team members and operators. A higher institutional volume of primary PCI (more than 33–48 procedures per year) correlates with faster D2B times and improved mortality rates [48,49]

The cardiac catheterization procedure itself should be streamlined to assess the coronary anatomy rapidly while attending to the medical treatment of the patient, with the goal of establishing and brisk (TIMI grade 3) flow as soon as possible while reducing to an absolute minimum the chance that new myocardial jeopardy could be created by the procedure itself. Cardiologists should develop clinical and angiographic selection criteria for primary PCI and transfer for bypass surgery such as those listed in Tables 5.2 and 5.3; these criteria should be documented in the patient care standards manual.

We recommend that immediate coronary angiography, with primary PCI when appropriate, should be considered in all patients who present with a clinical picture of AMI, even if ECG changes are not diagnostic, if they have ongoing ischemic pain for more than 30 minutes not controlled by optimal medical therapy. Patients with non-STEMI and uncontrolled ongoing ischemia represent a particularly high risk group and are not appropriate for fibrinolytic therapy [63]. These patients have greatly improved outcomes when admitted to hospitals with an early invasive rather than a conservative approach [64].

We also recommend no time cutoff for patients with clinical evidence for ongoing myocardial necrosis or cardiogenic shock [33,65,66], since the rate of progression of necrosis in AMI varies considerably with the degree of baseline antegrade flow and collateral flow, and the time of transition between unstable angina and AMI is often difficult to accurately ascertain.

Immediately after each procedure, positive reinforcement and feedback is particularly helpful to the ED physicians, nurses, and paramedics (e.g., providing photographs, report of D2B time, praise of rapid, and efficient care, if warranted; constructive troubleshooting if problems occurred).

The risk of access site bleeding in highly anticoagulated patients will require protocols for in-lab sheath removal and access site management in the nursing unit.

After the procedure, the patient can be effectively risk-stratified and triaged to appropriate in-hospital management. Low risk patients, those with a successful PCI, 1- or 2-vessel disease and ejection fraction $\geq$45% who are under age 70 and have no congestive heart failure or malignant arrhythmias can go directly to a cardiac step-down unit [67]. Critically ill patients may come to the Intensive Care Unit with indwelling sheaths, pulmonary catheters, temporary pacers, and/or intraaortic balloon pumps, along with multiple hemodynamic drips. This will challenge intensive care nurses to learn new skills.

Patients with low risk clinical and angiographic features can avoid admission to the CCU, avoid predischarge exercise testing, be targeted for discharge on hospital day three, and return to work within 2 weeks [67]. Telemetry unit and cardiac rehabilitation staff must initiate fast-track educational programs for such low risk patients, who may be discharged on day two or three, and thus have less opportunity for education about coronary disease, medications, and necessary life-style changes.

Periodic interdisciplinary conferences should be scheduled to examine current topics in AMI care and evaluate cases. The team should welcome input and allow time for problem solving suggestions from ED staff, EMS staff CCL staff, and ED physicians, and involve these staff in ongoing QI processes. Cardiac surgeons from the hospitals providing backup support should be welcomed at these conferences.

The AMI QI team should develop protocols for acuity-based interruption of elective procedures in progress and for emergency transfer to a cardiac surgery

Table 5.4 Elements of inter-hospital collaboration for primary PCI programs at hospitals with off-site cardiac surgery backup

1. Cardiologist will establish a good working relationship with cardiac surgeons at receiving facility.*
2. Cardiac surgeons from referral cardiac surgery hospital will formally agree to provide cardiac surgery back up for urgent and emergent cases at all hours.
3. Surgeon will assure that the patient will be accepted for services based on factors such medical condition, capacity of surgeons to provide services at the time of request, and availability of facility and staff resources.
4. Informed consent for PCI procedure includes information that emergency bypass surgery, if required, is not available on site and would require transfer to another facility with possible delay and risk.
5. Cardiologist will review with surgeon the potential needs and risks of the patient being transferred for emergency care.
6. Referring facility will establish a rigorous medical protocol for the safe and rapid transfer of patients to receiving cardiac surgery hospital.
7. EMS ambulance supplier will be formally contracted to be available on-site within 15–20 minutes of a call on a 24-hour, 7-day per week basis.
8. The hospital's transport team will include critical care nurses, paramedics, and CCL personnel with IABP expertise. All members of the team should be ACLS certified.
9. EMS ambulance provider will be available within 15 minutes and be able to accommodate portable cardiac ECG and pressure monitoring, oxygen supply, suction, multiple drips, ACLS drugs, resuscitation equipment, defibrillator, and IABP.
10. Transferring physician will obtain consent from patient or appropriate consenting party.
11. Review of transferred patients will be ongoing and include feedback from referring facility regarding problems in transfer process, teaching opportunities through catheterization conferences, and periodic review of the outcomes of the surgical program with special emphasis on outcomes of transferred patients.
12. Cardiac surgeon will be credentialed to visit patients and families at referring hospital to review medical options if time allows.
13. Hospital administrations from both referring and accepting facilities will endorse the transfer agreement.

*Cardiologists must collaborate with their cardiac surgeons to ensure a seamless transition of care from the primary hospital to the surgical center. Measures to foster a good working relationship include the surgeon's attendance at cardiac catheterization conferences and becoming credentialed at the referring hospital. This will enable bedside consultation on non-emergent in-patients with review of treatment options with cardiologists, patients and families, and encourage frequent personal interaction between the surgeon and the cardiologist. A very important element of this relationship will also include outcomes feedback from the surgeon to the referring cardiologist.

ACLS = advanced cardiac life support; CCL = cardiac catheterization laboratory; ECG = electrocardiogram; EMS = emergency medical services; IABP = intra-aortic balloon pump; PCI = percutaneous coronary intervention.

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center, and should develop formal transfer agreements with cardiac surgery centers (Table 5.4). A hospital-based critical care transport team should be formed, consisting of critical care nurses, paramedics, and CCL personnel, all with expertise in the intra-aortic balloon pump.

Ongoing Interdisciplinary Efforts to Reduce D2B Times

The D2B time is defined here as the time from ED arrival to first coronary intervention (balloon inflation or thrombectomy). The time of simply wiring the vessel or demonstrating coronary flow by contrast injection should not be counted as the "balloon" time. The D2B time is arguably the best single indicator of the overall quality of a primary PCI program. Indicators that use the incidence of infrequent events, such as PCI failures, major complications, or emergency bypass surgery for PCI mishap, may not provide a statistically meaningful basis for comparison of outcomes in small populations.

The D2B time depends on the efficiency and expertise of care in every phase, from pre-hospital care through early ED management (including speed of diagnosis and speed in notifying the CCL team) to the time to CCL arrival (including team travel time in off-hours cases) to the time from CCL arrival to first intervention. The AMI QI team should assure the tracking of these times: ED arrival, first ECG, call to cath team, cath lab arrival, and first balloon inflation or thrombectomy for every primary PCI patient, and should review these intervals monthly to see where opportunities for improvement may exist. The importance of such an ongoing quality review and improvement process cannot be overemphasized [58,59,68,69,70,71].

Table 5.5 includes our suggestions for how processes can be improved to reduce D2B times, separated into intervals between the times of first contact, diagnosis, call to interventional team, arrival at CCL and first intervention. This table also includes our suggested goals for the upper limits for each time interval. Any time greater than 20% above the goal for any interval, and any D2B time >90 minutes, should be investigated to eliminate correctable systemic problems and introduce new efficiencies. The exception would be patients with justified delay in the ED: those that require defibrillation, cardiopulmonary resuscitation, intubation in the ED, emergency imaging to exclude cerebral bleeding, or that initially refuse the procedure. All patients with STEMI that are not treated with an invasive approach should also be reviewed.

The time from first patient contact to diagnosis is the variable that is hardest to control. ED triage systems must be capable of obtaining an ECG within five minutes of arrival for patients with symptoms suggestive of myocardial ischemia, through heightened awareness of the variability of symptoms of ischemia, and through immediate access to 12-lead ECG in the triage area. This ECG must be presented to the ED physician as soon as it is performed. We suggest the ECG physician write the time that the ECG is seen on the tracing, in case future questions arise about any time delay from diagnostic ECG to cath team call. For patients brought in by ambulance, making the diagnosis by prehospital ECG and calling in the CCL team before ED arrival is perhaps the single factor that can most dramatically reduce the D2B time. Transmitting ECG's in from the field has demonstrated, both

Table 5.5 Improving D2B times

Interval/Time Goal	Steps to Streamline Process
1. First Contact To Diagnosis 5 minutes	• Regional educational programs on recognition of STEMI are established • EMS-developed chest-pain protocols are implemented • EMS classes in ECG interpretation are conducted • Rapid ECG assessment is performed in the field • ECG is transmitted from the ambulance to the ED • EMS communicates directly with ED physician • Bloods are drawn in the ambulance • ASA, IV beta-blockers, heparin bolus are administered in ambulance once diagnosis of STEMI is confirmed • If no ECG in field, this is obtained in ED within 5 minutes of arrival and is immediately shown to ED physician
2. Diagnosis To Calling Interventional Team 5 minutes	• "Diagnosis to decision" time is eliminated: all patients with STEMI are treated with primary PCI 24/7/365 • ED physician is empowered and expected to page directly the interventionalist and CCL team when diagnosis of acute STEMI is made, even prior to patient arrival • One page number is dialed to page all CCL personnel
3. Call To CCL Arrival 40 minutes	• CCL team lives <30 minutes from CCL • Team is paged with text-message of key information, that is, diagnosis, physician, location of patient, adjunctive services needed such as pacemaker, IABP, respiratory therapy • CCL team members confirm page received • ED physician begins to explain diagnosis, coronary angiography, and PCI to patient and family before arrival of interventionalist • Informed consent is obtained for the cardiac catheterization, possible PCI, IABP, and transfer to surgical center if needed. • Omit IV NTG and heparin drip after bolus for simplification; avoid routine multiple doses of NTG. ACT will be titrated with further heparin in CCL. • GP IIb/IIIa inhibitors are administered in ED • ED nurses clip both femoral areas if CCL not yet ready • ED secretary enters computer order for left heart catheterization to enable quick boot-up of CCL recording and imaging equipment • CCL team calls ED to transport patient when nearly ready to accept patient • Completed ED Chest Pain Assessment Sheet accompanies patient to the CCL
4. CCL Arrival To First Intervention 30 minutes	• CCL is left clean and "ready to go" • Basic angiographic and interventional supplies are set out on counter • Certain medication drips, such as phenylephrine, are pre-mixed • Completed ED Chest Pain Assessment Sheet is available in CCL as a ready source of information about patient • Nursing supervisor or ED nurse provides extra pair of hands during set-up, to aid in procurement of medications, equipment, communication with family members

Table 5.5 (continued)

Interval/Time Goal	Steps to Streamline Process
	• CCL control desk has easy access to computerized lab results • Cordless hospital telephone is provided for circulating nurse • Physician scrubs while patient is being draped • IABP should be placed initially for patients in shock, even though this may take extra time • Angiography of IRA is performed first to allow selection and preparation of interventional equipment while non-IRA is imaged • Physician prepares and introduces guiding catheter while scrub assistant prepares interventional equipment • Left ventricular catheterization and left ventriculogram is deferred until after intervention unless needed for hemodynamic assessment or infarct localization

AMI = acute myocardial infarction; ASA = aspirin; CCL = cardiac catheterization laboratory; ECG = electrocardiogram; ED = emergency department; EMS = emergency medical services; GP = glycoprotein; IABP = intra-aortic balloon pump; IRA = infarct-related artery; IV = intravenous; NTG = nitroglycerin; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.
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in our experience and in the literature, to significantly reduce D2B times [55,56,57,58,59,61]. During regular working hours, the CCL can be pre-alerted to clear any elective cases quickly; off-hours, the CCL team is given an important head start and can sometimes arrive at the hospital even before the patient arrives. If the CCL team can be called prior to the patient's arrival it is not unreasonable to expect a D2B time of 50–60 minutes, even off hours [58]. We endorse protocols such as those of the Cardiac Alert Program of Aurora, Colorado, which can serve as a model for future EMS and hospital AMI critical care pathways [57].

The time from diagnosis to calling the CCL team should be five minutes or less when the ED physician is empowered to call the interventional cardiologist and the CCL team directly as soon as the diagnosis of STEMI is made. Thus time from "diagnosis to decision" is reduced to zero when the decision is already made in advance to offer primary PCI as first-line treatment of choice to all patients with STEMI. Once the CCL team is alerted, the intervals to CCL arrival and to first coronary intervention are straightforward to address, standardize, and streamline: an experienced interventionalist and team that cover the CCL 24/7/365 should be able to move the patient into the CCL within 40 minutes of being called, even off-hours or with another elective case on the table, and should be able to perform the first intervention within 25 to 30 more minutes.

Conclusions

The lack of delivery of primary PCI to most patients suffering from STEMI represents a major public health problem. Access to this "best" treatment for one of the most common fatal illnesses in the US must be greatly increased. The three modalities to increase access include rapid transfer to PCI centers, pre-hospital ambulance diagnosis and triage to PCI centers, and encouraging the development of primary PCI programs at hospitals without cardiac surgery in broader geographic locations. Despite the controversy surrounding PCI at hospitals with only off-site surgical backup, this latter strategy is a most necessary component since pre- or post-hospital triage to PCI centers is often problematic for the many reasons described above. The literature has more than ample data that demonstrates that primary PCI can be provided safely and effectively at non-surgical hospitals, with outstanding outcomes similar to those reported from high-volume surgical centers. Expanding primary PCI to more qualified hospitals with off-site surgery backup would be greatly facilitated by completely uncoupling primary PCI from the requirement for on-site bypass surgery, a requirement still present in many state regulations.

All hospitals providing primary PCI, with or without on-site cardiac surgery, should commit to this strategy as routine, first-line therapy 24/7/365 for all patients with acute STEMI. Intensive efforts to reduce D2B times and streamline care paths should be ongoing at all centers providing PCI. The improved times-to-reperfusion, the increased institutional primary PCI volumes, and the streamlined acute critical care pathways, coupled with ongoing assessment of evolving protocols, continuous educational programs, and ongoing data collection and analysis will result in greatly improved emergency management of the AMI patient, yielding improved outcomes and reduced mortality rates [17,47,48,49]. These elements are far more important than the simple presence of cardiac operating rooms.

Because of the broader applicability, safety, and efficacy, we strongly assert that primary PCI should be advocated as the standard-of-care for patients with AMI at well-qualified hospitals that do not have on-site cardiac surgery. Offering this life-saving therapy to more patients with acute myocardial infarction in more hospitals in broader geographic regions will provide a major healthcare benefit to society. We would hope that the ACC/AHA/SCAI Guidelines for AMI and PCI would take this advocacy position in future updates.

Raymond Bahr, founder of the Society of Chest Pain Centers, emphasizes: "The morbidity and mortality for the heart attack problem remains the number one public health problem facing our nation. We are at a point in cardiology where we can exert a major impact on these horrendous statistics. . . the time is ripe for the nation to move ahead and set up quality PCI centers in properly trained community hospitals to serve as "centers of excellence" in this new strategy [72]".

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Chapter 6
Reducing System and Process Barriers: The RACE to Improve Door to Balloon Performance

James G. Jollis and Jenny C. Underwood

Introduction

Despite the accumulation of almost two decades of data in support of rapid reperfusion therapy for ST-segment elevation myocardial infarction (STEMI), the United States healthcare system still faces serious challenges in providing reperfusion to all eligible patients in a timely fashion. Myocardial infarction registries continue to show that approximately half of patients are treated too slowly, and for patients over age 65, up to half receive no reperfusion therapy at all. Given the wealth of data supporting mechanical or pharmacological restoration of coronary flow to improve STEMI survival, the current state can be attributed largely to deficiencies in the health care system rather than a lack of knowledge about these lifesaving strategies.

Systematic Barriers to Care

Characteristics of the United States health care system lead to systematic barriers in care. One of the most substantive barriers is local and regional competition among hospitals and physicians. While competition may provoke health care providers into improving the quality of care, this same competition prohibits them from collaborating in an effective manner. For example, within a given city, competing hospitals are more likely to encourage patients to seek care at their institution, rather than a competing facility capable of performing coronary reperfusion. Similarly, competing cardiology groups within the same hospital may be less likely to cooperate in assuming care of an STEMI patient in the most expedient fashion. Such competition between hospitals and physician groups can inhibit or even prevent the development of standard protocols and regionalized systems for coronary reperfusion.

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Another germane aspect of the United States health system that inhibits timely reperfusion involves emergency medical services (EMS). Depending on the locale, these services can be organized in a patchwork approach at the city, county, hospital, or private company levels. Training and standards are generally set at the state and local levels, and it is possible for an emergency medicine technician (EMT) who is able to diagnose and initiate therapy for a STEMI in one state to lose such credentials in crossing to a neighboring state. Federal direction of the emergency medical services is largely based in the National Highway Safety Administration with focus centered on motor vehicle accidents. Key components of timely STEMI care include "in the field" electrocardiography (ECG) and coordinated transport to the most appropriate facility able to rapidly treat the patient with STEMI. Thus, efforts to improve pre-hospital acute myocardial infarction (AMI) care must take into account not only organization and training standards but the larger geopolitical and regulatory issues.

A third significant potential challenge in providing timely reperfusion involves emergency departments (ED). Positioned on the frontline of health-care and mandated by mission and by statute to provide essential care to all persons presenting with illness or injury, EDs are often inundated with patients. Rapid STEMI care requires that patients be identified by history and ECG within 10 minutes of presentation. The relative infrequency of STEMI cases combined with overwhelmed facilities can lead to situations whereby AMI patients are hidden in waiting rooms or along hallways filled with ailing patients. The situation is often exacerbated by a lack of beds in hospitals, leading to logjams in the emergency department that consume available space and staff.

Reperfusion of Acute Myocardial Infarction in North Carolina Emergency Departments

Recognizing the significant gap between clinical trial findings and ongoing care of STEMI, we initiated a statewide program to organize and streamline timely diagnosis and treatment. The Reperfusion in Acute Myocardial Infarction in North Carolina Emergency Departments (RACE) project had two specific aims; to increase (1) the rate of appropriate use of reperfusion strategies, and (2) the speed of reperfusion in the acute STEMI patient. This chapter will describe our approach to these objectives including funding, organization, data collection, and interventions. The methods and materials for the RACE project are also available in an American Heart Journal publication [1]. Additional information may be found on the website of the North Carolina Chapter of the American College of Cardiology (ACC) [www.nccacc.org].

Funding, Leadership, and Oversight

Ideally, funding for the coordinated care of the STEMI patient should be an integral component of existing approaches to the private and public funding of the healthcare system. Potential existing resources that may be refocused on AMI can include national organizations in cardiac or emergency care, federal agencies such the Department of Health and Human Services, the Centers for Disease Control and Prevention, and the National Highway Traffic Safety Administration, and the state and local agencies that currently focus on public health or trauma care. Hospitals, particularly those that provide tertiary care, can shift resources from outreach programs or quality assurance activities to establishing regional STEMI care systems. In the case of the RACE program, we received four major sources of financial support. The largest private insurer in North Carolina provided substantial funding with a two-year unrestricted grant to establish the system. In order to further the range of our intervention, we were able to convince all participating hospitals who performed primary angioplasty to provide matching funds for regional coordinators. As will be outlined below, data measurement and feedback proved to be a critical component to system development. Prior to the conclusion of the National Registry of Myocardial Infarction (NRMI), Genetech, Inc provided customized data tools and reports to the North Carolina system and additional unrestricted funding in support of the program. A final major component involved the hundreds of healthcare workers focused on AMI care in EMS, EDs, catheterization laboratories, medicals schools, professional organizations, and local and state agencies. Of particular assistance was the North Carolina Office of Emergency Medical Services; this agency created a quality improvement "toolkit" based on the RACE program designed to establish standards for rapid coronary reperfusion. In short, we found that once statewide leadership had been identified, there were numerous persons and resources focused on AMI care that could be recruited to assist in instituting coordinated systems and removing barriers to care.

There were two key leadership elements in the RACE program. The first element included three academic cardiologists who initiated the project. These individuals had expertise in the clinical trials, hospital practice, and healthcare policies apropos to the acute STEMI issue. The second was a state director for the RACE program. The director was appointed once initial funding had been secured. This key person had prior nursing experience in both the in-hospital and outpatient facets of cardiology practices as well as industry funded clinical research in coronary reperfusion. Significant knowledge and experience in acute coronary syndrome (ACS) care, an ability to lead and build consensus among health care groups, and skills in fundraising proved to be important skill sets for the position. Another element in selection of this leadership team involved representation of the geographic dispersion of RACE, a program that spanned 200 miles and included both metropolitan and rural areas.

Building on clinical trial experience, an oversight board of regional and national leaders in cardiac and emergency medical care was appointed. This independent six member board, composed of physicians and health care executives, was charged with assuring that the RACE intervention did not adversely affect STEMI patients. The board met at the initiation of the project and intermittently throughout the course of the intervention, reviewing project design, health system data, and aggregated patient level data. The board was also charged with increasing the likelihood of success of the RACE project. From the outset, the strongest message from the board was that data collection and timely feedback would be required to effect change. The board recommended data feedback to system participants as frequently as logistically possible. The board also recommended extending the RACE project to an additional metropolitan area that was not included in the initial scope.

Organization and Development

Having established funding, leadership, and oversight, the state was divided into five regions according to the location of tertiary care primary percutaneous coronary intervention (PCI) hospitals and major urban and rural geographic areas, with the intention of covering as many persons and as much land area as possible. Using data from Medicare and private insurance, referral patterns of STEMI care were identified according to the zip code of discharge abstracts for AMI (International Classification of Disease codes 410.x0-.x1). These data allowed us to identify referral hospitals and primary PCI centers that collaborated in STEMI care. From east to west, the five regions were East Carolina, Durham / Chapel Hill / Greensboro, Winston-Salem, Charlotte, and Asheville. (Fig. 6.1) Within each region, we approached all hospitals that provided primary PCI (according to national guidelines) for participation in the system. Hospitals were approached individually in a meeting that included cardiologists, emergency physicians, and cardiac service line administrators. We conducted collaborative meetings on a regional basis when there was more than one primary PCI hospital within a region. Within each region, cardiology leadership under the auspices of the North Carolina Chapter of the ACC were instrumental in obtaining hospital support and for encouraging initial collaboration between competing physician groups and hospitals. The initial regional meetings were some of the most challenging, but essential organizational activities of the RACE project. Whenever possible, all RACE leaders and state and local STEMI experts actively supported these efforts. We also found it helpful to have a prominent physician from a different part of the state direct these meetings to lessen apprehension about competition.

Based on the experience of a pilot project in the Durham region, we asked that each participating primary PCI hospital co-fund a regional coordinator. Additionally, they were asked to have a single-number (“AMI hotline”) for the

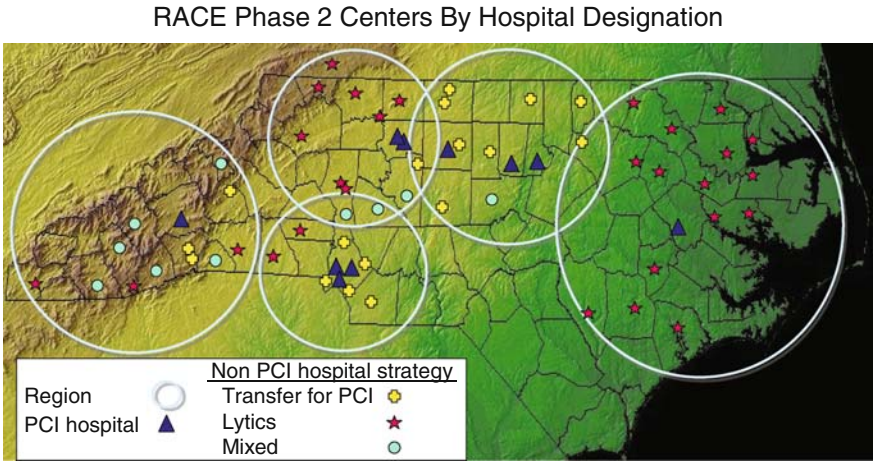

Figure 1 RACE phase 2 centers by hospital designatin

activation of the catheterization laboratory by emergency department physicians or emergency medical technicians. This designated line was to be available 24 hours, 7 days per week to accept all acute STEMI patients regardless of bed availability. All primary PCI hospitals were asked to collect data for NRMI for the duration of the project. While the financial expectations for hospital funding contributed to some delay in the initiation of the project, all ten hospitals that were approached ultimately enrolled and actively participated in RACE. With a fiscal stake in the system, we believe that the participating primary PCI hospitals became more actively involved in the project than they might have otherwise been.

Once regions were established and participating primary PCI hospitals had agreed to participate, regional coordinators were identified and hired. Candidates were selected according to three major criteria; extensive experience in, and thorough understanding of acute cardiac care, the ability to successfully organize institutions and health care personnel across large regions, and knowledge of quality improvement processes including data collection and feedback. While various health care professionals including administrators, emergency medical technicians, and pharmacists were considered candidates for these positions, the final group of coordinators was composed of nurses with cardiology, quality, and hospital outreach experience. Regional coordinators were selected by and reported directly to the RACE director. Employment arrangements varied according to the requirements of each region. Whenever possible, employment was based at the primary PCI hospitals, with funds being transferred from the RACE coordinating center to accounts at each of these hospitals. In situations where there was more than one major PCI hospital within a region, either the coordinator was hired by a contract through the RACE coordinating center, or in the case of one region, both PCI hospitals hired

half time coordinators who organized and attended all regional meetings in concert.

The initial charge of the coordinators was to approach each non-PCI hospital within the region for participation in the RACE project. The initial meetings with non-PCI hospitals involved an administrator, ED and EMS personnel, and local physician leadership. The RACE coordinator was sometimes accompanied by physicians from regional PCI hospitals if their assistance would help facilitate the meeting. Non-PCI hospitals were selected for affiliation with one or more PCI hospitals according to insurance data and local knowledge regarding existing referral relationships. In these initial meetings, non-PCI hospitals were asked to undergo a review of their existing STEMI protocols, use RACE protocols according to local resources and consensus, and allow for very limited data collection. Generally, non-PCI hospitals were enthusiastic in their support for the RACE system. RACE provided an opportunity for hospitals to work with physicians to improve a process of care under scrutiny by the Centers for Medicare and Medicaid Services and the Joint Commission on the Accreditation of Healthcare Organizations. With an established algorithm for STEMI treatment and the ability to transfer patients requiring urgent revascularization without consideration of bed availability, the project provided emergency physicians the authority to rapidly diagnose patients and determine the best reperfusion strategy.

We believe that three concepts assisted us in obtaining non-PCI hospital support and participation. First, our position was that every ED physician and paramedic should be able to rapidly diagnose STEMI. Thus, we did not "certify" hospitals in AMI care. Second, STEMI treatment algorithms were designed around locally available resources and consensus. Hospitals and physicians had the option of mechanical or pharmacological reperfusion according to the American College of Cardiology (ACC)/American Heart Association (AHA) STEMI Guidelines. By taking into account local needs, the RACE project was not viewed as an effort to transfer patients to larger hospitals in situations where such transfers were not felt to be in their benefit. A third concept involved keeping the expense and administrative burden of RACE to a minimum. As many smaller hospitals infrequently encounter STEMI patients, resource intense activities such as data collection or training were provided by the regional coordinators, affiliated PCI hospitals, and the RACE central office.

Once non-PCI hospitals agreed to RACE participation, regional coordinators reviewed their STEMI systems and collected two sets of data. The first data involved an inventory of processes and equipment for AMI care starting with patient registration and ending with reperfusion therapy. The second data set involved a review of 10 consecutive charts of STEMI patients identified by emergency room registries and discharge diagnosis codes. Chart review elements were focused on traditional reperfusion processes (door to ECG, ECG to decision, decision to needle, or transfer) and comprised two pages of data elements (Appendix).

Implementation and Interventions

Once data were collected, each hospital was asked to develop a reperfusion plan according to state and national guidelines and local resources and consensus. Statewide RACE recommendations were identified in regional meetings and published as a booklet document available on line [www.nccacc.org/Race_booklet_2.1.pdf]. Organized by point of entry to the healthcare system, optimum care recommendations were outlined. These recommendations were designed to overcome perceived barriers to rapid care and be practical to implement. A major focus of the ACC/AHA STEMI Guidelines involves obtaining an ECG as rapidly as possible in the field or in the ED. Thus, training EMS personnel to obtain and interpret 12-lead ECGs for ST-segment elevation became a priority. A second focus aimed at initiating parallel, rather than consecutive processes in order to save critical minutes. This approach also involved limiting the number of consecutive processes, grouped in five minutes segments, to reach the goals of 30 minutes to fibrinolysis (six segments) and 90 minutes (18 segments) to primary PCI. With a raised awareness of time critical tasks, the notion that "it only takes 5 minutes" no longer served as a reason for continuing superfluous steps. Many of the recommendations, such as accepting patients regardless of bed availability and streamlining the registration process with "dummy" patient identities, were modeled after the trauma system. A third focus was to simplify complex treatment algorithms, building consensus among emergency and cardiology physicians regarding a single preferred reperfusion strategy. The operations manual specified two simple "bare-bones" reperfusion regimens for primary angioplasty (regimen A) or fibrinolysis (regimen B) as a starting point for discussion [http://www.nccacc.org/Race_booklet_2.1.pdf].

The RACE regional coordinators provided the needed day-to-day operational support for the success of the project. One of the most effective strategies of the coordinators was to provide continuing education on STEMI care and 12-lead ECG interpretation to county EMS organizations and ED nursing staff. Education was made available on an individual, departmental, regional, and state-wide level in the form of one-on-one ECG review, one-hour case review sessions, and all-day seminars. Another responsibility of the regional coordinator was to support the RACE "team" at non-PCI centers by providing immediate feedback on all STEMI patients transferred for primary PCI. A summary e-mail of the case would be sent to the key personnel at non-PCI centers within 24 hours of STEMI patient presentation. The summary would include key time elements (symptom onset, first hospital arrival, first ECG, first hospital departure, primary PCI hospital arrival, arterial access, device activation, and outcome). Not only were all cases reviewed individually, but coordinators provided quarterly reports to all non-PCI centers. These reports compared the non-PCI center data to the data of "like-hospitals" (blinded). An additional role of the coordinators was to assist with grant application writing for needed ECG equipment for county EMS that did not have 12-lead

ECG equipment on their ambulances at the onset of the project. Ultimately, coordinators where the "go-to" person for any issues related to the care of a STEMI patient at both PCI and non-PCI hospitals, and served as a liaison between centers. This ongoing support and direction of the regional coordinators was ultimately responsible for the success of the project.

The major interventions regarding the emergency medical service centered on obtaining and interpreting pre-hospital ECGs and rapidly transferring patients to a non-PCI center for fibrinolytic reperfusion, or to a tertiary center for primary PCI. Pre-hospital ECGs became a standard recommendation. In North Carolina, there were three times as many EMTs with "intermediate" training compared with EMTs with "paramedic" training. Many counties had no paramedics. Thanks to the influence and combined efforts of the RACE project and the North Carolina Office of EMS, state law was changed to allow intermediate level EMTs to perform 12- lead ECGs. While ECG transmission capabilities increased during the time period of our intervention, we found that EMT recognition of an ST-segment elevation on an ECG was adequate to initiate activation of interventional cardiac catheterization teams without need for physician review of the ECG.

In some counties, intravenous (IV) tubing proved to be a significant issue. A number of EMS crews used IV tubing that was different from the transferring and receiving hospitals, requiring tubing changes at both ends of and STEMI transport. Eliminating IV drips also allowed EMS units to transfer patients who were otherwise restricted from managing patients with continuous infusions.

In rural areas with relatively few EMS units in operation, there was significant concern about leaving a county without EMS coverage in the event that the only available unit was transporting a patient to a hospital outside of the county. Three solutions were implemented. The first involved transferring patients from one EMS unit to another at county borders. A second involved having EMS units from neighboring counties cover emergency calls during the period of ambulance absence. A third involved establishing helicopter landing sites and protocols in rural counties lacking hospitals and associated landing sites. Prior to initiation of our system, a 911 call took priority over inter-hospital transfer calls, as it was assumed that patients in a hospital could be medically stabilized and at lower risk. In the setting of STEMI, particularly in situations where a patient was in a non-PCI hospital and had a contraindication to fibrinolysis or was in cardiogenic shock, these transfers are time critical, and protocols were changed to elevate their priority to equal that of a 911 call.

The most important and effective EMS intervention involved meetings between cardiologists, coordinators, and EMTs in the EMS facilities to review STEMI cases. Such meetings could include playback of the telephone communication, review of the ECGs, and presentation of the hospital course including coronary angiography, subsequent diagnoses, and outcomes. These face-to-face interactions between physicians, coordinators, and EMTs resulted in

highly effective communication between the EMS and affiliated hospital staffs, and substantially motivated the EMTs and the physicians to continue to focus on systems improvement.

Emergency department interventions were implemented at both PCI and non-PCI centers. For non-PCI centers, the goal was to establish and rapidly implement reperfusion regimens best suited to patients in that geographic location. For non-PCI centers located in areas where rapid transfer for primary PCI was not feasible, fibrinolytic therapy became the best reperfusion option, after which, patients were immediately transferred to primary PCI centers for rescue or elective PCI. For hospitals choosing to transfer patients for primary PCI (generally about 50 miles or less from primary PCI centers), time spent in the non-PCI center was kept to a minimum. By keeping treatment requirements to a minimum, significant time was saved. Patients received ASA, an unfractionated heparin bolus, and one IV access site before transfer. If time allowed, nitroglycerin paste, morphine sulfate, and beta-blockers were also administered, but only if they did not delay patient transport. For EMS-presenting patients in RACE counties, patients remained on the EMS stretcher for a rapid ED physician evaluation, administration of medication, and activation of the one-call "AMI hotline" before taking the patient back out to the ambulance, and transporting the patient to a primary PCI center. The goal "in-and-out" time for these patients was 20-30 minutes, with many patients spending less than 20 minutes in non-PCI EDs.

To improve time to ECG for both PCI and non-PCI centers, guidelines for obtaining a 12-lead ECG were implemented **[2].** Additionally, posters were placed in all of the RACE ED waiting rooms to alert the public of heart attack symptoms and to seek immediate medical attention. [http://www.nhlbi.nih.gov/health/public/heart/mi/poster.pdf] Another intervention in some hospitals was to implement a "nurse-first" approach to patient flow and management. Historically, a registrar would be the first person to greet a patient who walked into the ED. RACE encouraged centers to support a system whereby the registered nurse would be the first person to greet and triage the patient. Both nurses and ED technicians were trained to obtain a 12-lead ECG, and all ECGs were taken immediately to an ED physician for review. A dedicated ECG area was also critical to process improvement, particularly in EDs with frequent overcrowding.

Regarding the development of consensus for a single reperfusion plan, we found that many emergency departments already had protocols and treatment guidelines in place that could be adopted or modified to facilitate more rapid management. For those lacking protocols, coordinators arranged meetings between ED directors, ED physician staff, ED nursing leadership, and physician leaders from the RACE project to develop an individualized protocol. A major focus of protocol development was to have emergency physicians diagnose STEMI and initiate reperfusion, reserving cardiology consultation for

situations of uncertainty. Other time saving interventions included reducing the requirement for IV access from three to one IV site. We also integrated the "hotline" approach for rapid activation and transfer, whereby ED physicians made only one call to activate the medical cardiologist, the interventionalist, the interventional team, bed control, and other key personnel at the receiving facility. Patients being transferred from referring hospitals bypassed the PCI hospital ED and went directly to the cardiac catheterization laboratory.

Despite the geographic issues in North Carolina, our intervention did not impact the use of helicopter transport. By working with local EMS and EDs, our general experience was that patients within 50 miles of a primary PCI hospital could be transported faster by ground using the "leave the patient on the stretcher" approach. In settings such as longer distances or winding mountain roads, helicopter transport remained an important element. Our main focus with the helicopter crews involved picking up the patient as fast as safely possible (20 minutes landing to lift-off). Interventions to improve times included checking weather and crew availability in parallel with the initial call to the AMI hotline, the faxing of records from the initial hospital to the catheterization laboratory (rather than waiting for them to be copied and carried on the helicopter), avoiding or turning off IV drips when possible, and focusing patient assessment to the critical elements surrounding STEMI care. Helicopter transfer was also vital in providing a back-up transport plan when the usual mode of transfer was not available. In situations where neither helicopters nor ground crews could transfer patients in a timely manner, the reperfusion plan became fibrinolysis.

The final focus of the RACE program was the catheterization laboratory. As above, systems were changed so that the catheterization laboratory team could be activated by a single hotline call for primary PCI regardless of hospital bed availability. AMI hotlines were instituted at all primary PCI centers before regional interventions were undertaken. Given the volume and experience of the laboratories involved in our system, we found that modifications to expedite STEMI care could be quickly and expeditiously implemented compared to interventions affecting other, less experienced and resourced parts of the system. The greatest challenge involved the additional resources, commitment, and personnel issues (particularly lost sleep) necessary to support substantial improvements in the response time of the catheterization laboratory staff. When not already in place, call schedules were adjusted such that the lab was staffed within 30 minutes, with further adjustments such that one member of the call team lived within 10 minutes of the hospital so that room set-up would begin nearly immediately. One hospital had coronary care unit nurses cross trained to assist with initial catheterization lab staffing until all members of the team arrived. Rapid patient registration was a major focus, as some angiography suites cannot be initialized without patient registration information. Approaches included "dummy" registration numbers similar to the trauma system or having someone from the registration office follow the patient from the front door to the catheterization laboratory and registering them en route.

When possible, consent was obtained for emergency cardiac catheterization proximate to the patient arriving in the catheterization suite for the procedure. From a technical standpoint, most interventionalists elected to complete the ventriculogram only after PCI of the infarct-related artery, thereby shaving several additional minutes off of the door-to-balloon time.

Immediate data collection, review, and feedback to care providers proved to be another key feature of the PCI strategy. One key feedback element was a telephone call to the activating physician or EMT crew at the end of the case reviewing the outcomes, e-mail to the entire STEMI team within 24 hours of each case, and monthly review of times and cases. In one hospital, operator specific times were provided to further motivate physicians and teams to improve timely care. Benchmark time intervals were established including initial hospital arrival to ECG, ECG to AMI Hotline call, call to transport, departure from first hospital to arrival at primary PCI center, PCI center arrival to arterial access, and access to device activation. Overall times intervals included door to device for primary PCI center presenting patients, and first door to device or door to fibrinolytic for non-PCI center presenting patients.

Results

By almost every measure, reperfusion improved in the North Carolina RACE system over the course of the intervention [3]. Comparing data from the three months prior to the intervention to data one year following implementation for the 10 PCI hospitals, median time from door to intervention for patients presenting to these hospitals dropped from 87 to 75 minutes. By the end of the intervention, 72% of patients met to door to intervention goal of less than 90 minutes, compared to 51% at the start of the intervention. For patients transferred from another hospital, the first hospital door to intervention time dropped from 160 minutes to 128 minutes. For 55 non-PCI hospitals, patients receiving fibrinolysis initiation within 30 minutes of arrival increased from 35% to 52%. For presenting to non-PCI hospitals with a main strategy of transferring for PCI, the door in, door out times fell from 72 minutes to 40 minutes. All time differences were statistically significant below the $P<0.01$ level. The improvements in time were significantly better than improvements seen in corresponding national NRMI data, a registry composed mainly of high quality PCI centers.

Despite the substantial progress, these same data suggest that there remain targets for continued improvement. In particular, a median time of 128 minutes for patients transferred for primary PCI indicate that systems of STEMI recognition and patient transfer need much further development before primary angioplasty is considered the main method of reperfusion on a regional or national basis.

Appendix

RACE Referring Hospitals Data Collection Form

Data Abstracter Instructions: Please pull consecutive patient records for one month (or longer) to obtain a minimum of 10 patients. Include patients from *both* of these two sources; discharge charts coded with ICD-9 410.X0 – .X1 all AMI patients transferred from the emergency department to another facility

Purpose: To identify the subset of ST-elevation myocardial infarction patients and new left bundle branch block AMIs from chart pull and enter this subset of de-identified individual patient data for an aggregate data set. This will be repeated one year after RACE intervention at your center.

Process: You can use this worksheet for preliminary data abstraction or enter data directly onto the electronic data capture eCRF on nrmi.outcome.com.

Arrival mode (at your hospital): O Self-transport
O Ambulance
O Air ambulance/helicopter
O Other/unknown

	Month/Day/Year (mm/dd/yyyy)	Hour/min (24hr Clock)
Patient Arrival Timeline:		
MI symptom onset	____ ____ /____ ____ /____ ____ ____ ____	____ ____:____ ____
	O Date N/A	O Time N/A
First hospital arrival	____ ____ /____ ____ /____ ____ ____ ____	____ ____:____ ____
		O Time N/A

Did the patient have chest pain at presentation? O Yes O No O N/A

Year of birth: ____ ____ ____ ____ (yyyy)

Gender: O Male O Female O Unknown

First recorded blood pressure: _____/_____ mmHg or O N/A (Systolic/Diastolic)

First recorded pulse: _____ bpm or O N/A

First assessment of heart failure (HF) (*check one*) O Killip 1: No HF

O Killip 2: Rales, JVD
O Killip 3: Pulmonary edema

O Killip 4: Cardiogenic shock

Was a pre-hospital 12-lead ECG obtained? O Yes O No O N/A
If yes, by EMS? O Yes O No O N/A

	Month/Day/Year (mm/dd/yyyy)	Hour/min (24hr Clock)
First 12-Lead ECG date/time	____ ____ /____ ____ /____ ____ ____ ____ O Date N/A	____ ____:____ O Time N/A

First 12-Lead ECG results *(Select Yes or No for each item)*:
ST elevation > 2 leads O Yes O No # **of leads**: ____ or O N/A
LBBB (new/unknown) O Yes O No
Known LBBB (old) O Yes O No
Normal O Yes O No
Other/Unknown O Yes O No
Was the reperfusion checklist performed by EMS? O Yes O No O N/A
(This question is not on the regular eCRF – Record this information in Section 23, Custom Field 1 on the eCRF:
001 = Yes, 002 = No, 003 = N/A)
(This form continues on the other side of this page)
Was an IV thrombolytic administered? O Yes O No *(When entering online, see the Instructions)*
If the patient did not receive a thrombolytic, skip the thrombolytic timeline questions below.

Thrombolytic Timeline:	Month/Day/Year (mm/dd/yyyy)	Hour/min (24 hr Clock)
IV thrombolytic ordered	____ ____ /____ ____ /____ ____ ____ ____ O Date N/A	____ ____:____ O Time N/A
IV thrombolytic initiated	____ ____ /____ ____ /____ ____ ____ ____ O Date N/A	____ ____:____ O Time N/A

If the patient was not administered a thrombolytic, please provide the reason(s) from the list below. Please check <u>all</u> reasons that apply to this patient. <u>Skip this question if the patient did not receive a thrombolytic, but was transferred for consideration for primary PCI.</u>

O O Reason unknown/Not documented

O Active internal bleeding or known bleeding diathesis on arrival or within 24 hours
O History of CVA
O Recent surgery/trauma (< 2 weeks)
O Intracranial neoplasm, AV malformation or aneurysm
O Severe uncontrolled hypertension
O No ST elevation/LBBB
O ST elevation resolved
O MI diagnosis unclear
O MI symptom onset >12 hours
O Chest pain resolved
O No chest pain
O Quality of life decision
O Co-morbid disease
O Traumatic CPR
O Patient/family refusal
O Do not resuscitate order in effect at time when treatment decisions being made
O MI present, but not acutely recognized within 12 hours *(Record in Section 23, Custom Field 2 on the eCRF: 001 = Yes, otherwise, leave blank.)*

What was the discharge status for this patient? ***(Choose only one option from this list only)***

01-Discharged to home care or self care (routine discharge)

02-Discharge/transferred to another short term general hospital for inpatient care

07-Left against medical advice or discontinued care

20-Expired

	Month/Day/Year (mm/dd/yyyy)	Hour/min (24hr Clock)
Discharged/Expired/Left AMA/ Transferred-out from this hospital	____ ____ /____ ____ / ____ ____ ____ ____	____:____ ____ O Time N/A

If the patient was transferred from your hospital (discharge status 02), was the patient transferred for consideration for primary PCIO Yes O No *(Record in Section 23, Custom Field 3 on the eCRF: 001 = Yes, 002 = No)*

If yes, which hospital? _____

(Record in Section 23, Custom Field 4 on the eCRF. See the Instructions for the list of RACE tertiary hospitals and the codes to be entered in the Custom Field)

Was an Acute MI Hotline used (a single call line used to activate the cath lab at the PCI center)?

O Yes O No *(Record in Section 23, Custom Field 5 on the eCRF: 001 = Yes, 002 = No)*

How was the patient transferred to the next hospital? O EMS (dispatched locally)

O Ground (dispatched from PCI center)

O Air (dispatched from PCI center)

O Other/unknown

(Record in Section 23, Custom Field 6 on the eCRF: 001 = Local EMS, 002 = Ground, 003 = Air, 004 = Other/unknown)

Form prepared by (print name): _____

Signature:_____ **Date:** _____

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Chapter 7
Rescue Coronary Intervention for Failed Thrombolysis

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Introduction

Rescue or salvage percutaneous coronary intervention (PCI) is defined as PCI of the infarct-related artery (IRA) within 12 hours from the onset of ischemic symptoms, after failed fibrinolytic therapy, in patients with continuing myocardial ischemia [1]. Early restoration of patency of the infarct-related artery is a universally accepted goal in the treatment of acute ST-segment elevation myocardial infarction. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) angiographic sub-study, the 30-day mortality rate was 4.4% for patients with normal coronary artery flow at 90 minutes, whereas it was 8.9% for those with occluded arteries at 90 minutes, regardless of the subsequent therapeutic strategy ($P = 0.009$) [2]. Furthermore, the clinical benefit to restoring not only patency but also normalizing flow (Thrombolysis in Myocardial Infarction [TIMI] grade 3) was clearly demonstrated in that trial. In all patients, left ventricular ejection fraction and wall motion was significantly better both acutely and at 5–7 days in patients in whom TIMI grade 3 reperfusion was achieved after thrombolysis, compared to those with TIMI-2 flow. A beneficial trend in the 30-day mortality rate was noted as well with the achievement of TIMI-3 flow when compared to TIMI-2 flow (4.4% vs. 7.4%, $P = 0.08$) [2]. These data are consistent with those reported in earlier multicenter studies and meta-analyses, including a series of trials from Germany documenting a 2.7% in-hospital mortality among patients with TIMI 3 reperfusion, 6.6% with TIMI 2, and 7.1% for persistent occlusion of the IRA [3].

Either thrombolysis or PCI can be used to restore patency of the IRA, but at present and in the foreseeable future, thrombolysis is more globally available and will continute to be more widely used as the first-line approach. However, the patency rate (defined as TIMI grade 2 or 3 flow) at 90 minutes of even the

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most effective thombolytic regimen has only been 81%. The rate of TIMI grade 3 flow was only 54% in the GUSTO angiographic sub-study [2].

It is furthermore critical to note that, restoring IRA patency may not be sufficient to achieve adequate myocardial (as opposed to epicardial) blood flow as restoration might be jeopardized by the development of the *No-reflow phenomenon* [4,5]. In this situation, oxygenated blood does not reach the myocardium because of microvascular dysfunction. In the presence of the no-reflow phenomenon, even with angiographically successful rescue PCI, the clinical benefit is likely to be minimal. Unfortunately, the no-reflow phenomenon cannot be predicted, although it is more frequent after interventions in saphenous vein grafts than in native vessels. Possible causes of no-reflow include tissue edema, platelet microembolization from the intervention, neutrophil microvessel plugging, and microvascular spasm. Lesser degrees of myocardial malperfusion are difficult to ascertain by angiography alone, and intracoronary or even intravenous echocardiographic contrast application may allow detection of impaired myocardial perfusion in spite of restored epicardial coronary artery blood flow, possibly prompting more aggressive medical adjunctive treatment [6–9]. The no-reflow phenomenon is clinically relevant; Ito and colleagues demonstrated a higher incidence of heart failure in patients who had reduced myocardial reperfusion or no-reflow [8]. Sakuma and coworkers demonstrated a relative risk of 10.7 for the major cardiac events of death, MI, heart failure, and hospital readmission among patients with impaired myocardial perfusion after acute myocardial infarction when measured by contrast echocardiography [10].

Finally, while restoring flow in the IRA would appear to be the most logical strategy in patients who fail fibrinolysis, this strategy is limited by the lack of sensitive markers that can be used to accurately identify patients in whom fibrinolytic therapy has not restored normal antegrade coronary flow. Clinical markers of reperfusion, such as the relief of chest pain, partial resolution of ST-segment elevation and reperfusion arrhythmia, have limited predictive value in identifying failure of thrombolysis [11]. Clearly, failure to recognize unsuccessful thrombolysis in a timely fashion limits the opportunity to salvage ischemic myocardium.

Technical considerations

No specific strategy fundamentally distinguishes rescue PCI from other types of emergency PCI, such as primary PCI for myocardial infarction. Usually, only the infarct-causing lesion is treated, and “complete revascularization” is not attempted during the acute intervention (unless the patient is in cardiogenic shock). The use of stents is widely practiced in the setting of rescue PCI in the contemporary era, however the use of platelet glycoprotein receptor blockers has not been consistent [12,13].

Key clinical factors supporting the rescue angioplasty approach

As stated above, the diagnosis of success or failure of thrombolysis to achieve reperfusion by noninvasive means is notoriously difficult. Table 7.1 enumerates some clinically relevant criteria for failed thrombolysis. Resolution of ST-segment elevation within 3 hours from the start of thrombolysis has been shown to correlate with 35-day mortality. In the International Joint Efficacy Comparison of Thrombolytics (INJECT) study of 1398 patients, complete ($\geq$ 70%), partial (30% to 70%), and lack of ($<$30%) resolution of ST-segment elevation was associated with 2.5%, 4.3%, and 17.5% rates of 35-day mortality, respectively ($P<0.0001$) [14]. However, other reports are less optimistic regarding the diagnostic accuracy of ST-segment monitoring. In a GUSTO substudy, the significantly higher fibrinolytic potency of the accelerated tissue plasminogen activator regimen did not translate into earlier resolution of ST-segment elevation compared with other fibrinolytic regimens, thus casting doubt on the usefulness of this parameter [15]. No other reliable marker of reperfusion has been thoroughly validated, although early (60 minutes after reperfusion) release of cardiac troponin T subunits has been reported to indicate reperfusion [16]. Until the role of newer techniques (such as myocardial contrast echocardiography, magnetic resonance imaging, and nuclear scintigraphy) is well defined in clinical practice, the clinical non-angiographic assessment of the success of thrombolytic therapy remains one of the most difficult decisions a cardiologist has to make in the treatment of myocardial infarction, and at present is entirely based on symptoms, hemodynamics and ST-segment elevation.

Another critical issue is the time window during which to perform rescue PCI. Both the beginning and end of this window pose clinical dilemmas. On the one hand, patency rates and TIMI-3 flow rates after thrombolytic therapy increase over 24 hours [2]; on the other hand, there is ample evidence that patients fare better the earlier normal flow is restored. Unless unsuccessful thrombolysis is recognized and corrected (within 3–6 hours from symptom onset) meaningful salvage of myocardium is unlikely [17]. At the other end of the time window, although a limit of 6 to 8 hours after the onset of ischemic symptoms has been traditionally observed for reperfusion therapy, late recanalization of the vessel may benefit the patient independently from the acute salvage of ischemic myocardium. This extension of the "open artery theory" has been supported by clinical studies showing benefit of reperfusion therapy well into the 8- to 24-hour time frame and possibly later [18]. However, other

Table 7.1 Criteria for failed thrombolysis

- Persistent ST-segment elevation 75–90 minutes after thrombolytic therapy
- Persistent or recurrent angina 75–90 minutes after thrombolytic therapy
- Persistence or development of hypotension, tachycardia, decreased urine output after thrombolysis (other causes such as mechanical complications may also contribute to hemodynamic instability)
- Myocardial perfusion defect by contrast echocardiography

more objective studies, including the recently presented Open Artery Trial (OAT) [19] and the Total Occlusion Study of Canada (TOSCA-2) [20] trials, have failed to show the benefit of late infarct artery recanalization.

The evidence behind rescue PCI

Observational studies and retrospective subgroup analyses

Observational studies and retrospective subgroup analysis of large clinical trial databases have failed to show a definitive benefit of rescue PCI regarding mortality or ejection fraction [21–27]. A common observation in most of these observational studies is that failed rescue PCI (unsuccessful attempt at rescue PCI with failure to restore normal flow) is associated with much higher mortality than that noted in patients with a patent vessel after thrombolysis, with successful rescue PCI, or with an occluded vessel and no attempted rescue PCI. This, however, is at least partially explained by the fact that patients who failed rescue PCI were usually already *in extremis* prior to the procedure with a very high incidence of pre-procedure cardiogenic shock [24,26].

Randomized Clinical Trials

Patients who fail to reperfuse with thrombolytic therapy are difficult to randomize into clinical trials, as it has become the standard of care for such

Table 7.2 List of trials

Trial (year)	Number of patients	Major findings
Belenkie, et al. (1992) [28]	28	No difference in-hospital mortality (a trend favored rescue PCI)
RESCUE (1994) [29]	151	Rescue PCI reduced death or severe heart failure (6% vs. 17%, $p = 0.05$) and improved exercise EF (but not resting EF)
Vermeer, et al. (1999) [30]	224	No significant difference in death or re-infraction at 42 days and one year between rescue PCI and conservative management
MERLIN (2004) [13]	307	No significant difference in all-cause mortality at 30 days but improved event free survival secondary to reduced subsequent revascularization (6.5% vs. 20.1% with conservative management, $p<0.01$).
REACT (2005) [12]	427	No difference in all-cause mortality at 6 months. The need for revascularization at 6-months was reduced with rescue PCI (13.8% vs. 22.4%, $p = 0.05$) improving event free survival

PCI = Percutaneous coronary intervention; EF = Ejection fraction
MERLIN = Middlesbrough Early Revascularization to Limit Infarction Trial
REACT = Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolysis

individuals to undergo immediate rescue PCI if possible. To date, there have been five randomized trials of rescue PCI versus conservative treatment for patients failing pharmacological reperfusion (Table 7.2) [12,13,28–30]. The first trial included only 28 patients; 16 were randomly assigned to rescue PTCA, which was successful in 13 patients and unsuccessful in three patients, of which one patient died. Twelve patients were randomly assigned to conservative treatment, of which four patients died. The difference between the two strategies was not statistically significant [28]. The second randomized trial was a larger, multicenter trial that enrolled 151 patients with anterior myocardial infarction, thrombolysis, and an angiographically occluded vessel within 8 hours of chest pain. Patients in cardiogenic shock or with left main stenosis were excluded. A procedural success rate of 92% in the PCI group was associated with a 30-day mortality rate of 5%, whereas the conservatively managed group had a mortality rate of 10% (p = NS). There was a trend towards less severe heart failure in the PCI group. Exercise ejection fraction at 30 days, but not resting ejection fraction, was significantly higher in the PCI group (45% vs. 40%, p = 0.05) [29]. These two trials were followed by two small trials that were performed as a part of a three-way randomization – transfer to a primary PCI center, rescue PCI for failed thrombolysis, or conservative management following failed fibrinolytics [30,31]. In a multicenter randomized trial of 224 patients with acute extensive myocardial infarction (defined as total ST-segment elevation and depression of at least 15 mm), Vermeer et al. reported no significant difference in the rates of death or re-infarction within 42 days (14% in the rescue PCI versus 16% in the conservative arm) [30]. The PRAGUE trial reported a trend favoring rescue PCI with a 20% event rate (death, re-infarction, heart failure, or urgent revascularization) as compared to a 45% event rate in the conservatively treated group (P = 0.09) [31].

More recently, two larger trials addressed the role of rescue PCI for failed fibrinolysis. In the Middlesbrough Early Revascularization to Limit INfarction (MERLIN) trial, 307 patients with failed thrombolysis (defined as the failure of ST-segment elevation in the worst lead to resolve by at least 50% at 60 minutes) were randomized to emergency coronary angiography with or without rescue PCI versus conservative management. While all-cause mortality rates at 30 days were similar in both groups, the composite end point of death, re-infarction, revascularization, stroke, or heart failure occurred less frequently in the rescue PCI group (37.7% versus 50%, p = 0.02). This noted benefit was mostly driven by a reduction in the need for revascularization in the rescue PCI arm (6.5% versus 20.1%, $p<0.01$) [13]. In the conservative arm, re-administration of fibrinolytics was discouraged as was early crossover to rescue PCI (except when cardiogenic shock developed). Stents were used in about 50% of patients in the rescue PCI arm, while GP IIb/IIIa inhibitors were used in only 3.3%. The MERLIN trial was followed by the REACT trial, a multicenter trial of 427 patients in the United Kingdom, that compared rescue PCI following failed thrombolytic therapy (less than 50% resolution in ST-segment elevation at 90 minutes) with re-administration of fibrinolytic therapy or conservative

management [12]. Stents were used in 68.5% of patients and GP IIb/IIIa inhibitors (abciximab) were used in 43.3% of patients in the rescue PCI arm. All-cause mortality was the same in all treatment arms, however, the event free survival from death, re-infarction, stroke, severe heart failure at six months was 84.6% compared with 70.1% in the conservative arm and 68.7% in the repeated thrombolysis arm (overall $p = 0.004$). The noted difference in event rates was derived mostly by the reduction in re-infarction among patients assigned to the rescue PCI arm (2.1%) compared to those managed conservatively (8.5%) or with repeat thrombolysis (10.6%). Freedom from revascularization at six months tended to favor patients assigned to rescue PCI (86.2%) when compared with the other two arms of the study (77.6% in those managed conservatively and 74.4% in those managed with repeat thrombolysis, overall $p = 0.05$). Among patients assigned to rescue PCI, there was no significant difference in the event rates between patients that were transferred for intervention (16.4%) and those who were recruited in hospitals with on-site PCI facilities (14.6%).

Collet et al. conducted a meta-analysis to summarize the evidence regarding the role of rescue PCI following failed thrombolysis versus conservative management from the abovementioned five clinical trials [32]. The authors reported that rescue PCI, when compared to conservative management, reduced mortality (6.9% vs. 10.7%, OR 0.63; $p = 0.055$), and death or re-infarction (10.8% vs. 16.8%, OR 0.60; $p = 0.012$) (Fig. 7.1). In another meta-analysis, Wijeysundera et al. included eight trials enrolling a total of 1177 patients with follow-up duration ranging from hospital discharge to six months. Results showed that rescue PCI was associated with no significant reduction in all-cause mortality but was associated with significant risk reductions in heart failure and reinfarction when compared with conservative treatment. There was no increase in major bleeding, but there was a significant increase in minor bleeding (mainly access site bleeds) and stroke [33] (Fig. 7.2). Overall the data suggested rescue PCI to be associated with improved clinical outcomes for STEMI patients after failed fibrinolytic therapy, but these benefits must be interpreted in the context of potential risks. On the other hand, repeat fibrinolytic therapy is not associated with significant clinical improvement and may be associated with increased harm and should be avoided [33].

Finally, post-hoc analyses of data from other clinical trials have provided insight into the potential value of rescue angioplasty in the setting of partial early reperfusion (TIMI-2 flow). In the TAMI 1 study, performed during 1985–86, PCI was successful in 79% of these patients. There was no apparent benefit with regard to prevention of infarct artery occlusion, heart failure, or mortality, although there was a suggestion, particularly when PCI was performed within five hours of chest pain onset that left ventricular ejection fraction (LVEF) was improved [34]. In the TIMI 9B study, 328 patients with TIMI-2 flow after treatment with either tPA or streptokinase were treated at the discretion of the investigator and clinical outcomes were measured at 60 days. One hundred and ten patients were treated medically and 218 patients were

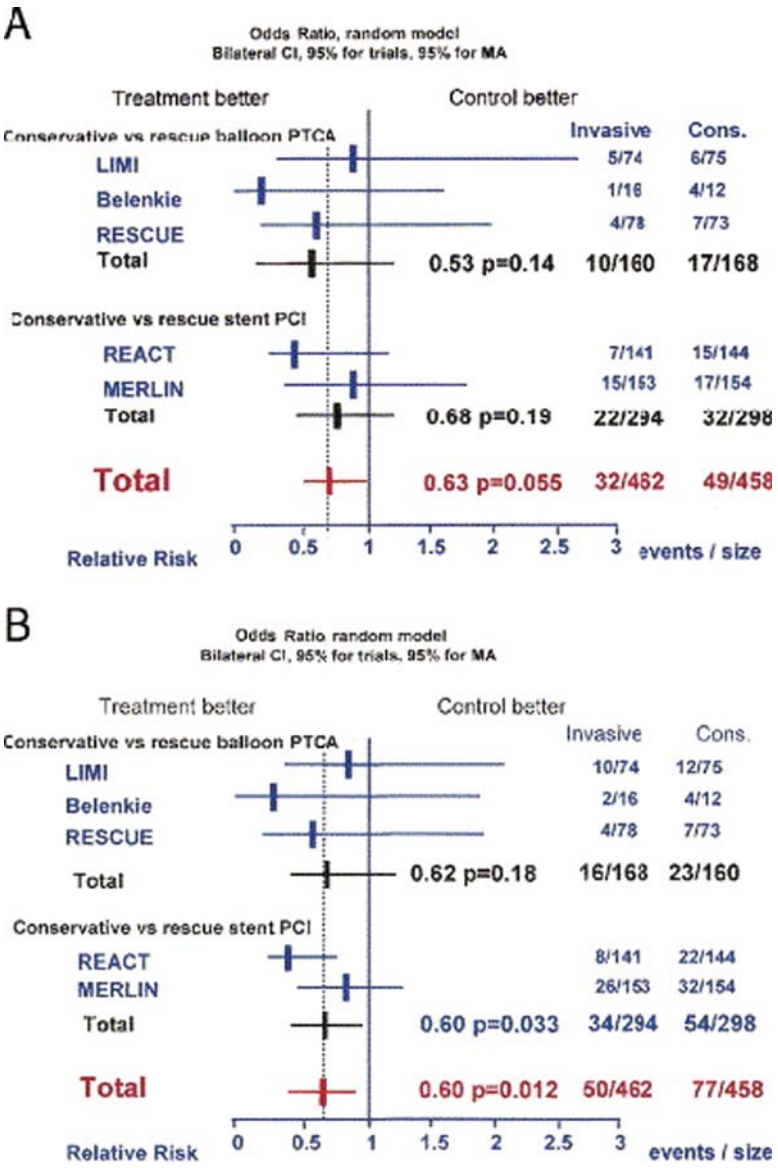

Fig. 7.1 Odds ratios for death with rescue angioplasty versus conservative approach within the first 30 days after randomization. The incidence of death rate was lower in the rescue group than in the conservative group. Overall odds ratio 0.63; 95% confidence interval (CI), 0.39 to 1.01; p = 0.055. The analysis for heterogeneity was nonsignificant (p = 0.53). **(B)** Odds ratios for death or reinfarction with rescue angioplasty versus conservative approach within the first 30 days of randomization. The incidence of death or reinfarction was lower in the rescue group than in the conservative group. Overall odds ratio 0.60; 95% CI, 0.41 to 0.89; p = 0.012. The analysis for heterogeneity was nonsignificant (p = 0.44). LIMI = LImburg Myocardial Infarction trial; MA = meta-analysis; MERLIN = Middlesbrough Early Revascularization to Limit INfarction; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; REACT = Rescue Angioplasty Versus Conservative Therapy or Repeat Thrombolysis Trial; RESCUE = Randomized Evaluation of Salvage Angioplasty with Combined Utilization of Endpoints. Adapted from Collet et al. [32]

revascularized. Baseline clinical and hemodynamic characteristics of the two groups were similar. Of the 218 patients who underwent revascularization, 19% had bypass surgery and 81% underwent PCI. Outcomes were better in the revascularization group (re-hospitalization 14% vs. 28%, p = 0.003; angina at

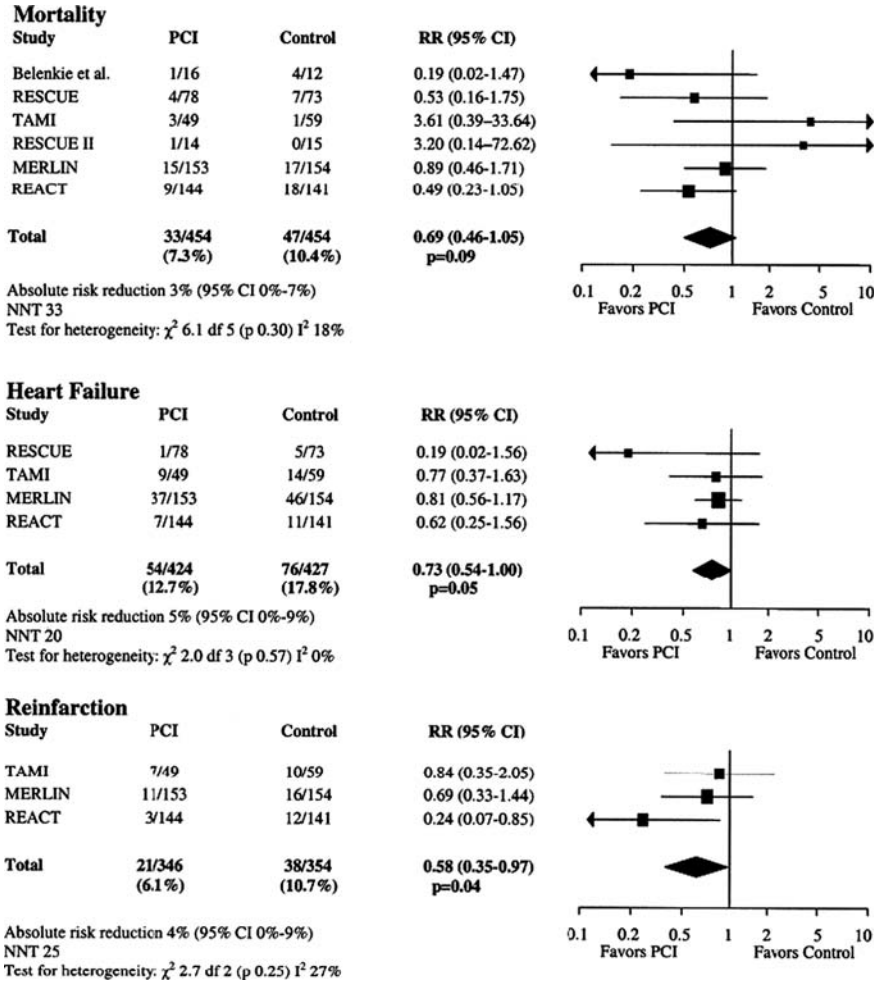

Fig. 7.2 **a** Efficacy End Points for Rescue PCI Versus Conservative Therapy, **b** Safety End Points for Rescue PCI Versus Conservative Therapy. Adapted with permission from [33] CI = confidence interval; MERLIN = Middlesbrough Early Revascularization to Limit Infarction trial; NNT = number needed to treat; PCI = percutaneous coronary intervention; REACT = Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolysis trial; RESCUE = Randomized Comparison of Rescue Angioplasty with Conservative Management of Patients with Early Failure of Thrombolysis for Acute Anterior Myocardial Infarction trial; RR = relative risk; TAMI = Thrombolysis and Angioplasty in Myocardial Infarction study; NNH = number needed to harm

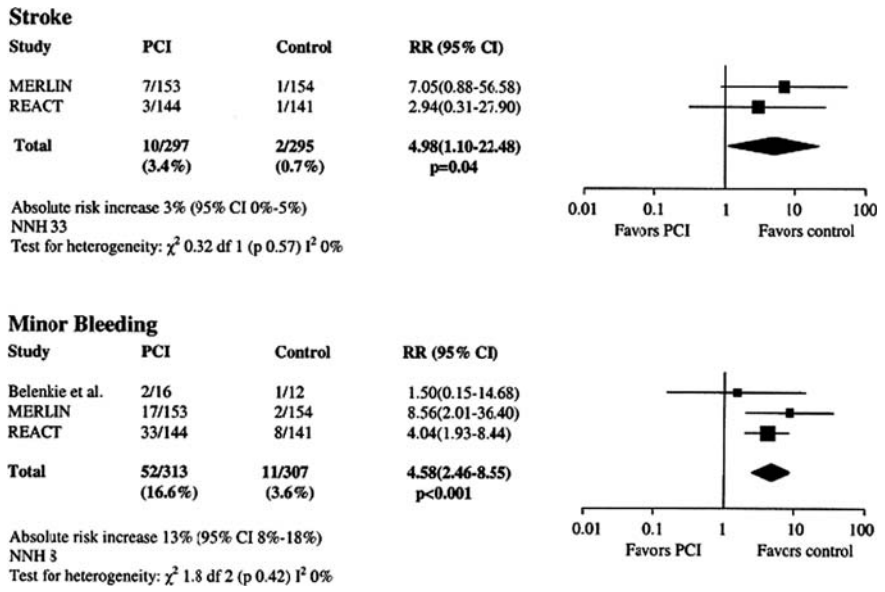

Fig. 7.2 (continued)

latest follow-up 18% vs. 29%, p = 0.017, re-infarction 4% vs. 9%, p = 0.05). There was also a trend favoring revascularization considering 60-day mortality (0.5% vs. 2.8%, p = 0.12) [22].

Role of Delayed PCI in patients with ST-segment elevation MI

While prompt restoration of antegrade flow in the IRA in patients with STEMI is associated with reduced mortality and improved LV systolic function, the role of delayed PCI to restore flow in the IRA days, weeks, or even months following the index MI has been the subject of ongoing debate. Retrospective analyses have suggested that such intervention may ameliorate LV remodeling, improve LV systolic function, and reduce sudden cardiac death (presumably by reducing late potentials in the viable myocardium surrounding the infarcted segment of the LV) [35–38]. However, recently concluded randomized controlled trials have shown no such benefits. In the TOSCA–2 trial, 381 patients with total occlusion of the IRA were randomized to undergo PCI with stenting of the IRA 3–28 days after MI (median 10 days) versus optimal medical management. The primary end points of the study were patency of the IRA and the change in the LV ejection fraction at one year. PCI was successfully achieved in 92% of the patients randomized to the PCI arm. At one year, the IRA was patent in 83% of PCI arm versus 25% in the medical management arm ($p<0.001$). The LV ejection fraction increased in both arms with no difference between groups [20]. This study was followed by the Occluded Artery Trial (OAT) in which

2166 stable patients with a totally occluded IRA who had one of two high-risk criteria (ejection fraction<50% or proximal occlusion) were randomized to PCI 3–28 days after myocardial infarction (median eight days) versus medical management. PCI was successful in 87%, with the majority of patients receiving at least one stent (92% received Bare Metal Stents (BMS). For medical therapy, 89% received beta blockers, 80% received an Angiotensin Converting Enzyme (ACE) inhibitor or an angiotensin receptor blocker, 82% received a lipid lowering agent and 97% received aspirin or thienopyridine. The four-year cumulative rate of the primary end point (a composite of death, myocardial re-infarction, or New York Heart Association (NYHA) class IV) occurred in 17.2% in the PCI arm and 15.6% in the medical management arm (the unadjusted hazard ratio for the PCI group was 1.6; 95% confidence interval of 0.92–1.45; p = 20). There was no statistical difference in the rates of individual end points between the two groups [19]. These finding were consistent among all pre-specified subgroups (age, sex, race, IRA, time from MI to randomization, diabetes, Killip class ejection fraction). These two important studies demonstrated no significant benefit from delayed PCI to the occluded IRA in the otherwise stable patient. It is important to note that the patients enrolled in these studies were stable (exclusion criteria included NYHA class III-IV heart failure, shock, renal insufficiency, left main of severe three vessel disease, angina at rest, or severe ischemia on stress test) and that patients managed in the conservative arm were given optimal medical therapy.

Conclusions

A substantial proportion of patients with acute ST-segment elevation myocardial infarction do not achieve tissue-level reperfusion despite contemporary thrombolytic therapy. Patients with failed pharmacologic revascularization (as defined by persistent ischemic symptoms or significant residual ST-segment elevation at 60–90 minutes from the administration of thrombolytic therapy) should undergo coronary angiography without delay. In aggregate, the limited existing data demonstrate that rescue PCI (preferably within 12 hours after symptom onset) as opposed to conservative watchful waiting reduces overall composite clinical events including re-infarction, angina and the need for future revascularization, and may potentially reduce overall mortality. The identification of patients who fail thrombolytic therapy remains a major obstacle in attaining mechanical (rescue) reperfusion in a timely fashion. Advances in the assessment of patency of the infarct-related artery and adequacy of myocardial perfusion will likely help further clarify the role of rescue PCI in this important subset of patients. On the other hand, there does not appear to be a current role for routine delayed PCI in patients with occluded infarct-related arteries.

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Chapter 8
Facilitated Percutaneous Coronary Intervention

Pantelis Diamantouros and Ing Haan Lim

Introduction

Primary percutaneous coronary intervention (PCI) is the preferred method of reperfusion for patients presenting with acute myocardial infarction (AMI). The effectiveness and safety of primary PCI has been proven in many large randomized-controlled trials (RCTs) and in a pooled analysis of the data from these trials [1]. A further analysis of these trials, however, demonstrated that the benefit conferred by primary PCI over fibrinolysis was equivocal after 60 minutes for mortality and after 90 minutes for the combined end-point of death, MI and stroke [2]. This analysis forms the basis of the recommended door-to-balloon (DTB) times in the latest ACC/AHA recommendations for AMI [3] and is the benchmark by which all cath labs are to be held. However, a DTB time of less than 90 minutes is a difficult standard to consistently meet [4] and failure can lead to worse outcomes in AMI patients [5–8]. As a result, the concept of facilitated PCI (facilitated PCI) is a potentially attractive and perhaps more forgiving alternative for reperfusion therapy for AMI patients, especially for those patients that require transport to a primary PCI facility.

Facilitated PCI is defined as a pharmacologic reperfusion treatment administered before primary PCI to bridge the delay between first medical contact and mechanical reperfusion [9]. It is a hybrid reperfusion strategy that combines various antithrombotic, antiplatelet, and/or fibrinolytic agents with PCI in an attempt to quickly achieve and maintain TIMI-3 flow in an infarct-related artery (IRA). In this strategy, the role of the medical agents is to achieve reperfusion as frequently and as quickly as possible and perhaps to reduce clot burden in the IRA. This could potentially offset delays to PCI and facilitate PCI by reducing the amount of thrombus encountered in the IRA. Definitive mechanical revascularization by PCI would then help ensure IRA patency. The intent is that the earlier establishment of TIMI grade 3 flow will result in smaller

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infarcts, higher success rates and better clinical outcomes. This strategy is distinct and should not be confused with rescue PCI where fibrinolysis is the sole, initial reperfusion therapy and patients are provisionally sent for urgent PCI only if there are signs that they have not reperfused.

The facilitation of primary PCI has been studied using various pharmacologic agents in the search for the optimal reperfusion strategy. A number of these strategies and the data concerning each will be the focus of this chapter.

Fibrinolysis-Facilitated PCI

Fibrinolysis was the principal reperfusion strategy for AMI prior to the advent of primary PCI. The rationale for administering a fibrinolytic agent prior to primary PCI would be to blunt the negative impact of delays in performing primary PCI and to overcome the modest reperfusion success rates seen with fibrinolytics alone.

Fibrinolysis Alone

A trial by O'Neill et al. [10] was conducted in the pre-stent era using streptokinase (SK) as the facilitative agent for primary balloon PTCA. The conclusions from this small, early trial were that SK-facilitated PTCA did not enhance early preservation of left ventricular (LV) function, improve arterial patency rates, or lower restenosis rates in AMI.

In the stent era, Plasminogen-Activator Angioplasty Compatibility Trial (PACT) [11], PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis (PRAGUE) [12], Grupo de Análisis de la Cardiopatía Isquémica Aguda-2 (Primary versus facilitated PCI [tenecteplase plus stenting] in patients with ST-elevated myocardial infarction) (GRACIA-2) [13], and Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention-4 (ASSENT-4) [14] are the trials that have been conducted to study the strategy of fibrinolysis-facilitated PCI (Table 8.1). It should be noted that the PRAGUE study was not randomized and that full-dose fibrinolysis was used for facilitation in all the trials except for the PACT trial. In PACT, patients received only a 50 mg bolus of recombinant tissue-type plasminogen activator (rt-PA). In the GRACIA-2 trial, there was a significant delay to PCI (9.1 hours vs. 4.3 hours) for the facilitated PCI compared to the primary PCI group.

ASSENT-4 is the largest and most recent of these trials. The investigators had planned to enroll 4,000 patients. It compared tenecteplase (TNK)-facilitated PCI to primary PCI and was prematurely interrupted due to a higher in-hospital morality in the TNK-facilitated group (6% vs. 3%, $p = 0.0105$). During the hospital stay, the TNK-facilitated group suffered more strokes (1.8% vs. 0%, $p<0.0001$) with 8 of these 15 strokes due to an intracranial hemorrhage (ICH) and 5 due to an ischemic event. As well, reinfarction (6% vs. 4%,

Table 8.1 Fibrinolysis-facilitated PCI trials

	Year	Facilitated PCI (n)	Primary PCI (n)	Fibrinolytic	Stent	Primary Endpoint
O'Neill, et al.	1992	58	63	SK	No	TIMI flow/LV function 24 hrs & 6 weeks
PACT	1999	302	304	rt-PA (50 mg)	Yes	IRA patency (TIMI 3) pre-PCI
PRAGUE	2000	100	101	SK	Yes	Death/reinfarct/ stroke 30 days
GRACIA-2	2004	103	102	TNK	Yes	Death/MI/Revasc 6 weeks & 6 months
ASSENT-4	2006	829	838	TNK	Yes	Death/CHF/shock 90 days

p = 0.0279) and target vessel revascularization (7% vs. 3%, p = 0.0041) at 90 days were significantly higher in the TNK-facilitated group. This significant excess of cerebral and cardiac events in the TNK-facilitated groups suggests a prothrombotic effect of fibrinolysis when given immediately before stenting.

Meta-Analyses

The data from the 4 stent-era trials has been pooled and analyzed by Collet et al. [15]. A total of 2,679 patients from the 4 trials were included in the analysis (Figs. 8.1 and 8.2). Fibrinolysis-facilitated PCI was associated with a non-significant increase in the rate of death at 90 days (OR = 1.30; 95% CI 0.92-1.83; p = 0.13) and a significant increase in reinfarction (OR = 1.68; 95% CI 1.12-2.51, p = 0.013).

In addition, a meta-analysis performed by Keeley et al. [16] included all five trials in Table 8.1 in addition to a trial by Vermeer et al. [17]. Despite the addition to the analysis of the Vermeer and O'Neill trials, the conclusions were the same as those of the Collet meta-analysis in this group of 1466 patients treated with fibrinolysis-facilitated PCI and 1487 patients treated with primary PCI (see Fig. 8.3). Specifically, PCI facilitated by thrombolytic therapy resulted in a significant increase in short-term death (6% vs. 4%, OR = 1.43; 95% CI 1.01-2.02, p = 0.042), non-fatal re-infarction (4% vs. 2%, OR = 1.81; 95% CI 1.19-2.77, p = 0.006) and urgent target vessel revascularization (TVR) (5% vs. 1%, OR = 4.81; 95% CI 2.47-9.37, P<0.0001). Major bleeding was not found to be significantly increased in the fibrinolysis facilitated PCI group compared to the primary PCI group, respectively, in this pooled analysis (7% vs. 5%, p = 0.17).

The data from these pooled analyses coupled with the data from the largest RCT, ASSENT-4, thus do not support the use of fibrinolytic therapy to facilitate primary PCI in acute MI given the increase in death, subsequent MI, and urgent TVR associated with this strategy.

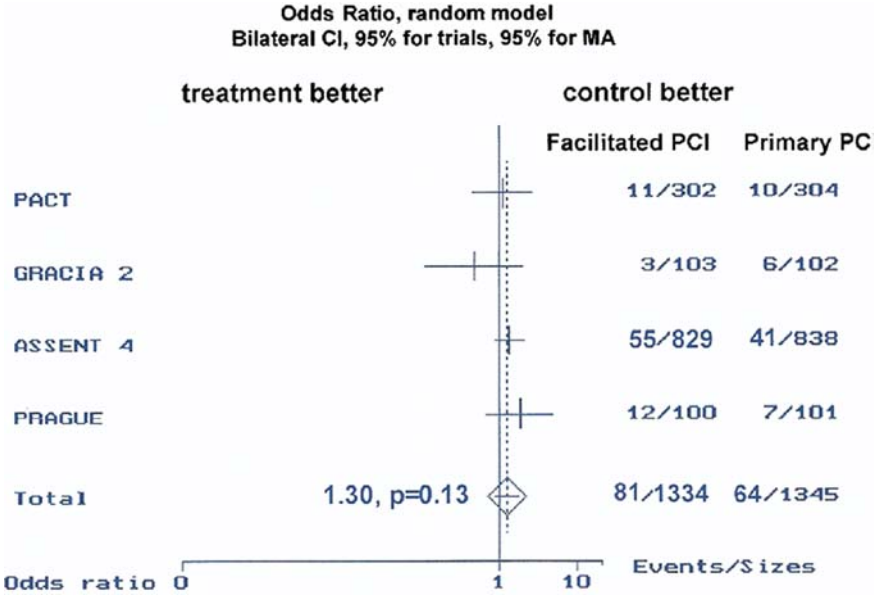

Fig. 8.1 Odds ratio of death within 90 days with facilitated primary PCI (treatment) versus primary PCI alone [Ref. 15, Fig 4A]

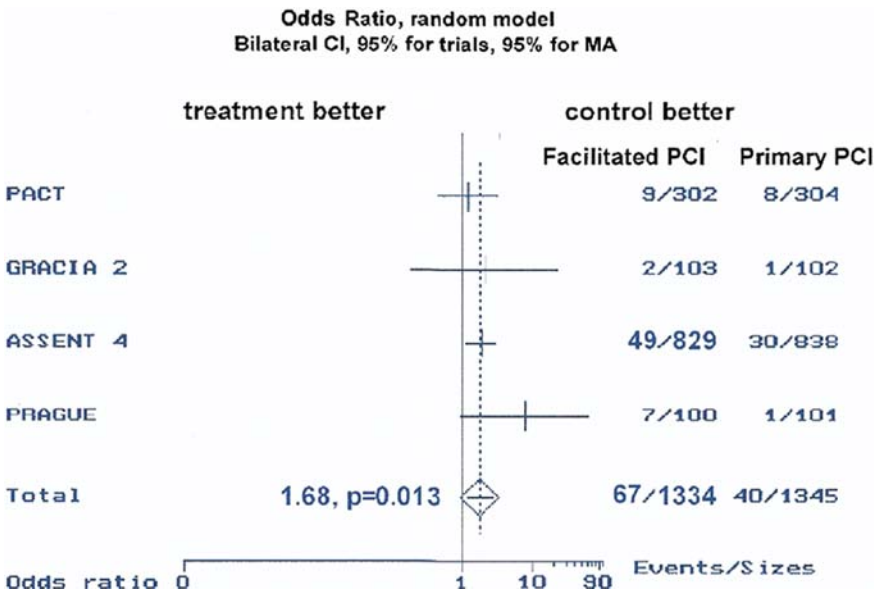

Fig. 8.2 Odds ratio of reinfarction within 90 days with facilitated primary PCI (treatment) versus primary PCI alone [Ref. 15, Fig. 4B]

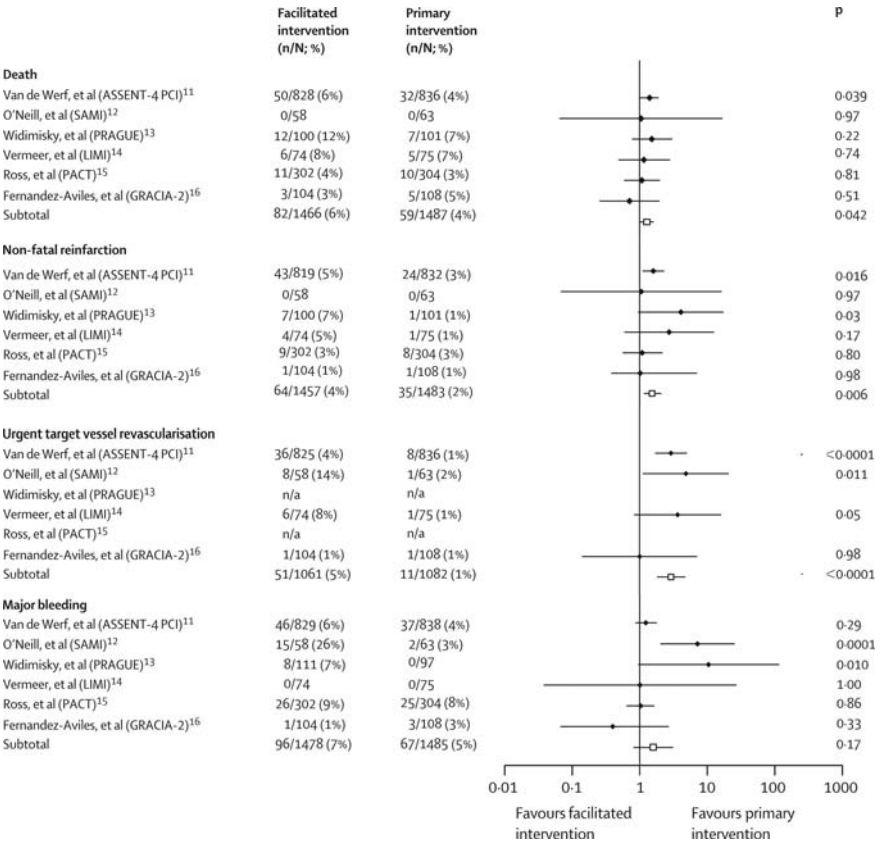

Fig. 8.3 Short-term death, non-fatal reinfarction, urgent target vessel revascularization, and major bleeding in patients treated with fibrinolysis-facilitated primary PCI versus primary PCI alone (Ref. [16], adapted from Figs. 1–4)

Reduced-Dose Fibrinolysis with Glycoprotein IIb/IIIa Inhibitors

In the ASSENT-4 trial, the excess reinfarction observed in the TNK-facilitated group related to early stent thrombosis might have been mitigated by glycoprotein (GP) IIb/IIIa inhibition but was expected to also substantially increase bleeding rates. Therefore, the use of glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors was appropriately lower (13% vs. 50%, $p<0.0001$) in the TNK-facilitated group [14] due to the unacceptable risk of bleeding complications with a combination of full-dose TNK and GP IIb/IIIa inhibition [18, 19]. The Addressing the Value of facilitated Angioplasty after Combination Therapy or Eptifibatide monotherapy in acute Myocardial Infarction (ADVANCE MI) [20] and Bavarian Reperfusion Alternatives Evaluation Study Investigators (BRAVE) [21] trials attempted to address the issues of early stent thrombosis and high risk of bleeding with combination therapy (see Table 8.2).

Table 8.2 Reduced-Dose Fibrinolysis with GP IIb/IIIa inhibitor trials

	Year	Fibrinolytic	GP IIb/IIIa	IIb/IIIa + Lytic	IIb/IIIa + Placebo	Stents	Primary Endpoint
BRAVE	2004	Reteplase two 5u boluses	Abciximab	125	128	Yes	Infarct size by PET study 5–10 days post-ranomization
ADVANCE MI	2005	TNK 0.25 mg/kg	Eptifibatide	69	77	Yes	Mortality/ worsening or severe CHF through 30 days

The ADVANCE MI trial used eptifibatide in combination with half dose TNK (0.25 mg/kg) and compared this combination to eptifibatide plus placebo for the facilitation of primary PCI. The BRAVE trial compared half dose reteplase (two 5 unit boluses, 30 minutes apart) plus standard dose abciximab to abciximab plus placebo in the same types of patients. ADVANCE MI was terminated prematurely due to increases in adverse clinical events (10% vs. 3%, $p = 0.09$) and higher rates of both major TIMI (25% vs. 10%, $p = 0.02$) and moderate-severe GUSTO (25% vs. 10%, $p = 0.02$) classified bleeding at 30 days in the patients treated with eptifibatide + reduced dose TNK group compared with those treated with eptifibatide + placebo [20]. Also of note, there was a significant increase in mortality in the facilitated PCI arm (7% vs. 0%, $p = 0.03$) compared to the primary PCI arm.

The patients in the BRAVE trial fared slightly better in that there was no increase in rates of adverse clinical events (6.4% vs. 4.7%; RR, 1.4; 95% CI, 0.5-3.9; log-rank $p = 0.56$) or major bleeding (5.6% vs. 1.6%, $p = 0.16$) observed at 60 days in the reduced-dose reteplase + abciximab group compared to the abciximab + placebo group [21]. However, the primary endpoint of infarct size as assessed by photon emission computed tomography (PET) was not different between the two treatment groups.

Meta-Analysis

Keeley et al. [16] pooled the results of BRAVE and ADVANCE-MI (see Fig. 8.4). This analysis included a total of 194 patients in the facilitated PCI group and 205 patients in the primary PCI group. The results showed that facilitated PCI using the combination of GP IIb/IIIa inhibitors and reduced-dose fibrinolysis did not differ significantly from primary PCI with respect to short-term mortality (4% vs. 1%, OR = 3.07; 95% CI 0.18-52.0, $p = 0.44$) or non-fatal re-infarction (1% vs. 1%, OR = 1.03; 95% CI 0.15-7.13, $p = 0.98$). However, there was a significant increase in major bleeding when compared to primary PCI (12% vs. 5%, $p = 0.006$).

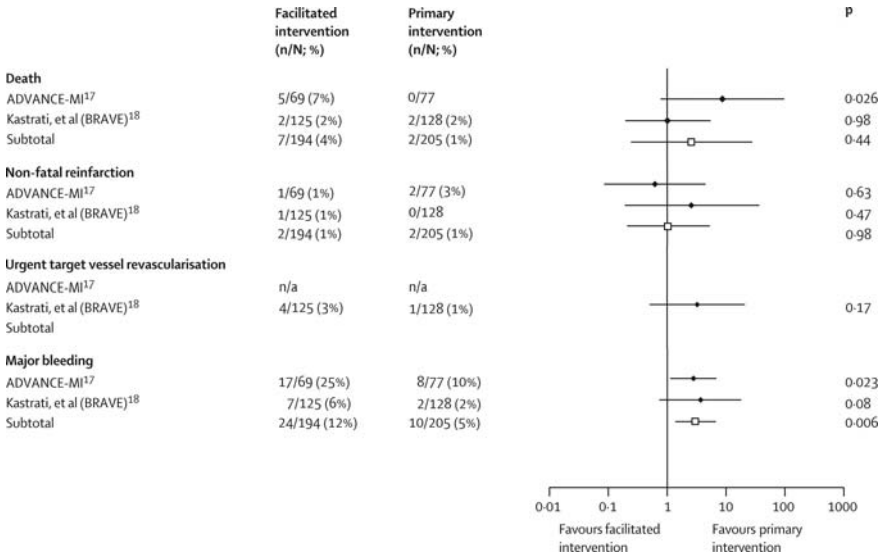

Fig. 8.4 Short-term death, non-fatal reinfarction, urgent target vessel revascularization, and major bleeding in patients treated with the combination of fibrinolysis and platelet glycoprotein IIb/IIIa inhibitors to facilitate primary PCI versus primary PCI alone (Ref. [16], adapted from Figs. 1–4)

Therefore, reduced-dose fibrinolytics with platelet GP IIb/IIIa blockade also does not appear to be an appropriate regimen for facilitated primary PCI given the lack of efficacy and increased rates of complications.

Non-Fibrinolysis-Facilitated PCI

Studies involving fibrinolysis-facilitated PCI and reduced-dose fibrinolytics plus GP IIb/IIIa inhibitors have not yielded an adequate facilitator for primary PCI. Heparin and GP IIb/IIIa inhibitors are commonly used medications during PCI and their use in the setting of AMI is considered to be the standard of care [3]. Therefore, unlike in the fibrinolysis-facilitated trials, the following studies compare a strategy of low vs. high or early vs. late dosing of these medications.

High Dose Heparin

The Heparin in Early Patency (HEAP) trial [22] studied the benefit of high-dose heparin on early patency in AMI. It randomized 299 patients with STEMI to receive high dose (300 IU/kg) heparin and 285 patients with STEMI to receive

low dose (0 or 5,000 IU) heparin prior to primary PCI. There was no benefit of high dose heparin on IRA patency. TIMI flow grade 2 or 3 was observed before primary angioplasty in 65 patients (22%) in the high dose group and 60 patients (21%) in the low dose heparin group ($p > 0.1$), whereas TIMI flow grade 3 was observed in 38 (13%) and 24 patients (9%), respectively ($p = 0.11$). There were no differences observed in the clinical end points between the two groups. In the high-dose heparin group, 10% of patients had bleeding requiring blood transfusion versus 6% in the low dose/no heparin group ($p = 0.07$).

These results demonstrate that there is no benefit of high dose bolus heparin on early patency compared with no or low dose heparin. There is also a non-significant trend towards more major bleeding in the high-dose heparin group. The results of this trial are concordant with other data that has established the safety and efficacy of low-dose heparin (<50 U/kg bolus, target ACT 200-250) for PCI [23–25]. Moreover, increased bleeding is associated with poorer outcomes in acute coronary syndromes [26] and following elective PCI [27]. Therefore, given the lack of efficacy and potential for harm, high-dose heparin is not recommended to facilitate primary PCI.

Glycoprotein IIb/IIIa Receptor Antagonists

Platelet glycoprotein IIb/IIIa blockade has been studied extensively in the setting of AMI. There are 2 potential benefits to GP IIb/IIIa blockade in this setting: (1) dethrombosis, the physiologic equivalent of thrombolysis, and (2) improved myocardial perfusion (at the cellular level) with reduction in the no-reflow phenomenon. Although the exact mechanism is unclear, it is postulated that the no-reflow phenomenon is caused by abnormalities at the level of the micro-vasculature [28]. IIb/IIIa blockade prevents platelet and neutrophil adhesion and helps mitigate against the no re-flow phenomenon by reducing microthrombus formation and relief of microvasculature obstruction [29, 30]. Eleven trials (see Table 8.3) have studied the use of GP IIb/IIIa inhibitors as facilitative agents [31–41].

Tirofiban

Although it is the least prescribed GP IIb/IIIa inhibitor for PCI, tirofiban is the GP IIb/IIIa inhibitor used in the majority of trials of GP IIb/IIIa inhibition to facilitate primary PCI. The Ongoing Tirofiban in Myocardial Infarction Evaluation (On-TIME) [31] trial was the largest of these trials and randomized 507 patients with AMI to either early (pre-hospital) or late (cath lab) initiation of tirofiban therapy. At initial angiography, TIMI-3 flow was present in 19% in the early group and in 15% in the late group ($p = 0.22$). TIMI-2 or -3 flow was present in 43% in the early group and in 34% in the late group ($p = 0.04$). TIMI-3 flow and myocardial blush grade were no different between the 2 group post-

Table 8.3 GP IIb/IIIa facilitated PCI trials

	Year	GP IIb/IIIa	Facilitated PCI	Primary PCI	Stents	Primary Endpoint
Zorman, et al.	2002	Abciximab	56	56	Yes	IRA patency before PCI/ST segment resolution
Arntz, et al.	2003	Abciximab	52	48	Yes	ST segment resolution/blush grade/Initial TIMI flow
TIGER-PA	2003	Tirofiban	50	50	Yes	Initial TIMI flow/corrected TIMI frame count (TFC)/ TIMI blush grade
Cutlip, et al.	2003	Tirofiban	28	30	Yes	Initial TIMI flow/corrected TIMI frame count
On-TIME	2004	Tirofiban	245	247	Yes	TIMI-3 flow before PCI
Gyongyosi, et al.	2004	Abciximab	28	27	Yes	Initial TIMI flow/corrected TFC composite:death + TVR + re-MI + major bleed + stroke
INTAMI	2005	Eptifibatide	53	49	Yes	IRA patency before PCI
**Bellandi, et al.	2006	Abciximab	27	28	Yes	Initial TIMI flow/corrected TFC/ST reduction/ salvage index/LV function recovery
ERAMI	2006	Abciximab	36	38	Yes	Initial TIMI flow
(TITAN)-TIMI 34	2006	Eptifibatide	180	163	Yes	Corrected TFC
RELAx-AMI	2007	Abciximab	105	105	Yes	Initial TIMI flow, corrected TFC, blush grade

**Sub-study of RELAX-AMI trial.

PCI. At 30 days, the combined incidence of death, recurrent MI, stroke and major bleeding was not clinically significantly different between the early and late groups (8.6% vs. 4.4%, $p = 0.06$). However, when analyzed individually, there was a significant difference in mortality between the early and late groups (3.7% vs. 0.8%, $p = 0.03$). At one year, there was no difference between the groups (7.0% vs. 7.0%, $p = 0.99$) with respect to the combined endpoint or its component of death and re-infarction.

The other trials investigating tirofiban in the setting of facilitated PCI [32, 36] yielded similar, unimpressive results.

Abciximab

Abciximab is the most widely used GP IIb/IIIa inhibitor for primary PCI. This use is supported by the results of many large RCTs included in the meta-analysis by Kandzari et al. [42].

The experience of abciximab in facilitated PCI is limited to 5 small trials that enrolled a total of 549 patients, 277 in the facilitated PCI arms and 272 in the primary PCI arms [33–35, 37, 41]. The endpoints in all these studies were

angiographic endpoints and included initial TIMI flow, corrected TIMI france count (TFC), and myocardial blush grade. The trial by Bellandi et al. [39] of 55 AMI patients receiving early or late abciximab before primary PCI is a scintigraphic sub-study of the RELAx-AMI trial [41] which also includes those same 55 patients in their analysis.

The largest of these trials was by Zorman et al. [35] and the RELAx-AMI trial [41]. The trial by Zorman et al. compared early (immediate) vs. late (at time of PCI) administration of abciximab for AMI. Fifty-six patients were randomized into both the facilitated PCI and primary PCI arms. There was a third arm ($n=51$) in the trial where no abciximab was administered at all. Both primary endpoints were statistically significant in favor of early initiation of abciximab. TIMI-3 flow at the time of initial angiogram was significantly greater in the early vs. the late administration groups (16% vs. 7%, $p=0.05$) and initial TIMI-2 or -3 flow yielded similar results (32% vs. 12%, $p=0.04$). ST-segment resolution post-PCI also favored the early administration group significantly. Although this was a small study with primary angiographic and electrocardiographic endpoints, the results of the clinical follow-up are interesting in that early administration of abciximab significantly decreased in-hospital heart failure (7% vs. 18%, $p<0.01$), death (0% vs. 7%, $p=0.03$) and six-month morality (0% vs. 9%, $p=0.02$).

The Randomized Early Versus Late Abciximab in Acute Myocardial Infarction (RELAx-AMI) trial [41] was the largest trial comparing early vs. late abciximab administration for the facilitation of primary PCI. Maioli et al. randomized 210 consecutive patients presenting with AMI to receive early (emergency room) vs. late (cath lab). There were 105 patients randomized to each arm. The primary endpoint of TIMI-3 flow pre-PCI was significantly higher in the early group (24% vs. 10%, $p=0.01$) as was the corrected TFC (78 ± 30 frames vs. 92 ± 21 frames, $p=0.001$) and the presence of myocardial blush grade 2 or 3 (15% vs. 6%, $p=0.02$). These tissue perfusion parameters continued to be significantly improved in the early vs. late group post-PCI as well. Clinically, MACE at one month was not significantly different between the early vs. late groups (5.7% vs. 8.6% , $p=0.42$), respectively, and neither were bleeding complications (8.6% vs. 5.7%, $p=0.44$), respectively.

The other 3 trials investigating abciximab for use in facilitated PCI yielded similar, encouraging results [33, 34, 37]. However, all were small trials with mostly angiographic primary endpoints that were not powered to detect clinically significant differences.

Eptifibatide

There is much less experience with eptifibatide in the setting of primary PCI, particularly given the strong evidence to support the use of abciximab. Eptifibatide, however, is commonly used for PCI in chronic stable angina or in acute coronary syndromes.

Eptifibatide has been studied in the setting of facilitated PCI in two trials [38, 40]. The largest and most recent of these trials is the Time to Integrilin Therapy in Acute Myocardial Infarction- Thrombolysis in Myocardial Infarction (TITAN-TIMI) 34 trial [40]. In this trial, a strategy of early (emergency room) vs. late (cath lab) initiation of eptifibatide therapy was studied to determine whether earlier initiation of eptifibatide therapy in AMI resulted in superior epicardial flow and myocardial perfusion. The primary end point of the

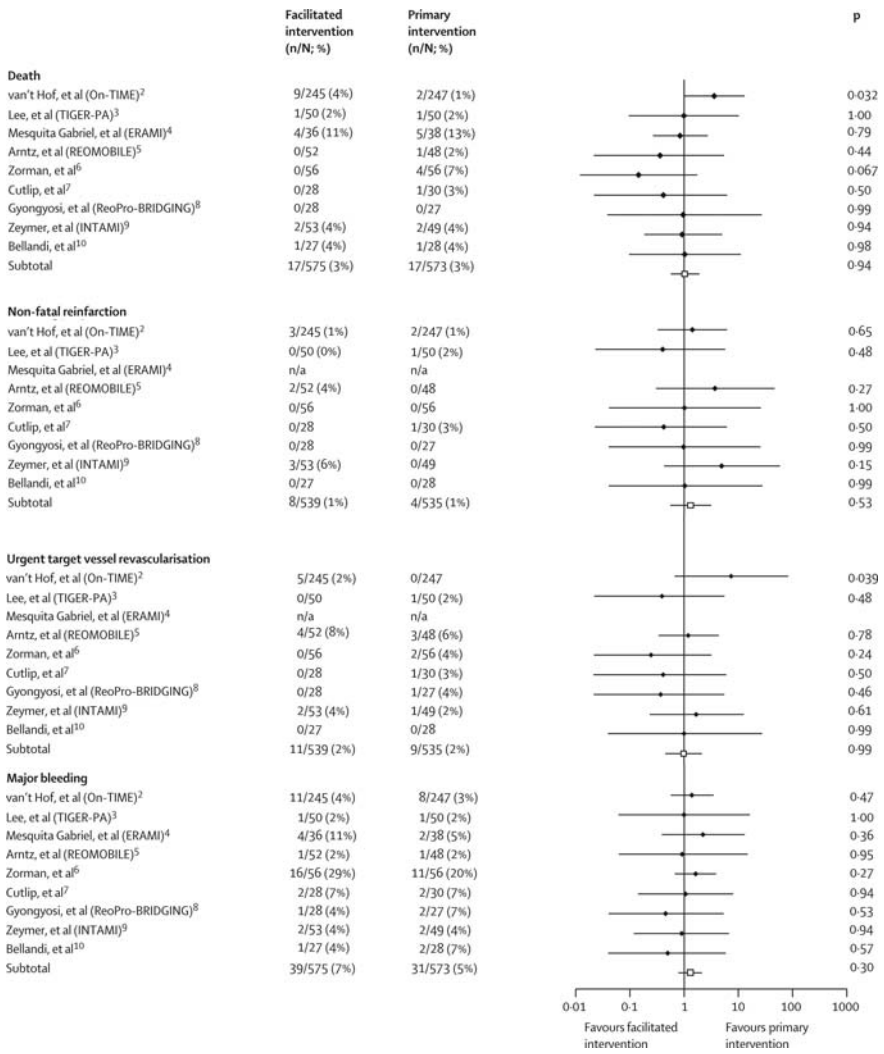

Fig. 8.5 Short-term death, non-fatal reinfarction, urgent target vessel revascularization, and major bleeding in patients treated with platelet glycoprotein IIb/IIIa inhibitors to facilitate primary PCI versus primary PCI alone. (Ref [16], adapted from Figs. 1–4)

study was corrected TIMI frame count while the secondary end point was the presence of TIMI-3 flow in the IRA. A total of 349 patients were randomized, with 180 randomized to early and 163 to late eptifibatide therapy. Pre-PCI corrected TFC was significantly lower in the early eptifibatide group (77.5±32.2 vs. 84.3±30.7, p = 0.049) compared to the late group and TIMI-3 flow was also significantly more prevalent pre-PCI in the early compared to the late group (24% vs. 14%, p = 0.026). There was no excess of TIMI major or minor bleeding between the early group compared to the late group, respectively (6.9% vs. 7.8%, p = NS). During the short (30-day) clinical follow-up, there was no difference between the 2 groups with respect to mortality (4.0% in the early group vs. 2.8% in the late group, p = 0.76) and re-infarction (1.2% early group vs. 1.4% late group, p = NS).

Meta-Analysis

Keeley et al. [16] pooled the results of the all the trials in Table 8.3 except for TITAN-TIMI 34 and RELAx-AMI (see Fig. 8.5). The 55 patients from RELAx-AMI included in the scintigraphic sub-study published by Bellandi et al. were included in this analysis. The meta-analysis included 575 patients in the facilitated PCI group and 573 patients in the primary PCI group. The analysis found no significant differences between GP IIb/IIIa facilitated PCI and primary PCI with respect to short-term mortality (3% vs. 3%, OR = 1.03; 95% CI 0.49-2.17, p = 0.94), non-fatal re-infarction (1% vs. 1%, OR = 1.40; 95% CI 0.49-3.98, p = 0.53), urgent TVR (2% vs. 2%, p = 0.99) and major bleeding (7% vs. 5%, p = 0.30). Not surprisingly, the meta-analysis confirmed the significantly better pre-PCI angiographic endpoints with the early GP IIb/IIIa strategy.

Discussion and Conclusions

Due to its lackluster performance in trials performed thus far, facilitated PCI cannot be recommended as the primary reperfusion therapy for the treatment of AMI. There is little clinical data to support its use since the majority of the trials performed used angiographic endpoints and were not powered to show clinically significant differences. The trials that do have clinical primary endpoints show a lack of efficacy of facilitated PCI and, in some instances, like the ASSENT-4 trial, were stopped early due to potential harm caused by the facilitated PCI approach.

The ASSENT-4 trial was the largest RCT peformed to answer the question of whether fibrinolysis-facilitated PCI was better than primary PCI. After enrolling less than ¼ of the planned 4,000 patients, [9] it was stopped early due to higher in-hospital mortality, strokes, reinfarction and urgent TVR in the facilitated PCI group. The meta-analysis by Collet et al. also showed that there

is a significant increased risk of non-fatal reinfarction in the group treated with fibrinolysis-facilitated PCI. These alarming findings are further supported by the meta-analysis performed by Keeley et al. which showed a significantly increased risk of non-fatal reinfarction and also a significant increase in mortality and urgent TVR in the fibrinolysis facilitated group. Therefore, given the results of this large RCT with primary clinical endpoints and the results of two separate meta-analyses all showing harm, fibrinolysis-facilitated PCI is contraindicated in the treatment of AMI.

A very compelling theory as to why fibrinolysis-facilitated PCI has not performed as expected has been put forth by Gersh and colleagues [9, 43]. Myocardial salvage and mortality reduction after reperfusion therapy is greatest in the first 2-3 hours after onset of AMI with this period being potentially prolonged by the presence of collaterals, ischemic preconditioning and reduced myocardial oxygen demand. After this initial 2-3 hour period, the potential for myocardial salvage is greatly diminished. The average AMI patient presents about two hours after the onset of symptoms and the fibrinolytic portion of facilitated PCI takes about 30 minutes to be administered and about 60 minutes to work (slightly faster if GP IIb/IIIa inhibitors are given). Therefore, 90 minutes is needed for lytic-induced perfusion. This timeframe is also the current benchmark for primary PCI. Thus, most IRAs will be reperfused at a time when opportunity for myocardial salvage has largely passed and, unless patients present within 60–90 minutes of symptom onset and primary PCI delays are more than 2–3 hours, there will be little benefit of facilitated PCI using fibrinolytic therapy (see Fig. 8.6).

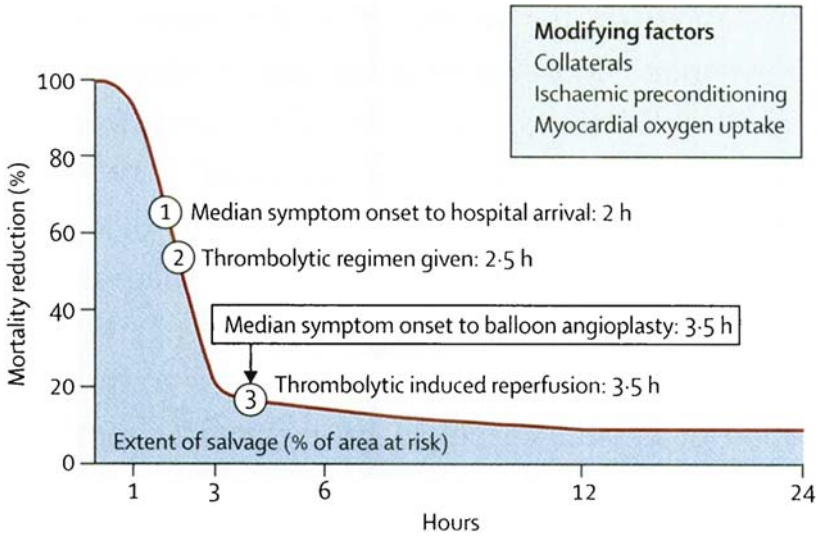

Fig. 8.6 Relationship of time of onset of acute myocardial infarction and the potential for myocardial salvage [43]

With respect to reduced dose fibrinolysis coupled with GP IIb/IIIa blockade, the ADVANCE MI trial compared facilitated PCI via eptifibatide and half-dose TNK to primary PCI. As with ASSENT-4, enrollment in ADVANCE MI was terminated prematurely due to an increased risk of adverse clinical events and bleeding in the study group. When the patients in ADVANCE MI and BRAVE were pooled and analyzed by Keeley et al., there was no difference in mortality, reinfarction or urgent TVR found between the facilitated PCI and primary PCI groups. The lower rates of reinfarction seen compared to fibrinolysis-facilitated PCI indicates that fibrinolysis-induced platelet aggregation could be important in the rates of reinfarction in the fibrinolysis-facilitated analysis. The recommendations regarding reduced-dose fibrinolysis and GP IIb/IIIa inhibition facilitated PCI are not as clear as those for fibrinolysis-facilitated PCI. With respect to harm, there was no increase seen in the meta-analysis, whereas, the RCTs showed conflicting results with the abciximab/reteplase combination being non-harmful in the BRAVE trial. With respect to benefit, there was none seen in the meta-analysis or in either of the RCTs.

By far, the most promising facilitated PCI approach involves the early administration of platelet GP IIb/IIIa antagonists alone, without concomitant fibrionlytic therapy. Trials performed thus far using early administration of abciximab for the facilitation of primary PCI have yielded consistent results showing improved patency and flow on initial angiography. That these results have not translated into improved clinical outcomes are likely a result of small trials that are underpowered to show a significant clinical difference. Unclear also is whether there might be differences between agents. Fortunately, there was no increase seen in adverse clinical outcomes with GP IIb/IIIa facilitated regimes alone. Given this lack of harm, an attractive alternative might therefore be to administer these agents even earlier in the time course of the patient presenting with an acute MI, namely the initial point of contact with emergency medical services.

Given these promising results and the results of the BRAVE trial, the Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) trial [44] is currently enrolling patients to investigate abciximab and abciximab with reduced-dose reteplase as facilitative regimens. The investigators are planning to enroll 3,000 patients in a 1:1:1 fashion to compare these to facilitated PCI regimens to primary PCI. The pimary endpoint will be 90-day all-cause mortality or post-MI complications. This important trial will bring more information to the issue of the early administration of abciximab +/– reduced-dose reteplase in patients with AMI transferred for primary PCI. Results are expected to be available in early 2008.

The meta-analysis by Keeley et al. also pooled all the results from the fibrinolysis, combination, high-dose heparin and GP IIb/IIIa facilitated PCI trials. Although these facilitated PCI regimens are all unique and may not lend themselves to being grouped together, the results showed that patients treated with facilitated PCI as a whole did worse than their primary PCI counterparts with

respect to mortality, reinfarction, urgent TVR and bleeding. All point-estimates favored primary PCI and none of 95% confidence intervals crossed unity.

Therefore, for AMI patients, a strategy of primary PCI remains the best reperfusion strategy. Given the weight of the current evidence, fibrinolysis-facilitated PCI is absolutely contraindicated. If long transfer-related delays are anticipated, a strategy of fibrinolysis in conjunction with a liberal rescue PCI policy and transfer to a PCI-capable facility for early invasive risk stratification is a reasonable alternate strategy to primary PCI [15, 45]. There is not enough evidence at this time to support the routine facilitation of primary PCI using GP IIb/IIIa inhibitors alone or in combination with reduced dose fibrinolytics. Hopefully the ongoing FINESSE trial will prove definitive about the question of facilitated PCI in the AMI patient.

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Appendix: Trial Glossary

PACT	Plasminogen-activator Angioplasty Compatibility Trial
PRAGUE	PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis
GRACIA-2	Grupo de Análisis de la Cardiopatía Isquémica Aguda-2 (Primary versus facilitated PCI [tenecteplase plus stenting] in patients with ST-elevated myocardial infarction)
ASSENT-4	Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention-4
ADVANCE MI	Addressing the Value of facilitated Angioplasty after Combination Therapy or Eptifibatide monotherapy in acute Myocardial Infarction

BRAVE	Bavarian Reperfusion Alternatives Evaluation Study Investigators
HEAP	Heparin in Early Patency
On-TIME	Ongoing Tirofiban in Myocardial Infarction Evaluation
ERAMI	Early ReoPro Administration in Myocardial Infarction
TIGER-PA	Tirofiban Given in the Emergency Room before Primary Angioplasty
INTAMI	Integrilin in Acute Myocardial Infarction
TIMI	Thrombolysis in Myocardial Infarction
TITAN	Time to Integrilin Therapy in Acute Myocardial Infarction
RELAx-AMI	Randomized Early Versus Late Abciximab in Acute Myocardial Infarction
FINESSE	Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events

Chapter 9
Therapies Targeted at Preserving Microvascular Integrity and Preventing Reperfusion Injury

Yeraldine Toledo and Alan W. Heldman

Microvascular Obstruction and Reperfusion Injury

While the timely restoration of infarct-artery patency is central to the optimal treatment of the patient with an acute myocardial infarction (AMI), the ultimate goal of early reperfusion therapy is to re-establish normal tissue-level perfusion and so restore normal myocardial metabolism. Epicardial coronary atherosclerosis and thrombosis initiate most acute ischemic events, but complete treatment of these conditions requires both rapid and effective epicardial coronary reperfusion and attention to preserving microvascular integrity. Technical and pharmacologic strategies designed solely to open the coronary artery are likely to be inadequate in many situations. The closely related phenomena of microvascular obstruction and reperfusion injury underlie the often-observed paradox of a patent epicardial infarct artery yet poor distal runoff, whether manifest as slow- or no reflow, reduced myocardial perfusion, or continuing or worsening ischemic injury after reperfusion. This chapter discusses strategies used in primary infarct angioplasty aimed at reducing or eliminating these microvascular and metabolic complications.

Kloner described reperfusion injury in the heart in a dog model [1]. Reperfusion after temporary ligation of the circumflex coronary artery resulted in a slow washout of dye which Kloner termed "no reflow." Reports of "no reflow" in humans emerged in several scenarios: in angiographic studies of thrombolytic therapy for AMI; in the setting of percutaneous coronary intervention (PCI) of thombotic lesions; and with the use of new angioplasty devices, in particular high-speed rotational ablation. Though one is an experimental observation and the other is a clinical and procedural complication, these two phenomena are both called "no reflow," and both share pathophysiologic features.

In the treatment of AMI, restoration of epicardial flow is critical, with the TIMI grading system [2] (Table 9.1) of epicardial flow being familiar to all

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Table 9.1 The Thrombolysis in Myocardial Infarction (TIMI) grading system for epicardial coronary flow

TIMI grade 0	No contrast penetration beyond the point of occlusion.
TIMI grade 1	Contrast penetrates the point of obstruction but does not reach the distal coronary bed.
TIMI grade 2	Contrast penetrates the obstruction and reaches the distal bed, but its rate of entry and/or clearance is slower than in non-involved arteries.
TIMI grade 3	Normal contrast entry to and clearance from the distal coronary bed.

interventionalists. A meta-analysis of five thrombolytic trials confirmed the tight association between death and the failure to achieve brisk epicardial coronary flow, with diminished 30-day survival in patients having TIMI-0 and -1 vs. TIMI-2 vs. TIMI-3 flow at 90 minutes [3]. In this meta-analysis, 30-day mortality was 8.8% for TIMI grade 0/1, 7.0% for grade 2, and 3.7% for grade 3. TIMI grade 3 flow was associated with improved outcome measures including extent of enzyme release, infarct size, and left ventricular dysfunction, while grade 2 flow was not much better than an occluded infarct artery.

Even among patients with normal TIMI-3 flow, angiographically-apparent microvascular obstruction (Tables 9.2 and 9.3) and reperfusion injury portend worse clinical outcomes after thrombolytic therapy for AMI. TIMI Myocardial Perfusion (TMP) grade 0 has no ground-glass myocardial blush, TMP grade 1 has a blush which does not clear, TMP grade 2 blush clears slowly, and TMP grade 3 blush largely clears within three cardiac cycles of the washout phase. In the TIMI 10b angiographic study, among patients who all had TIMI grade 3 epicardial flow after thrombolysis, TMP grade 0 or 1 was associated with 5.0% mortality at 30 days, TMP grade 2 with 2.9% mortality, and TMP grade 3 with 0.7% mortality [4].

Table 9.2 Myocardial Blush Grade (MBG)

MBG 0	No myocardial blush, *or* persistent "staining"
MBG 1	Minimal myocardial blush
MBG 2	Moderate myocardial blush
MBG 3	Normal myocardial blush

Table 9.3 The TIMI Myocardial Perfusion Grade (TMP)

TMP Grade 0	No blush in the distribution of the artery of interest.
TMP Grade 1	Contrast slowly enters causing blush, but does not exit; staining persists to the next injection.
TMP Grade 2	Delayed entry and exit of contrast from the myocardial microvasculature; blush strongly persists after three cycles of the washout phase.
TMP Grade 3	Normal entry and exit of contrast; blush largely or completely clears after three cycles of washout phase.

Over the last 20 years, primary percutaneous coronary intervention (PCI) has evolved as the optimal reperfusion therapy for AMI. However, just as for thrombolysis, the benefits of primary PCI are attenuated by microvascular obstruction and reperfusion injury. Patients with no-reflow during PCI for AMI have a higher release of creatine kinase and have more severe wall motion abnormalities on ventriculography and a higher incidence of mechanical complications (free wall or ventricular septal rupture) compared with those who do not have no reflow. In primary PCI studies, mortality is increased in patients with post procedural suboptimal angiographic coronary flow [5, 6]; this finding certainly results from an association between longer ischemic times and the development of microvascular obstruction, but may also relate to specific characteristics of the myocardium, the vasculature, the atheroma, the platelets, or other factors.

As is well-known, delays in performing the mechanical revascularization procedure translate into substantially worse outcomes [7]. While approaches to shorten the time-to-treatment for AMI are unquestionably important, there are also potential treatments directed at maintaining microvascular integrity, preventing reperfusion injury, and favorably altering myocardial metabolism during reperfusion therapy. This remains a fruitful area for investigation.

Reperfusion has been referred by Braunwald and Kloner as the "double edged sword" because the benefits of establishing early infarct-artery patency can be reduced by additional myocardial injury beyond that generated by ischemia alone. Reperfusion injury results in a unique form of myocardial damage, histologically characterized by the formation of contraction bands in the contractile proteins, calcific granules within mitochondria as well as cell swelling and the disruption of sarcoplasmic and mitochondrial membranes. Mechanisms involve the generation of reactive oxygen species (ROS), altered intracellular calcium handling, microvascular and endothelial cell dysfunction, altered myocardial metabolism, and the activation of neutrophils, platelets and complement. Reperfusion injury is manifested as stunned myocardium, reversible microvascular injury, and sometimes lethal myocyte necrosis [8].

Based upon the cellular mechanisms of reperfusion injury, rational therapeutic interventions may be designed. Both nitric oxide and adenosine are promising strategies for preventing reperfusion injury; these agents affect neutrophil-mediated phenomena, reduce vascular resistance, and modulate the myocyte response to ischemia. Beyond their direct cellular toxicity, ROS also modulate gene expression, including genes determining the apoptotic program for cell death [9], suggesting that antioxidant drug therapies might show an effect.

Imaging Microvascular Obstruction

To the coronary angiographer, "no reflow" with a static column of contrast represents a very high degree of damage, while a diminished degree of myocardial perfusion blush reflects lesser degress of microvascular impairment.

Myocardial contrast echocardiography (MCE) and cardiac magnetic resonance imaging (CMR) with contrast are both sensitive at detecting microvascular obstruction, and the combined use of angiographic and non-invasive techniques has been valuable for understanding the course of infarction [10]. Angiographic myocardial blush scoring predicts the extent of microvascular obstruction as determined by CMR [11]. Quantitative assessment of angiographic myocardial blush/time curves proved superior to the qualitative assessment of myocardial blush grade at predicting recovery of LV function after primary PCI [12].

Abnormal microvascular flow post-infarction, as demonstrated by MCE, CMR, and/or angiography correlates with fibrous scar formation, ventricular remodeling [13], LV dilation, congestive heart failure, reinfarction, target vessel revascularization, and death [14]. Imaging studies suggest that the territory affected by microvascular obstruction may continue to enlarge for many hours after reperfusion [15], evidence for an active process of reperfusion injury.

The TIMI frame count technique [16] has proved valuable for its ability to quantify the subjective perceptions of the angiographer about coronary flow. At a cine rate of 30 frames/sec, the number of frames is counted from the frame when contrast first enters the artery of interest, to the time when contrast reaches a distal landmark. The distal landmark for the left anterior descending (LAD) is its distal bifurcation (the "moustache"); for the circumflex, the distal bifurcation of the longest involved segment; for the right coronary, the first branch of the posterolateral artery. Because contrast progress from proximal to distal landmarks takes longer for the LAD than for the other major vessels, the frame count for the LAD is corrected by a dividing factor of 1.7.

While TIMI flow refers to flow though the epicardial coronary artery, the Myocardial Blush Grade (MBG) is a subjective assessment of contrast penetration into the microvascular space. The Zwolle Myocardial Infarction Study Group reported a study of 777 patients with AMI treated with primary angioplasty [17]. Higher blush grade was associated with smaller enzymatic infarction, higher ejection fraction at follow up, and lower mortality. At a mean of 1.9 years follow up, mortality with myocardial blush grades 3, 2, and 0/1 were 3%, 6%, and 23% respectively ($P<0.0001$).

A similar scoring system, the TIMI myocardial perfusion (TMP) grade also incorporates assessment of the myocardial washout, and also predicts outcomes after reperfusion with thrombolytic therapy [18].

Clinical Management of No Reflow

As interventional techniques moved into the era of new devices, operators (reluctantly) gained more experience with the complication of no reflow in PCI of degenerated vein grafts and in high-speed rotational atherectomy. In these situations, angiographic and clinical complications are often the result of

distal embolization of atherothrombotic material into the distal coronary bed, and are not necessarily the same as the no reflow seen following infarct reperfusion [19]. Reductions in angiographic flow are very serious; in the experience of the William Beaumont Hospital (1988–1993), PCI procedure-related no reflow was associated with a 10-fold increase in death or MI [20].

Intracoronary drugs and drug combination "cocktails" for the prevention of these events were adopted based upon local experience validated by published case series. However, despite two decades of experience, only intracoronary nitroglycerin is universally used, and no single strategy of intracoronary drug treatment has yet achieved broad acceptance.

Although no reflow is not specific to PCI reperfusion therapy for AMI, the incidence is certainly significant in this setting. For example, Piana et al. [21] reported an incidence of no reflow (defined as less than TIMI-3 flow) of 2% in almost 2000 PCIs performed at the Beth Israel Hospital between 1991 and 1993. In this series, PCI for AMI was associated with a seven-fold higher incidence of "no reflow" (11.5% vs. 1.5%). The PAMI group found that of 1192 patients who had primary PCI (balloon angioplasty or heparin-coated Palmaz-Schatz stent) and achieved TIMI-3 flow, transient no reflow occurred in 1.3%, with these patients having a much higher in-hospital (2% vs. 13%) and 6-month mortality (3% vs. 31%) [22]. In a population of AMI patients all treated with stents and with high utilization of GP IIb/IIIa inhibitors, Brosh et al. showed again that no reflow occurred during primary PCI (6.7%) and was associated with patient age, longer ischemic times, totally occluded arteries on initial angiography, and with higher CK peak; mortality after six months was higher (12.5% vs. 4.3%) among those with no reflow [23].

Certain lesion characteristics (IVUS finding of lipid pool; angiographic fissure or dissection [24]; large plaque volume; greater plaque compression by stenting; larger thrombus burden [25]) and technical approaches to intervention (stent oversizing [26]) all may predict a higher risk of developing no reflow during primary PCI. Certain patient characteristics (diabetes mellitus [27]) predict reduced myocardial blush grade after primary PCI, and pretreatment with statins [28] and ACE inhibitors [29] have been reported to be associated with less microvascular obstruction after primary PCI.

When performing primary, salvage, facilitated, or delayed PCI for AMI, the operator must make rational choices among several technical and pharmacologic therapeutic options. The ultimate goal is to provide solutions for all of the various forms of ischemic injury, including angiographic no reflow due to macroembolization and vasoconstriction as well as the (sometimes) more subtle derangements of metabolic no reflow and the "pure" no reflow of reperfusion injury. The discussion below is offered as a starting point, with a review of the scientific bases for and against these approaches. Note that many of these are "off-label" (not approved by the U.S. Food and Drug Administration) uses of available agents, and may or may not reflect "standard care" in a given community. Also discussed below are a number of compounds and strategies in preclinical or investigational development.

Endothelium-Independent Vasodilators

Relaxation of coronary vascular tone during PCI has several purposes. By reducing epicardial vessel spasm, the sizing of interventional devices may be optimized. More intriguing is the potential for limiting microvascular occlusion by dilating resistance arterioles and increasing the velocity and pressure gradient of perfusion through the capillary circulation. A number of vasospastic factors including serotonin are expressed from aggregating platelets. The combination of microvascular spasm and clumping of platelets, neutrophils and fibrin is a vicious cycle that is difficult to interrupt. As with most things in medicine, it would seem preferable to prevent rather than attempt to reverse this process.

Nitroglycerin

Nitroglycerin (NTG) has been used in cardiovascular medicine for more than 100 years, including via the intracoronary route for treatment of AMI since the first intracoronary thrombolytic procedures [30]. Nitroglycerin has a half-life of several minutes. It is rapidly converted to nitric oxide (NO) at or near the plasma membrane of the vascular smooth muscle cell. The NO or nitrosothiols formed from NTG cause a shift in intracellular calcium within the sarcoplasmic reticulum, resulting in a transient fall in intracellular calcium and subsequent vasorelaxation. Sytemic nitrates dilate venous and systemic conductance vessels, reduce cardiac wall tension and improve the balance between perfusion and oxygen demand. At higher doses, including the doses typically given via the intracoronary route, nitroglycerin dilates epicardial coronary arteries, and to some extent arteriolar resistance vessels, making it useful for the angiographic measurement of vessel size during PCI. While generally well tolerated, nitroglycerin's value for the treatment of serious microvascular complications is limited, and a number of studies have shown that other drugs are more effective.

Administration of nitroglycerin or another nitrate is routine in most labs. It loses activity in contact with polyvinylchloride plastic; specially designated syringes and containers should therefore be used. Hypotension may result, particularly when filling pressures are low, and generally responds to volume resuscitation.

Adenosine

Adenosine is an endogenously nucleoside produced in part by the degradation of adenosine triphosphate (ATP). During normoxia vascular endothelial cells maintain levels of adenosine in the coronary circulation; in the presence of ischemia the major source of adenosine is the myocyte. Adenosine has a variety

of effects at crucial signaling points. It is a potent short-acting vasodilator, giving it an autoregulatory effect in the case of ischemia [31]. Multiple lines of evidence suggest an important role of endogenous adenosine in the myocardial protection associated with ischemic preconditioning. In animal models, intracoronary adenosine infusion mimics the benefits of ischemic preconditioning at maintaining coronary perfusion despite stenosis and thrombosis [32]. Similar findings have been reported for patients undergoing PCI after pretreatment with intracoronary adenosine, or intracoronary dipyridamole (which may increase production of adenosine [33]). A direct protective effect against reperfusion injury on cardiac myocytes has also been proposed, including in cardiac surgery [34].

Adenosine prolongs conduction through the atrioventricular node. Administration of adenosine, whether intravenous or intracoronary, can produce heart block and profound bradycardia. This effect is short-lived;.in fact, some patients who are able to cooperate during the intervention can be taught to "auto-CPR" by repetitive forced deep coughing for a short period when an intrinsic heart rhythm is absent [35]. Heart block occurring during rotational ablation has been ascribed to increased endogenous adenosine activity, and some operators have prevented the bradyarrhythmia with theophylline or aminophylline. Given the important protective properties of adenosine in coronary ischemic events, however, inhibiting the effects of endogenous adenosine [36, 37] raises at least some theoretical concerns for the interventional use of theophylline or aminophylline. Other side effects reported with the use of adenosine include flushing, dyspnea, chest pain, abdominal discomfort, headache, hypotension, dizziness, and bronchospasm.

Marzilli and colleagues [38] specifically studied the effects of adjunctive intracoronary adenosine on mitigating reperfusion injury during primary angioplasty for AMI. In this study, 54 patients presenting within three hours of symptom onset were randomized to receive intracoronary adenosine vs. placebo infusion. Baseline demographics between groups were similar. Patients with TIMI-3 flow on the initial angiogram or a history of bronchospasm were excluded. Upon the initial inflation of an over-the-wire balloon across the obstruction in the infarct artery, the guidewire was withdrawn and a high dose of intracoronary adenosine (4 mg) was slowly infused through the central lumen of the balloon catheter over one minute. The treatment procedure, including initial balloon inflation and infusion of adenosine, was completed in less than two minutes in all cases, and the balloon was deflated, allowing reperfusion into the now-dilated distal bed. Interestingly, there were no episodes of bradyarrythmias or AV block with intracoronary adenosine. At the end of the procedure, all 27 patients in the adenosine-treated group achieved TIMI-3 flow, whereas only 19 of 27 patients exhibited TIMI-3 flow in the placebo group. There was a trend towards decreased CK release and there was a significant decrease in the cumulative clinical end points (recurrent ischemia, nonfatal MI, heart failure, and cardiac death) in the adenosine-treated group.

Improvement in LV function one week post infarct was significantly greater in the group treated with intracoronary adenosine.

Intravenous adenosine for AMI has also been studied, with mixed results. The Acute Myocardial Infarction Study of Adenosine (AMISTAD) trial [39] evaluated the administration of intravenous adenosine during thombolytic therapy for AMI. In AMISTAD, 236 patients were randomized to adjunctive intravenous adenosine (up to 70 mcg/kg/m for three hours) or placebo. The majority of patients received a 6-hour lidocaine infusion since an animal study suggested that adenosine exerted a beneficial effect on reperfusion injury only when administered with lidocaine. The primary end point was infarct size as determined by Tc-99m sestamibi SPECT imaging. There was a 33% relative reduction in infarct size ($p = 0.03$) and a trend towards a reduced composite of clinical endpoints (death, reinfarction, shock, congestive heart failure, and stroke. However, efficacy was limited to patients with anterior infarction and the trial was underpowered to detect improvement in clinical outcomes.

In AMISTAD-II, 2,118 patients with acute anterior ST-segment elevation MI in 13 countries were randomized to one of two dosages of intravenous adenosine (50 or 70 mcg/kg/min for three hours) or placebo, initiated prior to thrombolytic therapy, or PCI. In a subset of 243 patients, infarct size was measured by sestamibi scan at least five days after therapy delivery [40]. There was little difference between placebo and lower adenosine dose group, but the 70 mcg/kg/min adenosine group had significantly smaller infarcts (11% vs. 27% in the placebo group; $p = 0.023$). Nonetheless, clinical endpoints (heart failure or death within six months) were not significantly improved. The benefit of intravenous adenosine or analogues such as AMP579 may be greatest in anterior infarctions [41] and those receiving early reperfusion [42], but may be less significant than that suggested by the small trials of intracoronary high dose adenosine during primary PCI.

Nitroprusside

Nitric oxide (NO) is the principal "endothelium derived relaxing factor" [43] and may have other cellular effects including inhibition of platelet aggregation and modulation of ischemic preconditioning. Nitroprusside is a direct NO donor which has a greater effect on the microvasculature than nitroglycerin or other nitrates. Intracoronary nitroprusside produces sustained coronary hyperemia without detrimental systemic hemodynamics. Hillegas et al. analyzed 19 patients with no- or slow-flow following PCI who were treated with nitroprusside (50–200 μg per injection, up to 1000 μg total) either through the guiding catheter or through the angioplasty balloon. Fourteen of 19 patients responded with a significant increase in coronary flow velocity, without hypotension or other complications [44]. Airoldi et al. developed a protocol for intracoronary nitroprusside administration to treat slow flow after stenting,

and found that in AMI patients, the first 80 mcg dose of nitroprusside restored normal TIMI flow in 58% of patients, and the 120 or 160 mcg maximal dose restored normal flow in all the remaining patients. The efficacy of nitroprusside was less in cases of slow flow after vein graft intervention [45].

In a randomized, blinded trial of 98 patients presenting with ST-segment elevation myocardial infarction (STEMI), subjects received either intracoronary nitroprusside (60 mcg) or placebo, given through a probing/infusion catheter beyond the occlusion, followed by angioplasty and bare metal stenting. There was no difference in final TIMI frame count, the frequency of complete ST-segment resolution, or the myocardial blush grade. Nonetheless, the combined clinical endpoint of six-month death, MI, or target lesion revascularization (TLR) occurred in 6.3% of the nitroprusside group, and 20.0% of the placebo group ($p = 0.05$) [46]. Transient hypotension (SBP<90 mmHg) occurred in 7% of those treated with nitroprusside, and in no control patients.

In another trial, 40 STEMI patients who underwent primary angioplasty and still had <TIMI grade 3 flow were randomized to receive adenosine (60–120 mcg), nitroprusside (100–500 mcg), verapamil (100–500 mcg), or nitroglycerin (200–400 mcg). The greatest improvement in myocardial blush was associated with nitroprusside, and this also corresponded to the greatest improvement in LV ejection fraction [47].

Papaverine

Papaverine is an opiate derivative and a potent vasodilator. In an observational study, Ishihara and colleaugues [48] evaluated whether intracoronary papaverine could effectively treat angiographic "no reflow" (defined as TIMI-1 or -2 flow despite a less than 50% residual stenosis). Nine patients who developed "no reflow" despite adequate epicardial artery patency after primary angioplasty for a first MI received intracoronary papaverine (10 mg bolus) through the guiding catheter. Coronary flow was assessed by the mean number of cine frames required for contrast medium to pass two selected landmarks. By this measure, flow significantly improved after papaverine injection. However, papaverine may cause QT prolongation and polymorphic ventricular tachycardia, and is therefore not generally recommended for use in coronary intervention.

Calcium Channel Blockers

In many laboratories, this class of drugs is used frequently as adjunctive therapy. While they are classified as vasodilators, other effects including direct myocardial actions are possible. Studies of each of the available agents are described below.

Verapamil

Taniyama et al. [49] reported that intracoronary verapamil after primary PCI attenuates microvascular dysfunction and leads to improved outcomes compared with primary PCI alone. In this study, 40 patients were randomized to receive 0.5 mg intracoronary verapamil or placebo over one minute through the guiding catheter after restoring infarct vessel patency of the infarct artery. There were no adverse hemodynamic outcomes due to drug infusion. Microvascular function was assessed by myocardial contrast echocardiography (MCE) after infusion of sonicated ioxaglate, and a "no-reflow ratio" calculated as the size of the no-reflow zone over the area at risk. Despite the establishment of TIMI-3 flow in 70% of verapamil-treated patients (no difference from controls) immediately after PCI, MCE still revealed no or low reflow in 14 of 20 patients before verapamil. After verapamil treatment, the "low reflow" ratio decreased from 0.39 to 0.29. Left ventricular function improved more in the verapamil group vs. placebo group as assessed by a wall motion score index and left ventricular end-diastolic and end-systolic volume indices.

Verapamil (100–500 mcg) was compared to nitroglycerin (100–300 mcg) for intragraft infusion in the treatment of reduced flow during interventions on degenerated saphenous vein grafts. Verapamil restored TIMI-3 flow in 88% of cases, while nitroglycerin was ineffective [50]. When used in the setting of PCI in AMI, the early administration of intracoronary verapamil immediately prior to balloon inflation and at short intervals during the procedure thereafter improves postprocedural angiographic myocardial perfusion grade [51]. Possible side effects include atrioventricular block, depression of contractility, and hypotension [52].

Diltiazem

In an animal model, Herzog and colleagues [53] showed attenuated reperfusion injury and decreased infarct size with intracoronary diltiazem. Occlusion of the left anterior descending arteries for 50 minutes in 14 Yorkshire swine was followed by a 3 hour period of reperfusion. Eight animals were treated with intracoronary diltiazem (2.5 mg) at the onset of reperfusion while six were given a placebo saline infusion. Infarct size was significantly reduced in the diltiazem-treated vs. placebo group (0.13 ± 0.06 vs. 0.42 ± 0.04 g/kg, $p = 0.01$). The authors hypothesized that intracoronary diltiazem may be a valuable adjunct in patients undergoing coronary bypass surgery and PCI or thrombolysis for AMI.

In a large series of patients undergoing direct coronary atherectomy (DCA), Jalinous and colleagues demonstrated that intracoronary diltiazem (2–6 mg) given prior to DCA resulted in a significant decrease in non-Q-wave myocardial infarctions compared to historical controls (2.7 vs. 6.8%, $p < 0.04$) [54]

Pizzeti et al. [55] reported that AMI patients treated with thrombolytic therapy had decreased infarct size, increased residual viability, and recovered regional function in a group receiving intravenous diltiazem (n = 43; 10 mg bolus + 10 mg/hour for 3 days) compared with 47 patients in a placebo group.

Nicardipine

In a small sample of patients treated serially with intracoronary diltiazem, verapamil, and nicardipine and studied with a Doppler flow wire, the greatest and longest-lasting effect on coronary blood flow velocity was seen with nicardipine [56]. In a retrospective analysis of 72 consecutive patients who received intracoronary nicardipine (mean dose 460 mcg +/– 360) to reverse no reflow during coronary intervention, restoration of TIMI-3 flow was achieved in 71 of 72 patients (98.6%). TIMI flow grade improved from 1.65 +/– 0.53 prior to nicardipine to 2.97 +/– 0.24 after treatment ($P < 0.001$). Nicardipine therapy was well tolerated without adverse hemodynamic or chronotropic effects [57]. Nicardipine appears to be effective when administered in a flush solution with other drugs during rotational atherectomy and clot debulking with or without distal protection devices [58].

Anticoagulants, Platelet Inhibitors, and Thromobolytics

Proper management of anti-clotting drugs around the time of infarct angioplasty is critical to obtaining good outcomes. These agents are discussed next as related to issues around reperfusion injury.

Unfractionated Heparin

The Heparin in Early Patency (HEAP) trial [59] evaluated whether high-dose heparin prior to primary PCI improved rates of pre and post-procecedure TIMI flow. The treatment group (n = 299) received a heparin bolus of 300 IU/kg IV, while the control group (n = 285) either received a fixed 5000 IU heparin bolus (n = 73) or no heparin (n = 212). Heparin was administered in the emergency room of the angioplasty facility or at the referring institution prior to transportation. Median ischemic times (time from symptom onset to balloon inflation) were similar between groups (195 vs. 210 min for the high- vs. low-dose group, respectively). Initial pre-angioplasty grades of TIMI flow were similar between groups, as were grades of immediate post-procedure TIMI flow. Left ventricular ejection fraction and enzymatically determined infarct size were likewise similar between groups. The authors concluded that early high dose heparin was of no benefit.

In a study on the effect of early administration of heparin in patients with STEMI, 121 consecutive patients were allocated to an early heparin group

(heparin administered in ER) or a late heparin group (heparin administered after angiography). In the early heparin group, unfractionated heparin (60 U/kg bolus IV, then 14U·kg–1·h–1 IV infusion) or enoxaparin (1 mg/kg bolus SC) were administered 144±95 min before angioplasty. TIMI-2 or -3 flow was seen significantly more often in the early heparin group than in the late heparin group (48% vs. 22%, $p = 0.002$). However, no significant differences were noted between the two groups in terms of in-hospital major adverse cardiac events or major bleeding [60].

Thrombolytic Drugs with Primary PCI

Several case reports suggested that residual thrombus may be effectively treated with local injections of intracoronary t-PA, urokinase, or streptokinase. The Thrombolysis and Angioplasty in Unstable Angina trial (TAUSA) [61] evaluated the prophylactic use of intracoronary urokinase in patients undergoing PCI for rest angina in a randomized, double-blind, placebo-controlled study. The urokinase-treated group experienced a significant increase in acute closures (10.2 vs. 4.3%, $p < 0.02$) and a higher incidence of adverse in-hospital clinical endpoints including ischemia, reinfarction, or emergent bypass surgery (12.9 vs. 6.3%, $p < 0.02$). The worsened outcomes in the urokinase-treated group were hypothesized to be due to hemorrhagic dissection, lack of intimal sealing, or platelet-activating effects of urokinase.

Tenecteplase (TNK) is a triple-combination mutant variant of t-PA with 14-fold higher fibrin specificity than t-PA, a longer half-life, and an 80-fold greater resistance to inhibition by PAI-1. The use of IC TNK was evaluated in a retrospective analysis of 34 patients who developed an intracoronary thrombotic complication (angiographically visible thrombus 35%, no reflow 32%, or distal embolization 29%). An initial bolus dose of 5 mg was given and the dose was repeated at 5-minute intervals if the angiographic appearance of thrombus and/or coronary blood flow did not improve. A maximum dose of 25 mg of TNK was given. There was an improvement in angiographically visible thrombus and/or intracoronary blood flow in 31 (91%) patients. TIMI flow at the beginning of the case was 0.6 +/– 0.2 and improved to 2.5 +/– 0.1. TIMI-2 or -3 flow was present at the end of the procedure in 33 (97%) of 34 patients and improvement in flow with TNK-supported PCI was observed with or without adjunctive GP IIb/IIIa inhibitors [62].

GP IIb/IIIa Inhibitors

Several studies have suggested that the inhibition of platelet aggregation with platelet GP IIb/IIIa receptor antagonists during or prior to catheter-based reperfusion therapy for AMI improves microvascular flow. Neumann and

colleagues randomized 200 patients undergoing stenting for AMI to receive abciximab (n = 102) or placebo (n = 98). Primary endpoints included differences in peak coronary flow velocities and wall motion index scores immediately post procedure and at 14 days. Peak flows improved significantly at 14 days in the abciximab-treated group compared to those receiving placebo (18.1 cm/s vs. 10.4 cm/s, p = 0.024). Likewise, abciximab-treated patients exhibited a significantly greater improvement in their wall motion index scores. Left ventricular ejection fraction at follow-up was 62% vs. 56% (p = 0.003) for the abciximab-treated versus the placebo group [63].

Giri and colleagues [64] examined 650 consecutive patients who were treated with primary PCI for AMI (presenting within 12 hours of symptom onset) between August 1995 and December 1998. Patients were divided into one of four groups based on treatment received: (1) PTCA; (2) stent; (3) PTCA plus abciximab; (4) stent plus abciximab. Rates of TIMI-3 flow immediately post procedure were 82, 90, 93, and 97% (p = 0.0001) for the four groups, respectively. Rates of persistent "no reflow" were 14, 9, 4, and 2% (p = 0.0001), respectively. Significant reductions in death, recurrent myocardial infarction, and target vessel revascularization at 30 days were observed among groups in a graded fashion (24.5, 19.5, 16.5, and 6.1%, respectively for the composite endpoint; p = 0.0001).

The Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long term follow-up (ADMIRAL) trial suggested that the early administration of abciximab before angiography and PCI for AMI improved infarct artery flow. Rates of TIMI-3 flow before the procedure (16.8% vs. 5.4%, P = 0.01), immediately afterward (95.1% vs. 86.7%, P = 0.04), and six months afterward (94.3% vs. 82.8%, P = 0.04) were higher for the abciximab-treated than for the placebo group, respectively. Clinical endpoints of death, reinfarction, or urgent target vessel revascularization were reduced at 30 days (6.0% vs. 14.6% P = 0.01) and at six months (7.4% vs. 15.9% P = 0.02). A substudy showed that abciximab reduced platelet aggregate size in this setting [65].

The Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial [66] demonstrated that administration of eptifibatide reduced complications of stenting, primarily by reducing peri-procedural myocardial infarctions. In a substudy of that trial, Gibson and colleagues measured coronary flow reserve and angiographic myocardial perfusion and found both were significantly increased with eptifibatide [67]. Coronary flow reserve was calculated as the ratio of coronary flow velocity (by an angiographic technique, the corrected TIMI frame count) after microvascular vasodilation with adenosine over the velocity before adenosine. The rate of increase of myocardial contrast blush (myocardial perfusion) was calculated using digital subtraction angiography. Both measurements reflect function of the microvasculature; improvement with platelet inhibition may reflect reduced microvascular plugging.

Several case reports advocate the utility of ad hoc intracoronary abciximab [68] for persistent thrombus during primary PCI. It was hypothesized that the intracoronary route might be more effective, more timely, and potentially safer. Wohrle and colleagues performed a randomized study and showed a significant reduction in 30 day major adverse cardial events (MACE) with intracoronary bolus of abciximab compared with intravenous administration in patients with acute coronary syndromes undergoing coronary angioplasty [69].

Retrospective studies have evaluated the efficacy and safety of intracoronary eptifibatide in patients with unstable angina and STEMI; eptifibatide was administered via the guide catheter at a dose of 180 mcg/kg bolus x2 without IV infusion. No deaths, urgent revascularizations, or reinfarctions were observed among the patients who were treated with intracoronary eptifibatide. No major bleeding events were reported and TIMI myocardial perfusion grade 3 flow after PCI was noted in 54.4% of patients. No adverse events. including arrhythmias, were noted during intracoronary eptifibatide administration [70–71] Case reports have suggested the use of intracoronary eptifibatide in the treatment of no reflow phenomenon during vein graft stenting [72].

Clopidogrel

Platelets play a key role in the pathophysiology of thrombosis after plaque rupture. Plaque rupture occurs spontaneously in patients with ACS or may be iatrogenically induced in patients undergoing PCI. Clopidogrel is an inactive prodrug that requires oxidation by the hepatic P450 (CYP3A4) system to form its active metabolite that selectively and irreversibly binds to the $P2Y_{12}$ receptor, resulting in its blockade for the life span of the platelet.

Two recent studies – COMMIT (Clopidogrel and Metoprolol in myocardial Infarction) and CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Thrombolysis in Myocardial Infarction) evaluated the role of clopidogrel in addition to standard therapy in AMI, although not specifically using a primary PCI strategy.

The COMMIT trial [73] enrolled 45,852 patients with suspected AMI; patients were randomized to receive up to four weeks of treatment with clopidogrel (75 mg/day; n = 22,961) or placebo (n = 22,89). All patients were given aspirin (162 mg/day.) Dual antiplatelet therapy with clopidogrel and aspirin resulted in a 7% relative reduction in death (7.5% versus 8.1%, $P = 0.03$) and a 9% relative reduction in the risk of death, reinfarction, or stroke as compared with aspirin plus placebo (9.2% versus 10.1%, $P = 0.002$). Major bleeding was not significantly different.

The CLARITY-TIMI 28 trial enrolled 3491 patients who presented with ischemic discomfort at rest within 12 hours before randomization, had ST segment elevation or new left bundle branch block. Patients received clopidogrel (300 mg loading dose, then 75 mg daily) or placebo, along with aspirin and

thrombolytic therapy. Angiography was done 2-7 days later. There was 20% relative reduction in the combined end point of cardiovascular death, MI, or urgent revascularization at 30 days with the addition of clopidogrel.

Other Drugs and Experimental Strategies

Surfactants

Poloxamer 188 (first developed as RheothRX, later as Flocor) is a surfactant with hemorheological and antithrombotic properties. This surfactant associates with the cell membranes of erythrocytes, neutrophils, and endothelial cells, as well as circulating macromolecules, sterically hindering adhesive interactions between these components. This association was hypothesized to reduce red blood cell aggregation and blood viscosity, and to improve microcirculatory flow. Preclinical studies suggested that this agent could reduce infarct size [74].

Clinical trials tested the efficacy of RheothRX in preventing reperfusion injury with conflicting results. In a primary angioplasty study, O'Keefe and colleagues [75] randomized 150 patients undergoing primary PTCA to receive RheothRX vs. placebo. Drug was initiated prior to reperfusion. Primary endpoints included infarct size and myocardial salvage as determined by Tc-99m SPECT imaging, and left ventricular ejection fraction at 5 to 7 days as measured by radionuclide angiography. No differences in the primary endpoints were observed between groups.

However, in a companion thrombolytic study, Schaer and coworkers observed a beneficial effect for adjunctive RheothRX therapy in patients undergoing thrombolysis for AMI [76]. One hundred fourteen patients were included in this randomized, double-blind, placebo-controlled, multicenter trial. Patients treated with RheothRX (48-h infusion initiated immediately after the start of the thrombolytic therapy) exhibited a 38% reduction in infarct size compared with placebo (16 vs. 26%, $p = 0.031$), and a 13% relative improvement in LV function at 5 to 7 days (52 vs. 46%, $p = 0.02$).

The benefit of RheothRX was not substantiated in a larger study, a randomized, placebo-controlled trial of 2948 patients undergoing thrombolysis for AMI. The Collaborative Organization for RheothRx Evaluation (CORE) investigators concluded that adjunctive RheothRX provided no clinical benefit and may in fact be detrimental [77]. No differences were observed between RheothRX-treated and placebo groups with respect to mortality, reinfarction, and cardiogenic shock. RheothRX treatment, however, was associated with a reduction in left ventricular ejection fraction 5 to 7 days post infarct, along with increased rates of heart failure and renal dysfunction.

While the strategy of surfactant therapy with reperfusion for AMI has not been further developed, there continue to be intriguing reports of the effects of poloxamer 188 in cardiovascular disease. In a mouse model of Duchenne

muscular dystrophy cardiomyopathy, poloxamer 188 prevented the development of stress-induced cardiac myocyte injury and dystrophy, perhaps by a mechanism involving drug-facilitated repair of torn cell membranes [78]. We may not have heard the last of this approach.

ATP-sensitive Potassium Channel Openers: Nicorandil and Diazoxide

Nicorandil is an adenosine triphosphate (ATP)-sensitive potassium channel opener having the properties of a nitrate and a nicotinamide [79]. It is clinically available only outside the USA. Its nitrate action causes vasodilation of systemic veins and epicardial coronary arteries, while its ATP-sensitive potassium channel opener action causes vasodilation of peripheral and coronary resistance arterioles [80]. Ito et al. randomized 81 patients with a first anterior AMI (within 12 hours of symptom onset) to receive nicorandil vs. placebo. Prior to angioplasty, nicorandil was administered as a 4-mg IV bolus followed by a 6-mg/h infusion for 24 hours and then an oral dose of 15 mg/d for one month. Baseline characteristics between groups were similar. In-hospital complications were significantly reduced in the nicorandil-treated group vs. controls (VT or VF, 5 vs. 20%, $p = 0.048$; tamponade, 0 vs. 4%, $p = 0.043$; CHF, 15 vs. 37%, $p = 0.027$; in-hospital death, 0 vs. 10%; $p = 0.043$). MCE with sonicated ioxaglate revealed that the incidence of echocardiographic no reflow was significantly reduced in the nicorandil-treated vs. control group (6 of 40 vs. 14 of 41, $p < .001$) [81]. In another study, used during rotational atherectomy, nicorandil was superior to verapamil in decreasing the incidence of slow or no flow phenomena [82].

Nicorandil improves cardiac function and clinical outcomes in patients undergoing PCI during STEMI [83]. A randomized, double-blind trial was conducted among 368 patients with first STEMI undergoing percutaneous coronary intervention (PCI). They were randomly assigned to receive 12 mg of nicorandil or placebo intravenously just before reperfusion. Mean follow up was 2.4 years, and the incidence of cardiovascular death or rehospitalization for congestive heart failure after PCI as well as measures of epicardial flow and microvascular function were analyzed. A total of 12 (6.5%) patients receiving nicorandil and 30 (16.4%) receiving placebo had cardiovascular death or hospital admission for congestive heart failure (hazard ratio, $P = 0.0058$). Postprocedural TIMI-3 flow was obtained in 89.7% of the nicorandil group and in 81.4% of the placebo ($P = 0.025$). Corrected TIMI frame count was lower in the nicorandil group ($21.0 +/- 9.1$ versus $25.1 +/- 14.1$; $P = 0.0009$). ST-segment resolution $>50\%$ was observed in 79.5% and 61.2% of the nicorandil and placebo groups, respectively (hazard ratio, 2.45; 95% CI, 1.54 to 3.90; $P = 0.0002$). The addition of intravenous nicorandil to PCI thus demonstrated beneficial clinical effects in patients with ST-segment-elevation myocardial infarction [84].

The SMART trial was a 5-center study that evaluated the effectiveness and optimal administration of Nicornadil in AMI patients. Ninety-two patients with first AMI were randomly assigned to receive either intracoronary nicorandil, combined intravenous and intracoronary nicorandil, or no nicorandil. The combined intravenous and intracoronary administration of nicorandil improved angiographic flow (the corrected TIMI frame count, cTFC) and resolution of ST segment elevation in AMI [85]. Administration of nicorandil by combined intravenous and intracoronary routes was shown to be superior to intracoronary administration alone.

Another molecule with ATP-sensitive potassium channel opener effects, diazoxide, is an antihypertensive drug and is also used to suppress hypoglycemia associated with hyperinsulinemic states. In models, diazoxide protects from ischemic injury, preventing cellular damage and apoptosis [86]. It is a K^{+}_{ATP} opener which causes increased production of reactive oxygen species in cardiac muscle. This change in cellular redox state may serve a signaling function itself, altering protein biochemistry and cell processes. In fact, antioxidants block ischemic preconditioning, including that induced by diazoxide [87].

Agents for Direct Myocardial Protection: Cariporide and Trimetazidine

The sodium-hydrogen exchanger type 1 (NHE-1) channel has been implicated in the pathogenesis of myocyte necrosis during ischemia and reperfusion. Activation of NHE-1 during cytosolic acidosis results in increased intracellular Na+ and Ca2+ levels, leading to contractile dysfunction, apoptosis and necrosis [88]. Animal studies have demonstrated that NHE-1 inhibitors such as cariporide preserve myocyte viability and limit infarct size during ischemia-reperfusion, perhaps also by reducing the oxidative stress of reperfusion [89].

The Guard During Ischemia Against Necrosis (GUARDIAN) trial assessed whether cariporide reduced the frequency of death or MI in 11,733 patients with unstable angina, non-ST-elevation myocardial infarction, or while undergoing high-risk PCI or CABG [90]. Doses of 20, 80, and 120 mg of cariporide were given IV every 8 hours for 2–7 days. No benefit was observed overall for cariporide treatment compared to placebo; in the subset of CABG patients, treatment with the highest dose reduced MI, suggesting that the drug might be evaluated in the setting of reperfusion. Animal studies assigning the protective effect of cariporide to ischemia, rather than reperfusion following infarction [91], make these results no more clear.

In contrast (and in a very different set of conditions) Rupprecht and coworkers demonstrated a cardioprotective effect for cariporide in patients undergoing primary PCI for acute anterior myocardial infarction [92]. In this study, 100 patients presenting within 6 hours of symptom onset of an anterior AMI were randomized to receive a 40-mg IV bolus of cariporide prior to reperfusion

(n = 49) vs. placebo (n = 51). Only patients with TIMI 1/0 flow in the left anterior descending artery were included in the study. The ejection fraction over a 3-week period remained unchanged in the placebo group at 40 ± 2 vs. 40 ± 3%, whereas an increase from 44 ± 2 to 50± 2% was observed with cariporide treatment ($p < 0.045$). The area-under-the-curve (AUC) for CK-MB was significantly reduced in the cariporide-treated vs. placebo group; however, peak total CK and the AUC for total CK were similar for both groups. Clinical outcomes at 3 weeks including death, heart failure, acute reocclusion, and emergency bypass surgery were similar although the number of events was small.

Trimetazidine is an antianginal agent used outside the US; its mechanism of action remains incompletely understood, though it seems to alter myocardial metabolism, shifting away from fatty acid oxidation and towards glucose oxidation [93]. Steg and colleagues randomized 94 patients undergoing primary angioplasty for AMI (within 6 hours of symptom onset) to receive trimetazidine vs. placebo. Baseline and procedural characteristics were similar between groups. A 40-mg IV bolus of trimetazidine was administered prior to PCI followed by a 60-mg/d IV infusion. Although the trimetazidine group experienced a more rapid resolution of ST-segment elevations, clinical outcomes including left ventricular function and infarct size (determined by myoglobin mass) were similar to controls [94].

Modulators of Free-radical Injury: Recombinant Human Superoxide Dismutase (h-SOD) and Fluosol

The generation of reactive oxygen species is an important mechanism of reperfusion injury. Molecular oxygen, when reintroduced into ischemic myocardial tissue, is reduced to form oxygen free radicals, which in turn alter cellular calcium, and cause lipid peroxidation, cell membrane damage, and cell swelling. Reperfusion also stimulates neutrophil activation and attraction.

Flaherty et al. studied whether treatment with human superoxide dismutase (h-SOD) prior to primary PCI reduced free-radical mediated reperfusion injury and improved clinical outcomes [95]. In this study, 120 patients were randomized to receive h-SOD (n = 61) as a 10-mg/kg IV bolus followed by a 60-min IV infusion at 0.2 mg/kg/m vs. placebo (n = 59) immediately prior to PCI. Primary clinical endpoints were similar between h-SOD treated and placebo groups (rates of death or in-hospital urgent revascularization were 29.5% vs. 35.6%, respectively, p = NS). Improvement in LV function was no different between groups.

Fluosol, a perfluorochemical emulsion, offers a potential means to improve oxygenation of the heart during periods of ischemia-reperfusion. Fluosol contains 2.7% RheothRx. In a small pilot trial of nine patients presenting within 4 hours of symptom onset of an anterior AMI and having TIMI-0 or -1 flow,

Forman and co-workers found that intracoronary Fluosol delivered immediately after primary angioplasty (40 ml/m over 30 m) resulted in a significant reduction in infarct size and greater improvement in regional LV function [96].

In contrast, the TAMI-9 investigators found no benefit for adjunctive Fluosol therapy in a randomized, open-labeled trial of 430 patients undergoing thrombolysis for AMI. Fluosol infusion was initiated at 15 ml/kg IV over one hour immediately after the start of t-PA therapy. Primary endpoints included infarct size and changes in left ventricular function [97].

Other Strategies

A number of adjunctive therapies for primary PCI have been proposed. Magnesium is much studied yet remains unclear as to its value; in a trial of intravenous magnesium with primary PCI, no benefit was found [98].

Glucose-insulin-potassium (GIK) infusion is hypothesized to protect ischemic myocardium, and has a long history of controversial study [99]. The mechanism of action may be mediated by insulin's effect activating the K_{ATP} channel [100]. In a study of 73 STEMI patients randomized to receive GIK (30% glucose, 50 IU of insulin, and 80 mEq of potassium chloride, infused at 1.5 ml/kg/hr for 24 hours) or saline beginning before catheterization, the group receiving GIK had a higher frequency of MBG 3 after intervention, and a much lower frequency of ventricular enlargement remodeling at 6 month follow-up [101].

Table 9.4 Intracoronary drugs

Agent	DOSE	DELIVERY	EFFECTS	
Nitroglycerin	50–200 μg	Injected through guiding catheter.	Epicardial coronary dilation.	
Adenosine [102]	18–24 μg	"High velocity boluses" with a 3 ml syringe injected through guiding catheter.	Reversed no-reflow caused by vein graft stenting.	Dose repeated 10–40 times.
Adenosine HIGH DOSE	4 mg	Through inflated balloon's wire lumen, before reperfusion	Increased TIMI-3 flow, improved LV function and clinical endpoints.	
Adenosine IV infusion	70 mcg/kg/min Per 3 hours	Continuous IV infusion	Decreased Infarct Size and adverse clinical events	
Papaverine	10 mg	Via guide catheter		
Nitroprusside	50–1000 (mean 200) μg injections	Via guide catheter or angioplasty balloon	Improved flow velocity after PCI-related no reflow	No effect on blood pressure at this dose.
Verapamil	100–500 μg	IC	Maximal effect on coronary resistance	100 μg IC did not affect

Table 9.4 (continued)

Agent	DOSE	DELIVERY	EFFECTS	
			at 1.0 mg into left coronary artery [104]	BP, but 1.0 mg did reduce BP [103]
Diltiazem	1 –2 mg	IC	Heart block	
Nicardipine	200 μg 100 mcg up to 800 mcg	IC	More potent & prolonged effect on coronary flow velocity than Diltiazem (1 mg) or Verapamil (200 μg) Reverse no reflow during PCI	
Urokinase	250,000–1,000,000 units	IC infusion	Increased complications, acute closure	
Urokinase	300–500 units	Local delivery	No benefit.	
Tenecteplase	5–25 mg	IC	Improvement on TIMI flow	
Abciximab	10 mg	IC bolus	Case reports	
Eptifibatide	180 mcg/kg bolus x2 Or 0.75 mg/ml (5–10 ml) plus IV bolus	Via guide catheter	Associated with restoration of TIMI-3 flow in USA and STEMI	

Note: While frequently administered via the intracoronary route, most drugs are not approved nor recommended for intracoronary use by the manufacturer or regulatory agencies. Medical literature, local experience, and individual catheterization laboratory standards should be considered. Literature citations include those noted in the text above.

Catheterization Technique

Considerations for Drug Delivery

Over-the-wire balloon systems are useful for angioplasty of infarct vessels and total occlusions, allowing the injection of contrast through the central channel and thus confirmation of intraluminal position. By the same route, drugs can be administered to the distal coronary bed, even prior to reperfusion. Attention to technique makes this a safe and useful maneuver. Balloon catheter position beyond the area of trouble should be secure before temporarily removing the guidewire. Using a 3–5 cc syringe, aspirate from the central lumen until blood is seen. Injection of air into the closed distal bed is to be avoided with at least the same degree of caution given to angiographic or guiding catheters. Support,

infusion, or probing catheters can also be used for drug delivery in this way; we have also used the AngioJet rheolytic thrombectomy system [105] – with this last device; such "off label" use requires careful attention so as not to entrain air. The volume of dead space in a 0.014" compatible coronary balloon's central lumen is <1 ml, but with potent drugs this volume may be significant and will be infused when the wire is reinserted.

Fischell and colleagues showed the potential of adenosine to reverse no-reflow phenomenon precipitated by angioplasty of coronary bypass vein grafts [106]. They administered high-velocity bolus injections through the guiding catheter, using small (3 ml) syringes to generate high pressure jets of drug. Repeated injections of 18–24 μg adenosine reversed no-reflow in 10 of 11 cases. Compared with drug delivery via a distal coronary catheter, infusion of drugs through the guiding catheter might be hypothesized to be less effective when coronary flow is already severely impaired. If this technique is used, a smaller syringe (which allows higher developed pressure and velocity of drug delivery) may facilitate reaching the distal bed.

When injecting drugs with negative chronotropic (slowing) effects, pacing should be available. Judgment is required to decide the extent of pre-preparation for the potential for bradycardia or asystole; the range of options includes having transvenous pacing equipment at hand, placing electrodes for transcutaneous pacing, gaining venous access, inserting a temporary pacing wire, or teaching the patient how to cough to perform auto-CPR. This last may be a particularly appropriate standby measure for adenosine with its short duration of action.

Finally, as the number and complexity of drugs being used in the catheterization lab increases, care should be taken that agents are clearly labeled to avoid medication administration errors.

Local Drug Delivery to the Arterial Wall

Acute myocardial infarction is initiated by the interaction of local phenomena in the vascular wall with systemic factors. As such, it is intriguing to speculate on the possibility that drug therapy delivered locally to the site of the atherosclerotic/thrombotic event might offer additional benefits beyond the systemic drug therapies that are currently being employed. A variety of catheters have been developed for the purpose of applying drugs to a local segment of the coronary artery. Urokinase (300–500 U) loaded onto a hydrogel-coated balloon, or a control balloon, was used for PCI in patients with acute coronary syndromes. There was no effect on the acute results, but more patients receiving urokinase had ischemic events in follow-up. These results may be attributable to persistent elevation of fibrinopeptide A in the urokinase group but not in the control group [107].

Stents provide a platform for drug delivery, being implanted into direct and permanent contact with the diseased artery, and have the potential to carry significant quantities of therapeutic compounds, either with or without polymeric vehicle coatings. Heparin-coated stents have been associated with excellent clinical results including in AMI trials [108, 109]. Randomized comparisons of heparin-coated with uncoated stents, however, are lacking.

Antiproliferative drug coatings reduce stent restenosis; drug-eluting stents are not specifically indicated for primary PCI in AMI, but have been commonly used. Lemos et al. [110] reported the consecutive treatment of 186 AMI patients with sirolimus-eluting stents (SES), and compared with historical bare metal stent controls. The major difference at 300 day follow up was reduced reintervention in the drug-eluting stent series; there was no increase in adverse events associated with SES in this study.

Chechi et al. [111] randomized 80 patients with AMI to be treated either with bare metal or with paclitaxel-eluting stents (PES). At seven months, the PES group had much lower neointimal volume obstruction in the stented segment; clinical events were not different except for reintervention, which was reduced in the PES group.

Ischemic Preconditioning and Postconditioning

In 1986, Murry et al. published a remarkable study showing that it was possible to render the myocardium myocardium less susceptible to ischemia-induced infarction. They protected hearts against infarction by subjecting them to several brief periods of ischemia prior to the prolonged lethal ischemic insult. This "ischemic preconditioning" (IPC) resulted in infarct sizes that were approximately 25% of those observed in untreated hearts. Preconditioning with brief periods of ischemia protects the myocardium from subsequent ischemic injury, with an early phase of protection elicited within minutes [112] and a delayed phase [113] appearing hours later. In cellular and tissue preparations, as well as in clinical conditions, brief periods of hypoxia and ischemia confer protection against subsequent ischemia and reperfusion injury.

In a subanalysis of the TIMI-4 study, out of 416 AMI patients, the 218 who experienced angina preceding the infarction had smaller infarctions, better left ventricular function, and fewer ventricular arrhythmias; preconditioning was hypothesized to have occurred in humans [114]. Harnessing this phenomenon as a therapy for emergency coronary revascularization procedures would be a breakthrough, particularly if the protective effect could be achieved after the initiation of ischemia. Other initiators of a similar effect include adenosine receptors, α_1-adrenergic receptors, opioid receptors, protein kinase C agonists, and reactive oxygen species [115]. These triggers phosphorylate and open ATP-sensitive potassium (K^+_{ATP}) channels in myocardial mitochondria which seem to mediate the protective effect, and which may further influence the redox state

and redox-sensitive cellular processes [116]. Both nitric oxide [117] and adenosine [118 119] enhance the opening of mitochondrial K^+_{ATP} channels, a recent finding which brings together the concepts of microvascular dilatation and ischemic preconditioning.

Staat et al. tested the hypothesis that "post-conditioning" could be generated in AMI patients by cyclic balloon inflation and deflation [120]. In their study, 30 AMI primary PCI patients were randomized. After direct stenting, the treatment group underwent 4 cycles of 1 minute inflation and 1 minute deflation. The area under the CK curve was reduced 36%, and myocardial blush grade was higher in the patients randomized to post-conditioning.

Contrast Agents

While often not thought of as a drug, radiographic contrast has effects beyond the primary purpose of facilitating coronary imaging. Contrast media are vasodilators [121]. Nonionic contrast can initiate platelet degranulation [122]. In animal models, contrast has protective effects suggesting the induction of ischemic preconditioning [123]. It is controversial whether the selection from among the current generation of contrast media can impact clinical outcomes in the setting of PCI, but there are certainly reasons to wonder. Older contrast media such as diatrizoate (Renograffin, Hypaque) have a high osmolality of approximately 2000 mOsm/kg. These high-osmolar agents are associated with increased rates of hemodynamic and electrophysiologic perturbations as well as clinical complications compared to the low- and isosmolar agents. Modern contrast media can be categorized as nonionic vs. ionic and low-osmolar (600 mOsm/kg) vs. isosmolar (290 mOsm/kg).

From the TIMI 14 trial of tissue plasminogen activator (tPA) or reteplase (rPA) vs. low-dose lytic + abciximab, the angiographic, electrocardiographic, and clinical outcomes were related to the (non-randomized) selection of ionic or non-ionic contrast for the 90 minute angiogram and PCI. While there was no effect of contrast on the rate of TIMI 3 epicardial flow, ionic contrast was associated with a longer duration of ischemia, suggesting microvascular obstruction as a possible mechanism [124].

Patients (n = 856) undergoing high risk PCI in the COURT trial, a multicenter prospective double-blind study, received the isosmolar nonionic dimer iodixanol (Visipaque) vs. the low osmolar ionic agent ioxaglate (Hexabrix) [125]. Baseline characteristics, index presentations, extent of coronary disease, stent implantation (~30%), adjunctive device use, abciximab use, and ACT levels were similar between groups. Approximately half of the patients presented with unstable angina, one-third with acute myocardial infarction, and the remainder with post-infarction angina. The composite in-hospital primary end point (abrupt closure, emergency repeat catheterization, stroke, periprocedural CK > 3 times control, emergency coronary bypass surgery, and cardiac death) was less frequent in those receiving iodixanol compared to those

receiving ioxaglate (5.4% vs. 9.5%, respectively, p = 0.027). There was a trend toward lower total clinical events at 30 days in patients randomized to iodixanol (9.1% vs. 13.2% for ioxaglate, p = 0.07). Interestingly, the use of abciximab eliminated the difference between the two contrast agents.

Angiographic contrast (or the mechanical force of injecting the contrast) opened arteries before intervention in patients already treated with intensive antiplatelet therapy. An angiographic analysis from the TITAN-TIMI 34 study found that in STEMI patients pre-treated with eptifibatide before catheterization, contrast injection itself decreased coronary stenosis, presumably by disaggregating thrombus; in patients randomized to receive eptifibatide only after diagnostic angiography, the effect of contrast was not seen [126].

Conclusions

A major limitation of reperfusion therapy is the consequent impairment of the microvasculature. Defining treatments directed at preserving the microcirculation during reperfusion therapy is therefore an active area of investigation. The outlook does appear optimistic since basic mechanisms are being clarified, and the tools necessary to study microvascular integrity (such as MCE and MRI in addition to the angiographically derived TMPG) have been validated. A number of small studies have revealed promising candidates; however, definitive data from large-scale trials is currently lacking.

At present, optimum management of patients with acute myocardial infarction undergoing percutaneous revascularization must be guided by judgment, with careful attention to good technique, anticoagulation and inhibition of platelet aggregation. For now, prevention and treatment of microvascular and reperfusion complications can begin with consideration of the vasodilator drugs nitroglycerin, adenosine, calcium channel blockers, and nitroprusside. Intracoronary nitroprusside and adenosine, in particular, appear as promising candidates to help the interventionalist achieve the goal of true reperfusion in acute myocardial infarction.

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Chapter 10
Platelet Glycoprotein IIb/IIIa Receptor Blockade in Primary Coronary Intervention

Adnan K. Chhatriwalla and Sorin J. Brener

Rationale for Utilization of Platelet Receptor Blockers in Acute Myocardial Infarction

Platelet Activity in Acute Myocardial Infarction – Thrombus Composition

The acute coronary syndromes, including acute myocardial infarction (AMI), share a common pathophysiologic mechanism: atherosclerotic plaque disruption followed by platelet aggregation and thrombus formation. In addition, inflammation has been linked strongly to plaque vulnerability and may be present not only in the vulnerable atheromatous plaque, but also systemically throughout the vascular tree. Plaque rupture leads to the release of thrombogenic plaque components, including collagen, fibronectin, and von Willebrand factor. These components, together with local high shear stress and increased inflammatory cytokines, lead to platelet adhesion, activation, and aggregation. Platelet aggregation facilitates thrombin generation and conversion of fibrinogen to fibrin. Ultimately, a thrombus composed of platelets and fibrin causes complete occlusion of the coronary artery and results in AMI [1].

While platelet activation occurs via several pathways (Fig. 10.1) [2], aggregation is funneled through one final common pathway: the binding of fibrinogen to the glycoprotein (GP) IIb/IIIa receptor on the platelet surface [3]. In the resting, quiescent state, the GP IIb/IIIa receptor has a configuration that permits only slow ligand binding. With platelet activation, a conformational change in the GP IIb/IIIa integrin complex occurs that facilitates the binding of fibrinogen and the subsequent processes of platelet aggregation and thrombosis [4].

Increased numbers of circulating aggregated platelets and platelet hyperactivity is well described in patients with AMI [5–8]. Given the central role of the

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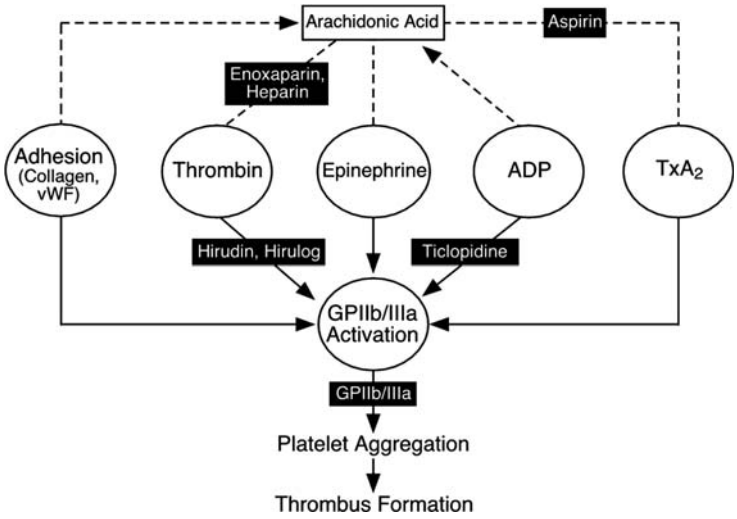

Fig. 10.1 Pathways of platelet activation and inhibition by various therapies. (From Greenbaum AB, Harrington RA, and Ohman EM.: The use of glycoprotein IIb/IIIa inhibition in Acute Myocardial Infarction. In Lincoff AM and Topol EJ (eds): Platelet Glycoprotein IIb/IIIa Inhibitors in Cardiovascular Disease. Totowa, New Jersey, Humana Press. 1999, P. 230.)

platelet in the thrombotic response to plaque rupture, interference with the functioning of platelets has become a prime focus of investigation to improving outcomes of the AMI patient.

Rapid and durable reperfusion of the occluded coronary artery is the immediate aim of treatment in patients with AMI. Fibrinolytic therapy [9] and primary angioplasty [10] are the two main treatment modalities used to achieve reperfusion; this chapter will focus on the latter.

Primary Angioplasty and Platelet Activation

Although a successful strategy, primary angioplasty is still complicated by ischemic events including death, reinfarction, and urgent revascularization procedures in as many as 10–20% of patients by six months [11]. The additional plaque disruption caused by angioplasty and the interaction of the atherosclerotic plaque contents, exposed endothelium, platelets, and coagulation factors lead to thrombosis and compromise arterial patency in up to 10% of patients.

Intravascular ultrasound (IVUS) performed after angiographically successful primary angioplasty can detect predictors of abrupt vessel closure such as the presence of residual disrupted plaque and intraluminal thrombus [12]. Platelets may adhere more avidly to the preexisting coronary thrombus or disrupted vessel surface [13, 14]. Reocclusion can be difficult to treat in the

presence of a large thrombus burden, and repeat angioplasty may be further complicated by abrupt closure where there is persistent thrombus. Effective blockade of platelet aggregation may substantially reduce this risk and eliminate the consequences of plaque-thrombus embolization.

Compounding the platelet hyperactivity of AMI, percutaneous intervention adds insult to the injury and induces additional platelet activation [14]. Treatment with aspirin results in a significant reduction in mortality [15] and reduces the risk of early reinfarction and recurrent ischemia [16]. However, aspirin is a weak antiplatelet agent, [17] inhibiting only the thromboxane A_2-mediated pathway of platelet activation. Platelet activation continues to occur through thromboxane A_2-independent pathways, leading to platelet aggregation and thrombin formation [18]. The glycoprotein (GP) IIb/IIIa receptor antagonists, by blocking the final common pathway responsible for platelet aggregation, might thus be expected to mitigate platelet activation regardless of the activation pathway.

Experimental Evidence – The Concept of Dethrombosis

In early experimental studies in dogs, administration of 7E3 (a monoclonal antibody directed against the platelet GP IIb/IIIa receptor) during coronary angioplasty resulted in less platelet aggregation and vessel closure than aspirin alone [19]. A second canine study demonstrated that after induction of coronary thrombus, 7E3 administration could lead to coronary reperfusion [20]. Furthermore, once flow had begun through the thrombus, reocclusion did not recur. Figure 10.2 is a scanning electron micrograph of the thrombosed

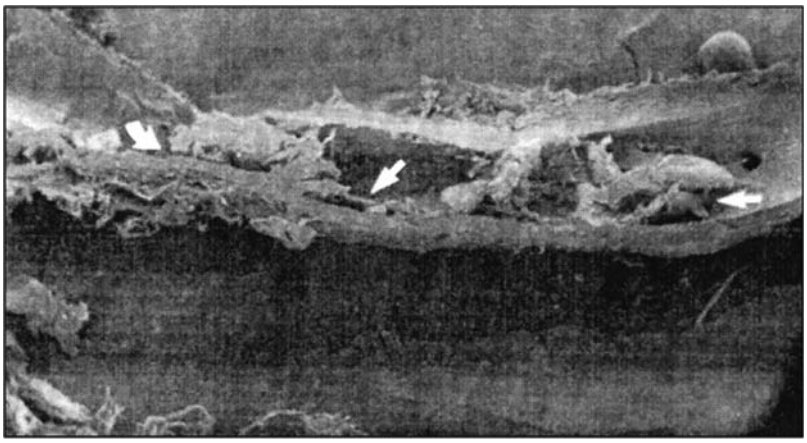

Fig. 10.2 Scanning electron micrograph at low magnification of the thrombosed segment of the left anterior descending coronary artery in a dog treated with 7E3, heparin, and aspirin. Reflow was from right to left. The lumen contains large residual thrombi, penetrated by small channels (*arrows*). The external stenosis is shown at the curved arrow. (Reproduced from ref. [20])

Table 10.1 Infusion protocols and coronary artery reperfusion and reocclusion with rt-PA and 7E3 in a canine model of thrombosis and thrombolysis (Adapted from ref. [21])

	Agents infused			Reperfusion		Reocclusion	
Experimental group	7E3(mg/kg)	rt-PA(mg/kg/bolus)	Number of dogs studied	Number/total	Time(min)(Mean ± SD)	Number/total	Time(min)(Mean + SD)
I	0.8	–	6	2/6	19±37	0/2	–
II	–	0.45	7	5/7	33±15	5/5	11±11
III-A	0.8	0.45	6	6/6	6±3	0/6	–
III-B	0.6	0.45	5	5/5	8±5	1/5	4
III-C	0.4	0.45	4	3/4	9±9	3/3	7±1
III-D	0.2	0.45	3	3/3	35±23	3/3	3±1
III-E	0.1	0.45	4	3/4	34±18	3/3	3±2
IV	0.6	0.225	4	3/4	12±8	1/3	19
Total			39				

segment of a canine left anterior descending artery obtained one hour after 7E3-induced reflow. Channels are seen through a large, segmented residual thrombus. This study demonstrated the ability of 7E3 to restore coronary flow in the absence of exogenous plasminogen activator. 7E3 was further shown to potentiate the effects of thrombolytic therapy in the canine model, as dogs with coronary thrombosis treated with recombinant t-PA bolus followed by 7E3 infusion achieved reperfusion more quickly than dogs treated with t-PA alone. Furthermore, none of the subjects treated with full-dose combination therapy had reocclusion of the coronary vessel during the 100 minute observation period (Table 10.1) [21].

The No-Reflow Phenomenon

The no-reflow phenomenon is a reduction in epicardial coronary artery blood flow without overt mechanical obstruction. First described in animal studies, the phenomenon was observed after release of prolonged coronary artery occlusion causing sustained ischemia, and was attributed to an ischemic, time-dependent injury to the microvasculature [22]. More recently, no-reflow has been observed after a relatively brief ischemic period in the setting of percutaneous coronary intervention [23–25]. It has been reported to occur in between 12% to 48% of cases of primary angioplasty for AMI [23, 26], and has consistently been demonstrated to be a negative prognostic indicator. Patients with no-reflow have larger infarctions, an increased incidence of cardiac rupture and congestive heart failure, and higher mortality [27, 28]. Several structural and functional alterations at the microcirculatory level have been proposed as mechanisms for the no-reflow phenomenon. Animal and postmortem histologic studies have documented varying degrees of small vessel vasospasm, neutrophil plugging, myocyte contracture, interstitial edema, and hemorrhage. Platelets have also been consistently implicated as contributors to the genesis of no-reflow [29, 30]. Obstructive platelet aggregates within myocardial capillaries and platelet degranulation have been experimentally and clinically observed in reperfused ischemic tissue. The substances released from platelet granules contain multiple vasoactive and chemotactic mediators that exacerbate tissue ischemia and increase neutrophil infiltration. Because of the potential role of platelets in inducing the no-reflow state, the GP IIb/IIIa inhibitors may be of benefit in preventing and treating this phenomenon [31].

One of the important observations in primary angioplasty for AMI has been that stenting is associated with a lower rate of final TIMI flow grade 3 than balloon angioplasty [32, 33] This is presumably due to distal embolization of plaque-platelet material during the high pressure inflation associated with stent deployment. Thus, considering the common occurrence of no-reflow after percutaneous intervention in AMI and the role platelets play in this phenomenon, GP IIb/IIIa inhibition in this setting may be of significant benefit.

Observational Data

The EPIC Trial

The Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial was designed to assess the efficacy of the GP IIb/IIIa inhibitor c7E3 (abciximab) in preventing ischemic complications in the high risk percutaneous coronary intervention (PCI) setting. Patients were randomized to receive an abciximab bolus, abciximab bolus plus 12-hour infusion, or placebo before PCI. Of the 2,099 patients enrolled in the trial, only 64 underwent PCI for AMI. In this group, bolus and infusion of abciximab resulted in a reduction in the composite endpoint of death, reinfarction, emergency coronary artery bypass surgery (CABG), or repeat emergency angioplasty by 83% (26.1% vs. 4.5%) at 30 days. This suggested an even greater efficacy of abciximab in AMI than in the other patients in the trial, for whom the reduction in these endpoints was 35% (12.8% vs. 8.3%, respectively) [29, 34]. At six-month follow-up, abciximab bolus plus infusion was associated with a 91% reduction in the composite endpoint of death, MI, or repeat percutaneous or surgical revascularization when compared with placebo (47.8% vs. 4.5%, $P = 0.002$), while the reduction in this composite endpoint was 23% in the whole cohort of patients

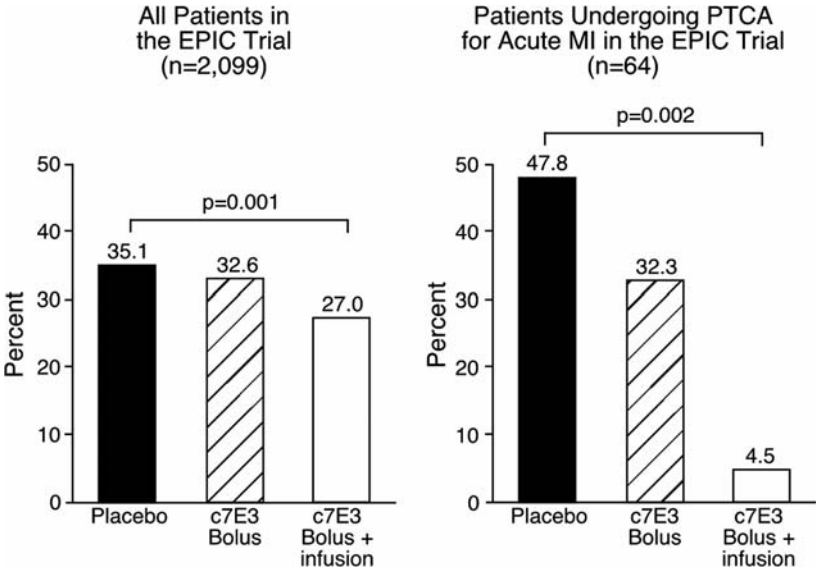

Fig. 10.3 Comparison of six-month composite event rates of death, reinfarction, and emergency revascularization between patients undergoing percutaneous transluminal coronary angioplasty (PTCA) for acute myocardial infarction (AMI) in the Evaluation of c7E3 for Prevention of Ischemic Complications (EPIC) Trial and the overall EPIC trial patient population. (Adapted from ref. [34])

(35.1% vs. 27%, P = 0.001) (Fig. 10.3). There was a clear dose response with abciximab in the reduction of reinfarction (17.4%, 5.6%, and 0%, P = 0.05 for placebo, bolus, and bolus plus infusion respectively), and in the incidence of repeat revascularization (34.8%, 11.6%, and 0%, P = 0.003, respectively) [34]. Major bleeding events were more frequent in patients who received abciximab. The only hemorrhagic stroke and all three major spontaneous hemorrhages occurred in abciximab treated patients. However, 9 of the 13 major bleeding episodes (including the case of intracranial hemorrhage) occurred in rescue PTCA patients, all of whom had received thrombolytic therapy within the previous 12 hours.

IMPACT-II and RESTORE Trials

The Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis-II (IMPACT-II) and the Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) trials evaluated respectively the use of eptifibatide and tirofiban, two specific non-antibody inhibitors of the GP IIb/IIIa, in the PCI indication [35, 36]. In IMPACT-II, 126 of 4010 patients (3%) underwent primary or rescue angioplasty for AMI; in RESTORE, 139 of 2141 (6.4%) underwent primary PTCA for AMI. The use of these two GP IIb/IIIa inhibitors was associated with a trend toward a reduction at 30 days in the primary endpoint of death, myocardial infarction, coronary artery bypass surgery, percutaneous revascularization, or coronary stent implantation for abrupt closure. Prespecified subgroup analyses of patients undergoing percutaneous revascularization for AMI revealed trends similar to those of the entire cohort with respect to reduction in ischemic events in both studies. There was no increase in the risk of major bleeding.

The Mayo Clinic Registry

Data retrospectively analyzed from the Mayo Clinic PTCA registry also suggested improvements in short and intermediate term outcomes with abciximab in primary PTCA. Of 292 patients treated with primary PTCA for AMI, 52 received abciximab (0.25 mg/kg bolus followed by 10 mcg/min infusion over 12 hours) and 240 did not. Abciximab use was associated with a trend towards a decreased in-hospital incidence of death, reinfarction, and CABG (5.8% in the abciximab vs. 13.8% in the no abciximab group, P = 0.17), and a significantly reduced incidence of both death (5.8% vs. 17.1%, P<0.05) and the composite of death, reinfarction, or the need for CABG at one year (5.8 vs. 28.8%, P<0.05) [37].

In summary, the observational and post-hoc data from EPIC, IMPACT-II, RESTORE and the Mayo Clinic Registry suggested a significant benefit from

GP IIb/IIIa receptor inhibition in primary angioplasty for AMI and provided the impetus for the design and conduct of randomized trials of abciximab in primary PTCA.

Data from Randomized Clinical Trials

The GRAPE Trial

In the Glycoprotein Receptor Antagonist Patency Evaluation (GRAPE) pilot study [38] 60 patients less than six hours from onset of AMI and eligible for primary angioplasty were treated in the emergency room with 160 mg oral aspirin and 5000 IU of heparin. All patients were then treated with a bolus of abciximab 0.25 mg/kg and a 12-hour infusion of 10 mcg/min followed by coronary angiography. The endpoint of the study was patency of the infarct-related artery at first contrast injection [39]. In 36 patients (60%), TIMI flow grade 0 or 1 was seen at first contrast injection. TIMI flow grade 3 was seen in 11 patients (18%), and TIMI flow grade 2 or 3 was seen in 24 patients (40%). This study demonstrated the positive effect of abciximab bolus given in the emergency room on early infarct-related artery patency. In patients treated early, the TIMI flow grade was 2 or 3 in 40% at 45 minutes; more typically, no more than 25% of patients are expected to have TIMI grade 2 or 3 flow after 90 minutes with standard heparin and aspirin treatment [39–41].

The RAPPORT Trial

The Reopro in Acute myocardial infarction and Primary PTCA Organization and Randomized Trial (RAPPORT) was the first prospective, randomized study to evaluate GP IIb/IIIa blockade during primary angioplasty for AMI and tested the hypothesis that abciximab administration would reduce both acute events (death, reinfarction, and urgent revascularization), as well as late ischemic complications. Enrollment consisted of 483 patients presenting within 12 hours of AMI onset who were referred for primary angioplasty. Patients were randomized to receive abciximab (241 patients), or placebo (242 patients) before revascularization [42]. Only balloon angioplasty and directional atherectomy were permitted; stent implantation was allowed only for bail-out purposes. The activated clotting time was maintained at >300 seconds during the procedure and early sheath removal was strongly encouraged. The primary efficacy endpoint was the composite of death, reinfarction, and target vessel revascularization (TVR) within six months. The acute phase endpoints were the composite of death, reinfarction, or urgent target vessel revascularization at 7 and 30 days. Safety was assessed as the incidence

of major bleeding (intracerebral hemorrhage, or a >5 g% adjusted decline in hemoglobin). On an intention to treat basis, abciximab administration prior to angioplasty resulted in a significant reduction in ischemic events at 7 and 30 days (9.9% vs. 3.3%, P = 0.003 and 11.2% vs. 5.8%, P = 0.03 respectively). The incidence of death, reinfarction, or urgent target vessel revascularization at six months was also significantly reduced (17.8% vs. 11.6%, P = 0.048) (Fig. 10.4). However, the six-month composite endpoint of death, reinfarction, and any (not just urgent) target lesion revascularization was not statistically different. Abciximab administration prior to PTCA reduced the need for bail-out stenting by 33% (17.4 vs. 11.6%, P = 0.057). Analysis of the data by actual treatment received (study drug and PTCA) revealed an even more pronounced benefit with 73% (2.8% vs. 10.5%) and 62% (4.6% vs. 12.0%) reductions in the 7-day and 30-day composite endpoints, respectively. There was a 49% reduction in the six-month incidence of death, reinfarction, or urgent target vessel revascularization (10.6% vs. 19.9%, P = 0.004) (Table 10.2).

Abciximab-treated patients in RAPPORT had a higher incidence of major bleeding (16.6% vs. 9.5%, P = 0.02), and blood product transfusion (13.7% vs. 7.9%, P = 0.04) than placebo patients. Most of the excess major bleeding was confined to the access site. There were no intracranial hemorrhages in either group. Abciximab resulted in a 27-second prolongation of the median activated clotting time (ACT) compared to placebo (364 vs. 337 seconds, respectively). This prolongation in ACT and the generally high intensity of anticoagulation contributed to the increased bleeding observed in RAPPORT with abciximab, and can be reduced by using less heparin when GP IIb/IIIa inhibitors are used.

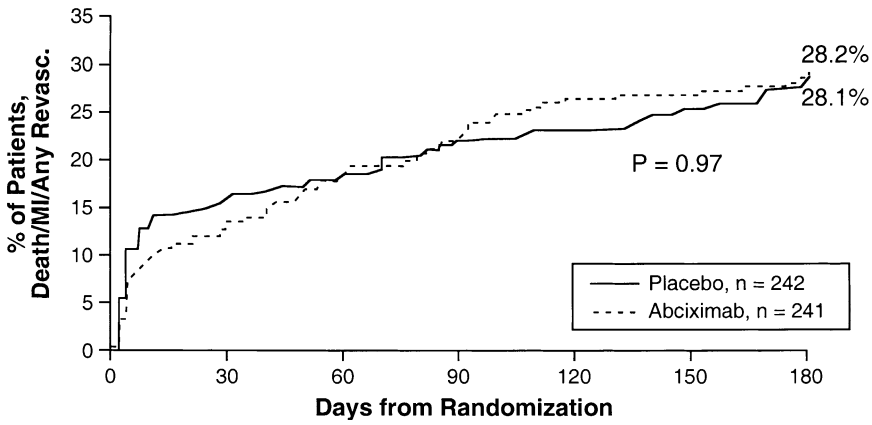

Fig. 10.4 Incidence of death, reinfarction, or urgent TVR at 7 days, 30 days, and six months in the RAPPORT trial. (From ref. [42])

Table 10.2 Outcome in the Treatment Groups by Actual Treatment Analysis in the RAPPORT trial (Adapted from ref. [38])

End point	Placebo, %(n = 191)	Abciximab, %(n = 218)	OR (95% CI)	Log-RankP Value
7 Days				
Death/reinfarction	4.7	1.4	0.28 (0.08, 1.06)	0.047
Urgent TVR	6.3	1.4	0.21 (0.06, 0.75)	0.008
Death/MI/Urgent TVR	10.5	2.8	0.24 (0.10, 0.62)	0.001
30 Days				
Death/reinfarction	5.8	3.2	0.54 (0.21, 1.43)	0.20
Urgent TVR	7.9	1.8	0.22 (0.07, 0.67)	0.004
Death/MI/urgent TVR	12.0	4.6	0.35 (0.16, 0.76)	0.005
6 Months				
Death/reinfarction	12.0	6.9	0.54 (0.27, 1.07)	0.07
Urgent TVR	10.5	3.7	0.33 (0.14, 0.76)	0.006
Death/MI/urgent TVR	19.9	10.6	0.45 (0.26, 0.80)	0.004
Death/MI/ any TVR	31.9	28.0	0.83 (0.54, 1.27)	0.31

The Munich Experience

In a prospective randomized trial, Neumann et al. [43] assigned patients undergoing stenting within 48 hours of AMI symptom onset to receive either standard dose heparin or abciximab plus low-dose heparin. Immediately after the procedure, coronary flow velocities in the stented segment were measured with the Doppler FloWire, basal and peak coronary flow velocity after intracoronary papaverine were determined, and left ventriculography was performed. Fourteen days after the intervention, coronary and left ventricular angiography and flow velocity measurements were repeated.

The study enrolled 200 consecutive patients; 98 were assigned to usual care and 102 to abciximab. At the initial study, both treatment groups had similar basal and peak flow velocities in the recanalized coronary artery. Within 14 days, peak flow velocities increased significantly in both treatment groups and basal flow velocity increased significantly in the abciximab group. The increase in peak flow velocity in patients assigned to abciximab was significantly larger than that in the control group. In both treatment groups coronary flow reserve in the infarct-related artery increased significantly. Improvement of regional LV function within the first two weeks, as assessed by wall motion index or number of chords with hypokinesis, was significantly greater in patients assigned to abciximab than in those not receiving it (Table 10.3). A significant correlation between changes in peak flow velocity and changes in

Table 10.3 Doppler Flow Velocity Measurements and Ejection Fraction in the Munich trial (Adapted from ref. [39])

	Usual Care(n = 72)	Usual Care(n = 72)	P
Immediately after stent placement			
Basal flow velocity, cm/s	23.9±9.3	23.7±11.8	0.89
Peak flow velocity, cm/s	40.8±14.8	40.5±18.7	0.91
Flow velocity reserve	1.79±0.49	1.80±0.53	0.93
Global ejection fraction	55.7±12.4	53.5±13.5	0.30
At 14-day follow-up			
Basal flow velocity, cm/s	27.4±11.6	24.5±8.9	0.085
Peak flow velocity, cm/s	58.9±21.2	50.9±16.9	0.012
Flow velocity reserve	2.29±0.65	2.19±0.67	0.36
Global ejection fraction	62.2±13.2	55.9±12.6	0.003

wall motion index was found, and a similar trend was observed for the relation of changes in peak flow velocity to changes in LV ejection fraction. At the 30-day follow-up, death, MI, or target lesion re-intervention was significantly less frequent in patients in the abciximab group than in the control group (2% vs. 9%, P = 0.031).

This study presented evidence that abciximab has important effects beyond the maintenance of epicardial vessel patency after stent placement in AMI, suggesting that peri-interventional administration of abciximab improves the recovery of coronary microcirculation function and of regional wall motion. This effect could not be attributed to differences in angiographic parameters, hemodynamic characteristics, or epicardial artery patency. Instead, the larger increase in peak flow velocity after administration of abciximab compared to usual care is more likely explained by the prevention of embolization of platelet aggregates to the microvasculature, as well as attenuation of capillary dysfunction following such an event [44, 45]. In addition, blockade of the vitronectin receptor and other integrins, such as MAC-1, might also be responsible. Through the MAC-1 receptor, abciximab may attenuate the interaction of leukocytes with the reperfused microvasculature, [46] effects known to generate procoagulant and cytotoxic inflammatory responses [47, 48].

The ADMIRAL Trial

The Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long term follow-up (ADMIRAL) trial was a placebo-controlled study to evaluate abciximab as an adjunct to primary PTCA and stenting in AMI patients [49]. In this multicenter trial, 300 patients

presenting with AMI were referred for emergency coronary angiography and percutaneous revascularization. They were randomly assigned to receive either abciximab (0.25 mg/kg bolus and 0.125 mcg/kg/min infusion) or placebo before intervention. All patients received heparin, ASA, and ticlopidine. The abciximab treated patients had a significantly higher rate of TIMI-3 flow before PTCA (16.8% vs. 5.4%, p = .01), but not at 24 hours after intervention (95.9% vs. 92.6%, p = .33). The primary combined endpoint of death, reinfarction, and urgent TVR at 30 days was significantly reduced from 14.6% in the placebo group to 6.0% in the abciximab group. Moreover, abciximab improved each of the individual components; there was a 50% lower mortality, 50% lower incidence of reinfarction, and a 60% lower rate of TVR.

Abciximab use was associated with a similar rate of major bleeding as placebo (0.7% vs. 0%, respectively), but an increased incidence of minor bleeding (12.1% vs. 3.3%, respectively p = 0.004). At six-month follow-up, the incidence of death, reinfarction, or urgent TVR was significantly reduced from 15.9% to 7.4% with abciximab treatment (Fig. 10.5). In diabetic patients, the incidence of death, reinfarction, and any revascularization was also reduced from 50.0% to 20.7% (p = 0.02). Impressively, patients who received abciximab early, that is, in the mobile intensive care unit or emergency removed had a substantially lower incidence of the primary endpoint of death, reinfarction or urgent TVR at 30 days (0.12 vs. 0.67) and at six months (0.11 vs. 0.69).

The ADMIRAL trial provided further evidence that abciximab can improve TIMI flow grade and decrease the incidence of death, MI, and urgent TVR. In addition the composite endpoint of death, reinfarction, and any TVR was reduced in diabetic patients, a group at particular risk for restenosis. Furthermore, a trend toward a mortality benefit and a significant decrease in ischemic events has been demonstrated on three year follow-up [50].

The CADILLAC Trial

The Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complication (CADILLAC) Trial compared balloon angioplasty (with or without abciximab) to stenting (with or without abciximab) in patients with AMI [33]. A total of 2082 patients met the clinical and angiographic criteria for enrollment and were randomized to one of four arms: PTCA with abciximab, PTCA without abciximab, stenting with abciximab, or stenting without abciximab. The primary endpoint of the study was the six-month composite of death, MI, stroke, or ischemic TVR. Patients were treated with aspirin, ticlopidine, heparin, and intravenous beta-blockers in the emergency room. Following percutaneous intervention, patients were treated with aspirin, ticlopidine (if stenting was performed), and heparin for 60 hours if abciximab was not used. The incidence of the composite primary endpoint was 20.0% in the PTCA group, 16.5% in the PTCA + abciximab group, 11.5% in the stent group, and 10.2% in the stent + abciximab group ($p<0.001$). Stenting with abciximab resulted in a high rate of TIMI flow grade 3 (96.7%), but no significant

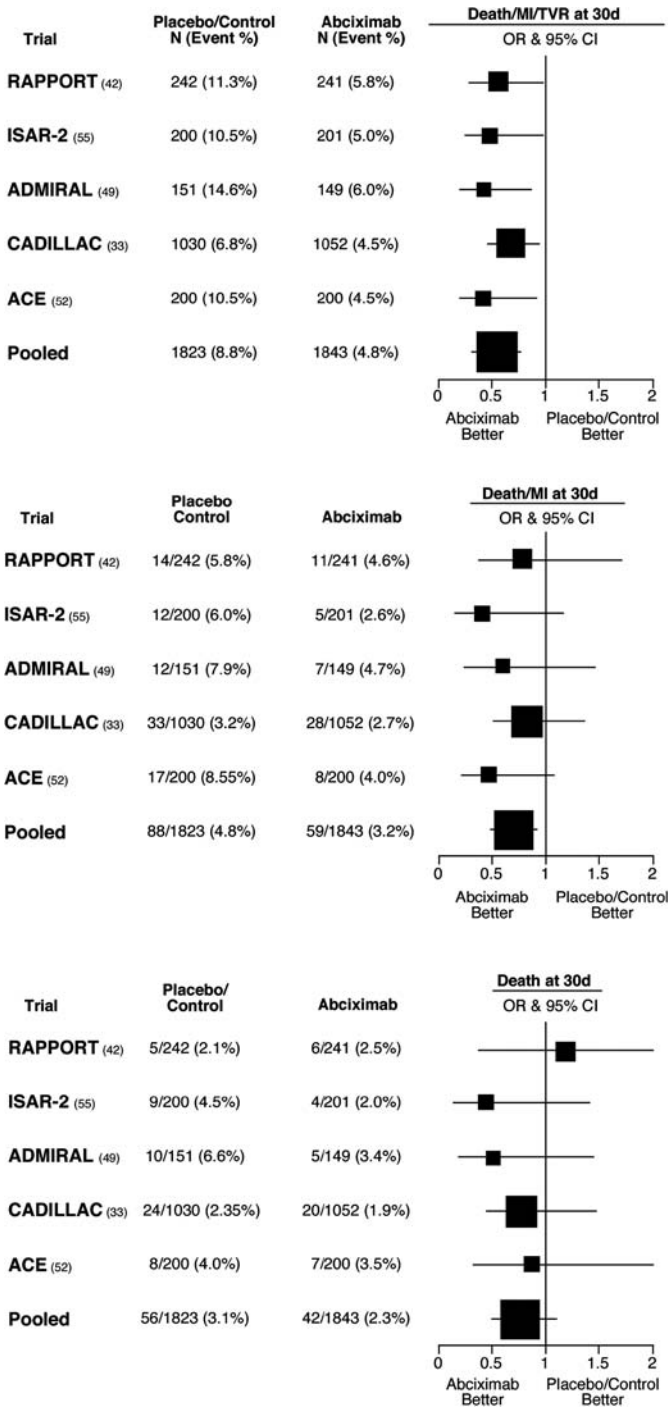

Fig. 10.5 Pooled analysis of the incidence of death, MI, or TVR at 30 days from five randomized trials. (From ref. [54])

difference in flow was observed between the groups. The incidence of major in-hospital adverse events was low. These data clearly suggest that abciximab obviates some of the flow abnormalities related to stenting attributable to plaque-platelet embolization.

The INAMI Study

The Integrilin in Acute Myocardial Infarction (INAMI) study was a small pilot study of 55 consecutive patients with AMI treated with eptifibatide (two boluses of 180 mcg/kg 10 minutes apart followed by a 24-hour infusion of 2 mcg/kg/hr) in addition to aspirin and clopidogrel prior to primary PCI [51]. The primary endpoint was the composite of death, reinfarction or urgent TVR within 30 days. Secondary endpoints included TIMI flow grade and TIMI myocardial perfusion grade. Although grade 3 TIMI flow and grade 3 TIMI myocardial perfusion were observed in 93% and 86% of patients, respectively, this study was halted prematurely due to an unacceptably high rate of subacute stent thrombosis (9%) within 3–5 days of the procedure. Furthermore, follow-up angiography demonstrated a decrease in TIMI grade 3 flow rates and TIMI grade 3 myocardial perfusion rates (86% and 78% respectively) prior to hospital discharge. The incidence of the combined primary endpoint was 12.7% at 30 days, with all of the patients with subacute stent thrombosis requiring urgent TVR. These results did not compare favorably to the data demonstrating the benefit of abciximab in primary PCI.

The ACE Trial

The Abciximab and Carbostent Evaluation (ACE) Trial was an unblinded, randomized, controlled trial comparing abciximab to placebo in patients undergoing primary PCI for AMI [52]. A total of 400 patients were enrolled and randomized to abciximab vs. placebo. The primary composite endpoint included death, reinfarction, TVR and stroke at one month. All patients were treated with aspirin prior to catheterization. Patients randomized to the abciximab group received the drug immediately before the procedure (0.25 mg/kg bolus and 0.125 mcg/kg/min infusion for 12 hours). Heparin was administered as a bolus of 70 U/kg with additional boluses given to maintain the ACT at 200–300 seconds. In the abciximab group, heparin was continued for 12 hours, while in the placebo group, heparin was continued for two days. All patients were treated with aspirin and either clopidogrel or ticlopidine following the procedure. Stenting was successful in 99% of patients and the incidence of the composite primary endpoint was lower in the abciximab arm (4.5% vs. 10.5%, $p = 0.023$). The incidence of each of the components of the primary endpoint was lower in the

abciximab group. Furthermore, the incidence of death and reinfarction were lower in the abciximab groups at six months and at one year [52, 53].

Topol Pooled Analysis

A pooled analysis of five clinical trials involving over 3,600 patients demonstrated the benefit of abciximab therapy on rates of death, MI and TVR in patients undergoing primary PCI (Fig. 10.5) [54]. The RAPPORT, [42] ISAR-2, [55] ADMIRAL, [49] CADILLAC [33], and ACE [52] trials were included in the pooled analysis. These data demonstrated a 26% reduction in death, a 34% reduction in death or reinfarction, and a 46% reduction in death, reinfarction or TVR with abciximab use. These combined data establish the basis for the indication of abciximab treatment in patients undergoing primary coronary intervention with or without stent placement for AMI. Furthermore, the authors observed that early administration of abciximab was associated with improved angiographic outcomes in the ADMIRAL trial and that similar findings had been demonstrated with early tirofiban administration, suggesting a direction for further clinical investigation.

The (TITAN)-TIMI 34 Trial

The Time to Integrilin Therapy in Acute Myocardial Infarction [(TITAN)-TIMI 34] trial was a randomized, open-label multicenter trial to evaluate the efficacy of early versus late administration of eptifibatide on angiographic parameters in patients undergoing primary PCI for AMI [56]. The primary endpoint was the corrected TIMI frame count on diagnostic angiography, and the secondary endpoint was the incidence of TIMI flow grade 3. The TITAN-TIMI 34 trial recruited 343 patients, with 180 receiving eptifibatide early, in the emergency department, and 163 patients receiving eptifibatide following diagnostic angiography. All patients were treated with aspirin (160–325 mg) and unfractionated heparin (60 U/kg bolus and 7 U/kg infusion). Eptifibatide was administered as a 180 mcg/kg bolus followed by a 2.0 mcg/kg infusion, with a second 180 mcg/kg bolus administered 10 minutes after the first. The median time from eptifibatide bolus to first coronary angiogram was 30.5 minutes in the early administration group. Median time from first coronary angiogram to eptifibatide administration was 5 minutes in the late administration group. Pre-PCI corrected TIMI frame counts were significantly lower in the early administration group (77.5 ± 32.2 vs. 84.3 ± 30.7, $p = .049$), and the incidence of TIMI flow grade 3 was higher (24.0% vs. 19.0%, p = NS), indicating improved coronary flow in the early administration group. The incidence of death, reinfarction and rehospitalization for ACS were low at 30 days, and did not differ between groups.

Montalescot Meta-Analysis

In a meta-analysis evaluating early vs. late administration of GP IIb/IIIa inhibitors in patients undergoing primary PCI for AMI, Montalescot, et al. reported that early administration appeared to improve coronary patency [57]. The On-TIME, [58] TIGER-PA, [59] Cutlip et al., [60] Zorman et al., [61] REOMOBILE [62] and Early ReoPro administration in myocardial infarction (ERAMI) [63] trials were included in this analysis, which found that early GP IIb/IIIa blockade improved the incidence of TIMI grade 2 or 3 flow at the time of diagnostic coronary angiography (OR 1.69, 95% CI 1.28-2.22, p<.001). Importantly, early GP IIb/IIIa inhibitor administration improved the incidence of TIMI grade 3 flow at the time of diagnostic coronary angiography (OR 1.85, 95% CI 1.26-2.71, p<.001, Fig. 10.6). While no mortality benefit was observed in any of the six trials, the pooled data did demonstrate a trend towards a mortality benefit with early GP IIb/IIIa inhibitor administration (3.4% vs. 4.7%, p = NS, Fig. 10.7). Favorable trends were also demonstrated with regard to a composite ischemic endpoint (OR 0.78, p = .32) and myocardial infarction (OR 0.73, p = .64). These data, in combination with the (TITAN)-TIMI 34 data, [56] demonstrate the efficacy of GP IIb/IIIa inhibitors in improving coronary artery patency when administered early, and highlight the potential benefit in clinical outcomes from strategies of early administration.

De Luca Meta-Analysis

In a meta-analysis evaluating abciximab therapy in patients with AMI, De Luca, et al. reported that the mortality benefit observed with adjunctive abciximab therapy was present only in patients treated with primary PCI, and not in patients treated with fibrinolytic therapy [64]. Eleven randomized trial were

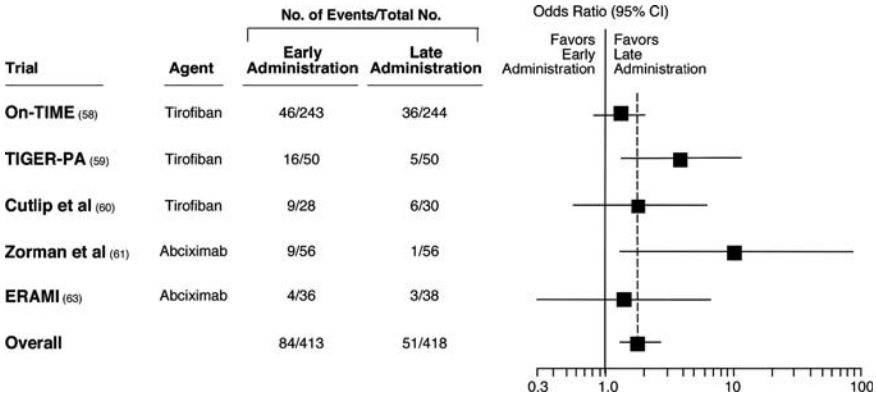

Fig. 10.6 Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow with early vs. late administration of Glycoprotein IIb/IIIa inhibitors (From ref. [57])

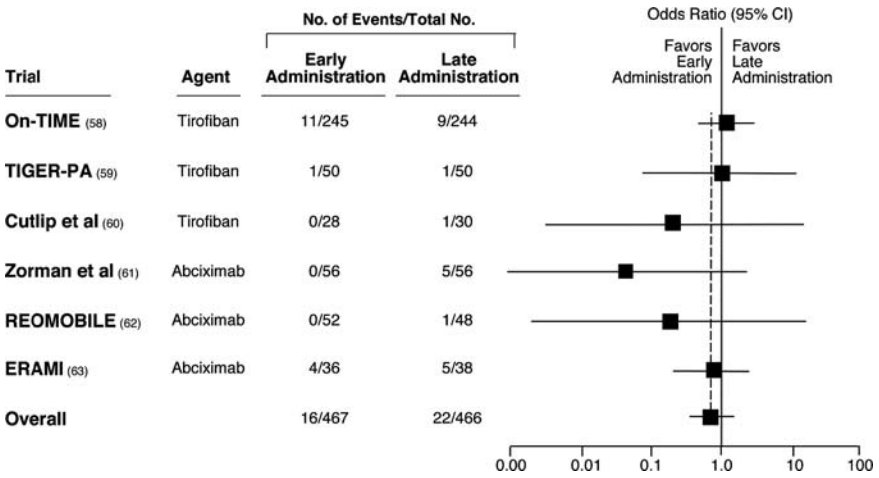

Fig. 10.7 Mortality with early vs. late administration of Glycoprotein IIb/IIIa inhibitors (From ref. [57])

included in this analysis, which demonstrated a reduction in 30-day mortality with abciximab therapy in patients undergoing primary PCI (OR 0.68, $p = .047$), but not in patients undergoing fibrinolytic therapy (OR 1.0, $p = 0.95$). Long-term (6–12 month) mortality was similarly reduced in abciximab-treated patients undergoing PCI (OR .69, $p = .01$), but not in patients undergoing fibrinolytic therapy (OR 1.04, $p = 0.41$). Furthermore, while abciximab use was associated with a significantly higher incidence of bleeding complications in patients undergoing fibrinolysis, (OR 1.66, $p < .001$), this was not observed in patients undergoing primary PCI (OR 1.16, $p = .36$).

Glycoprotein IIb/IIIa Inhibitors and Reduced dose Fibrinolytics

Studies evaluating the administration of GP IIb/IIIa inhibitors and reduced dose thrombolytic therapy for AMI have been conducted in the hopes of demonstrating improvements in rates of coronary patency while reducing the incidence of hemorrhagic complications associated with full-dose fibrinolytic therapy. Several small studies reported favorable outcomes for such a strategy, [65] leading to two large randomized trials, GUSTO V and ASSENT-3. In GUSTO V, 16,588 patients were randomized to abciximab plus half-dose reteplase or full-dose reteplase. No mortality benefit was seen with combination therapy (5.6% vs. 5.9%), and only small reductions in investigator-reported recurrent non-fatal MI (2.3% vs. 3.5%) and recurrent ischemia (11.3% vs. 12.8%) were observed [66]. Additionally, a significant increase in intracranial hemorrhage was present with combination therapy in patients over the age of 75. In ASSENT-3, 6,095 patients with AMI were randomized to

full-dose tenecteplase + enoxaparin, half-dose tenecteplase + abciximab + unfractionated heparin, or full-dose tenecteplase + unfractionated heparin. Again, no mortality benefit was present with combination therapy (6.6% vs. 6.0%), and the incidence of bleeding complications was increased [67]. The recently completed Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) trial [68] randomized patients with AMI to either abciximab with reduced-dose reteplase upon diagnosis, abciximab alone upon diagnosis, or abciximab after angiography and prior to PCI and showed similar results. Given the present evidence, combination therapy with GP IIb/IIIa inhibitors and reduced dose fibrinolytics in AMI thus cannot be recommended.

Future Directions

Upstream GP IIb/IIIa Inhibitor Administration and Facilitated PCI

The concept of facilitated PCI refers to a strategy aimed at achieving partial coronary reperfusion through pharmacologic means, followed by transfer to a center specializing in coronary intervention, when such transfer is likely to result in a substantial delay in treatment. Nearly all of the benefit seen with abciximab administration in the ADMIRAL trial was confined to the subgroup of patients who received abciximab early, in the emergency room or in the pre-hospital setting [49]. The (TITAN)-TIMI 34 trial [56] and the Montalescot meta-analysis [57] have demonstrated the efficacy of early GP IIb/IIIa inhibitor administration in improving coronary artery patency, and highlight the potential benefit in clinical outcomes from strategies of early administration of these agents. Additional data is needed to establish whether even earlier administration of GP IIb/IIIa inhibitor therapy, for example, "in the field" or in-ambulance, can improve coronary artery patency and/or clinical outcomes even further. The Bochum Feasibility Study [69] was an open-label pilot study to assess the practical application and safety of eptifibatide administered in the pre-hospital setting to patients with symptoms typical of acute coronary syndrome (ACS) or AMI. The investigators included 356 patients in the analysis, and no significant difference was observed in a primary composite end-point of death, reinfarction, repeat TVR, or major bleeding. The authors concluded that administration of eptifibatide in the pre-hospital setting was feasible and safe in patients with typical symptoms; however, a large-scale randomized study is needed to evaluate the potential benefit of such a strategy in reducing clinical events. The strategy of facilitated PCI is discussed more extensively in the following chapter.

Intracoronary GP IIb/IIIa Inhibitor Administration

Although early GP IIb/IIIa blockade has been shown to improve epicardial flow in the setting of AMI, its effect on the incidence of "no-reflow" following PCI is

not clear. It has been hypothesized that intracoronary administration of these agents may provide incremental benefit in reducing the incidence of "no-reflow," by disaggregating thrombus and decreasing distal embolization [70]. The safety of intracoronary administration of abciximab and eptifibatide has been demonstrated in several studies, and data from experimental models have demonstrated a dose-dependent improvement in thrombus dissolution with these agents [70, 71]. Two retrospective studies have reported improved outcomes with regard to death, myocardial infarction, and major adverse cardiovascular events in patient treated with intracoronary rather than IV abciximab [72, 73]. There may be a benefit to achieving high local levels of GP IIb/IIIa blockade at the PCI site, especially in patients at high-risk for the "no-reflow" phenomenon; however, further data are needed from randomized prospective studies before recommendations regarding the intracoronary administration of these agents can be made.

Supplementary Recommendations

Heparin Dosing

A low-dose, weight-adjusted heparin regimen, given as an initial bolus of 50–70 U per kilogram (maximum 7,000 U), adjusted to achieve and maintain an ACT greater than 200 seconds, is recommended when abciximab therapy is planned [74]. Abciximab therapy has been frequently used as a rescue treatment, albeit without clearly demonstrated benefit [75]. In this situation, heparin is typically given initially in a higher dose to achieve an ACT >300 seconds. When abciximab is added during the procedure, higher than desired levels of ACT may be reached; the addition of abciximab elevates the ACT by approximately 30–40 seconds. This excessive anticoagulation leads to prolongation of sheath dwell time and a doubling of major bleeding events [76]. An initial heparin dose aimed at maintaining an ACT in the 250–300 sec range should be a good strategy if abciximab therapy is not intended and would allow administration of abciximab on a rescue basis, thus avoiding very high levels of anticoagulation. If the ACT is already very high (>350 seconds) before bail-out abciximab administration, a small dose of protamine (5–10 mg) may lower it sufficiently to prevent major bleeding complications [77]. There are no data to suggest that heparin after a successful intervention adds benefit beyond administration of abciximab. Heparin dosing with eptifibatide and tirofiban treatment has not been thoroughly investigated, but the small molecules tend to increase the ACT to a lesser degree than abciximab.

Vasodilator Therapy

There are recent data indicating that the use of some vasodilators can attenuate microvascular dysfunction and reverse the no-reflow state after percutaneous

coronary interventions. Taniyama et al. [78] documented that intracoronary verapamil given after PTCA for AMI augmented myocardial blood flow as demonstrated by myocardial contrast echocardiography, and improved TIMI flow grade by angiography. Fischell et al. [79] demonstrated the ability of adenosine to reverse slow-flow complicating stenting of diseased vein grafts. Nicorandil acts as a combination nitric oxide donor and potassium channel opener, and has been demonstrated to improve TIMI flow, enhance ST-segment resolution, and even improve long-term clinical outcomes when administered adjunctively during primary PCI [80]. Although the data are limited, it is also the authors' experience that the use of such vasodilators reverses and may prevent many instances of this phenomenon.

Sheath Removal

Vascular access sheaths should be removed as soon as possible post-procedure, during abciximab infusion, once the activated partial thromboplastin time is less than 50 seconds, or the activated clotting time is less than 175 seconds. In two large randomized trials of planned abciximab use, this strategy has been shown to be safe [74, 81]. After sheath removal, pressure should be applied for at least 30 minutes followed by bed rest for 6–8 hours. Recently, femoral artery closure devices have been used with increased frequency; however, it remains unclear whether closure devices reduce complication rates [82]. The advantage of early ambulation [83] may be less critical in patients with AMI, and may not significantly alter the duration of hospitalization. However, these devices may decrease patient discomfort [84] and lessen the burden for the medical staff.

Summary and Conclusions

The available data on the use of GP IIb/IIIa inhibition in primary angioplasty for AMI provide robust evidence that this strategy is beneficial in this high risk group of patients. When treatment is given to patients presenting with AMI in the emergency room, it increases infarct-related artery patency by the time coronary angiography and PTCA are performed. While these agents do not lyse fibrin, they assist the endogenous fibrinolytic system in dissolving the thrombus, can promote dethrombosis, and by inhibiting platelet aggregation, diminish further accumulation of thrombus and prevent reocclusion. GP IIb/IIIa inhibition yields marked and consistent benefits in the prevention of major ischemic events. This benefit is particularly pronounced with respect to reinfarction and need for urgent revascularization. The reduction in urgent revascularization is especially important in patients undergoing primary angioplasty as it is a surrogate endpoint for reinfarction; repeat angiography is generally reserved for severe recurrent ischemia. The Munich trial presented evidence that

this treatment has positive effects on the microvasculature, which translates into an increase in flow velocity in the infarct-related artery and improvement in left ventricular function. These effects are probably related to the prevention of platelet embolization and adhesion to the injured endothelium. These same mechanisms may also explain the increase in TIMI flow grade 3 and the beneficial effects on the no-reflow phenomenon with IIb/IIIa blockade.

From the present data, it appears that all patients undergoing primary PTCA should receive GP IIb/IIIa inhibitor therapy unless a specific contraindication exists. Abciximab was the drug used in most of these trials and should be considered the drug of choice in this setting. The 2004 ACC/AHA guidelines for management of STEMI offer a class IIa recommendation that it is reasonable to administer abciximab as early as possible in patients undergoing primary PCI; however, consideration of eptifibatide or tirofiban therapy is only a class IIb recommendation due to less robust data [85]. As highlighted in the INAMI study, outcomes with eptifibatide use in primary PCI have not compared favorably to those observed with abciximab use, and in the 2005 ACC/AHA/SCAI PCI guidelines no recommendation for eptifibatide or tirofiban is given in the setting of AMI [86].

GP IIb/IIIa blockers are relatively expensive and financial concerns have been raised about using them routinely in primary angioplasty. Abciximab costs $\sim$ \$1,400 per patient (bolus plus 12-hour infusion) and eptifibatide costs $\sim$ \$ 800 per day. It is important to recognize, however, that the reduction in ischemic complications by the use of GP IIb/IIIa blockers may actually translate into cost savings. In an economic assessment of GP IIb/IIIa inhibitor use for the prevention of ischemic complications in high-risk coronary angioplasty in the EPIC trial, Mark et al. [87] demonstrated that abciximab use resulted in a cost savings of \$ 622 per patient during initial hospitalization from reduced acute ischemic events and \$ 1270 during the six-month follow-up by reducing repeat hospitalization and revascularization. In this trial, however, the initial hospitalization savings were offset by a rise of \$ 521 in costs from an increase in bleeding episodes. Thus, considering these savings and the ability to reduce bleeding episodes by using low-dose heparin, the net cost of using these drugs may become much lower than their actual prices, and in fact their use might even be cost-saving.

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Chapter 11
Cell Therapy in Acute Myocardial Infarction

Geraldo A. Ramos, Joshua M. Hare, and Alan W. Heldman

Introduction

The field of myocardial regeneration has revolutionized our understanding of the heart. Old principles – that the heart is a terminally differentiated organ; that damage to the myocardium (most commonly by infarction) was irreversible; that healing consisted solely of scarring, fibrosis, and remodeling of the organ – have been overturned. The experimental finding that certain conditions and cell applications could contribute to myocardial regeneration has led to expectation of new therapies. This chapter briefly reviews the rapidly evolving field of cell therapy for acute myocardial infarction (AMI).

Stem cells, or progenitor cells, have two fundamental characteristics: they are self-replicating, and in a specific environment (or "niche") they differentiate into tissue-specific cell types. Stem cells have been found in the blood, bone marrow, and in adult solid organs. A great number of laboratories have developed techniques for enriching, isolating, or preparing stem cells for therapeutic purposes; preclinical and clinical trials of a variety of cell types for myocardial regeneration have already been conducted.

Among the cell types studied for cardiac myocyte therapy are mixed cell populations of whole bone marrow; specific bone marrow constituents, including mesenchymal stem cells; peripheral blood-derived cells, including those in umbilical cord blood; skeletal myoblasts; and stem cells from the adult heart itself. The finding that the heart contains cells capable of self-replication and differentiation indicates that the classical belief in a terminally differentiated heart may have been mistaken, and identifies cardiac stem cells as a potential therapy. Furthermore, activation of endogenous cardiac stem cells may be a therapeutic target. The young field of cell therapy for cardiac regeneration has revolutionized biological paradigms and appears to have

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enormous potential for treating patients with AMI, and perhaps with other related conditions including heart failure, refractory ischemic heart disease, and arrhythmias.

Preclinical Science

Orlic and colleagues reported in 2001 that when cells derived from bone marrow bearing specific surface markers of "stem cell-ness" (c-kit + /lin-) were injected into infarcted myocardium, tissue regeneration occurred [1]. Similar regeneration could be achieved by administration of cytokines that mobilized stem cells from the bone marrow [2], suggesting that bone marrow derived cells migrated to the site of injury and promoted myocardial repair [3]. The timing of cell delivery was reported to affect the results, with reduced effect when stem cells were delivered early after myocardial infarction [4].

A related critical finding for the field was that cells found in the heart itself were associated with regenerative capacity. Myocardial tissue specimens from patients dying after AMI contained a cell-cycle marker, Ki-67, indicating that cells were dividing around the site of injury [5]. The finding of chimerism, Y-chromosomes in the cells of the heart after a female donor heart was transplanted into a male recipient, further indicated that the heart's cellular makeup was not fixed but rather participated in turnover involving migration of stem cells from the recipient into the transplanted heart [6].

A variety of cell types proved to have regenerative effects in small animal models of MI; with remarkable haste, clinical trials ensued, far in advance of a complete understanding of the mechanisms of benefit. The remainder of this chapter comprises a brief review of significant human trials.

Clinical Trials, Cell Types, and Delivery Strategies

Autologous Whole Bone Marrow by Intracoronary Infusion

Within 12 months of Orlic's publication, a clinical trial was reported. Strauer and colleagues treated successfully reperfused AMI patients seven days after MI; autologous whole bone marrow (AWBM) was aspirated from the iliac crest, and its mononuclear fraction was isolated by Ficoll density separation and expanded in culture. Washed and filtered cellular material was then infused into the infarct-related artery via the center lumen of a balloon catheter. In this pilot study, 10 patients received autologous intracoronary mononuclear bone marrow cells, and 10 patients served as controls; three month ventriculography showed smaller infarcts in the treated group and, more importantly, this trial was the first important demonstration of the safety and feasibility of coronary cell infusion [7].

Further clinical trials of AWBM therapy have included over 400 patients, with attention to safety effects including ventricular arrhythmias and re-infarction. The bone marrow transfer to enhance ST elevation infarct regeneration (BOOST) trial was a randomized study of 60 patients receiving AWBM or placebo following acute MI [8]. Subjects underwent Holter monitoring and electrophysiologic studies along with coronary angiography at six months to evaluate effects on stent restenosis. No differences were detected between control and AWBM groups with respect to either ventricular arrhythmias or infarct vessel patency.

The efficacy of AWBM delivered intracoronary after AMI remains uncertain. Three trials reported in a single issue of the New England Journal of Medicine (September 21, 2006) showed discrepant results. The largest of these, REPAIR-AMI [9], was a multi-center randomized trial, enrolling 204 patients who had a recent ST elevation MI (STEMI) who were successfully reperfused with stenting and had residual left ventricular dysfunction (defined as a left ventricular ejection fraction (LVEF) ≤ 0.45). Bone marrow aspiration was done in all patients 3 to 6 days after reperfusion, following which patients were randomized to receive placebo (medium alone) or infusion of a cell suspension. Bone marrow progenitor cells were enriched from 50 ml of aspirate by gradient centrifugation and then were resuspended in medium. Left ventriculography was done before cell infusion and four months later, and a mixed population of cells (numbering $236 \pm 174 \times 10^6$ cells) was infused into the infarct related artery through an over-the-wire balloon catheter.

Between the baseline and 4-month studies, the mean LVEF in both REPAIR-AMI groups improved, but the absolute increase in LVEF was greater in the cell-treated group. The benefit of cell therapy was confined to patients with a lower baseline LVEF. The benefit of cell therapy was also confined to patients who received cell therapy more than 4 days after reperfusion. Composite endpoints were lower in the cell-treated group, including death or MI, death, MI or revascularization, and death, MI or rehospitalization for heart failure.

In contrast, another study published in the same issue used single photon emission computed tomography (SPECT), echocardiography, and magnetic resonance imaging (MRI) to assess LVEF, end-diastolic volume, and infarct size [10]. Only anterior infarctions were studied, and density-gradient enriched mononuclear cells (mean number of cells 68×10^6) from autologous bone marrow were infused into the coronary artery in 50 patients, 4 to 8 days after infarct vessel stenting; the control group did not undergo bone marrow aspiration nor sham infusion. No significant differences were detected between the groups for change in LV function or infarct size.

The BOOST trial [11] showed that LVEF improved six months following AWBM cell infusion. However, after 18 months, improvement in the control group [12] narrowed the difference.

The selection of intracoronary infusion as the delivery strategy is supported by the ability to target the risk region of an infarct-related artery, but is also based in part upon its relative simplicity. Transendocardial injection is a more complex technique that may improve the efficiency of delivery and allows delivery to non-revascularizable territories. Perin and colleagues treated

21 patients (14 with cell therapy, followed sequentially by seven controls) with severe heart failure and no revascularization option with endocardial injection of AWBM cells, using the NOGA^{TM} electromechanical mapping system to guide and direct injections into ischemic, viable territories [13]. Fifteen injections of 0.2 cc each were given, totaling $25.5 \pm 6.3 \times 10^6$ cells/patient. Global and regional LV function improved in the treated group, with improved exercise capacity and reduced SPECT ischemia at six and 12 months [14].

Discrepant results among different trials may have resulted from variations in cell preparation, timing, and delivery methods. Mechanistic explanations for efficacy (or the lack of efficacy) remain debated, but include effects of cells on angiogenesis or on microvascular function [15], on cardiac myocytes, or upon the forming scar [16]. The hypothesis that these cells would simply become cardiac myocytes in the heart's niche seems probably to have been overly optimistic and simplistic [17, 18].

Circulating Progenitor Cells

The transplantation of progenitor cells and regeneration enhancement (TOPCARE) investigators compared AWBM with circulating progenitor cell (CPC) therapy [19]. Circulating mononuclear cells were isolated from venous blood and expanded via in vitro culture. These cells, or AWBM cells, were delivered by intracoronary infusion 4.3 days following infarct vessel reperfusion. Both groups had improved LV function at 4 months and one year follow up [20]. These investigators subsequently compared AWBM vs. CPC infarct-related intracoronary infusion in patients >3 months after MI. In this study, the effects on LV function were significantly greater after AWBM cell treatment than after CPC cell infusion [21].

In a different strategy, the intracoronary infusion of CPCs after recanalization and stenting of coronary chronic total occlusion (CTO) lesions was tested in a randomized blinded study [22]. Following successful CTO angioplasty and stenting, granulocyte colony stimulating factor (G-CSF) was administered to increase the circulating proportion of progenitor cells. After enrichment and culture, CPC cells ($69 \pm 14 \times 10^6$) were infused. After three months, treatment was associated with increased coronary flow reserve (CFR), reduced MRI-assessed infarct size and increased LVEF. The mechanism, however, remains unclear; while endothelial progenitor cells are found in the circulation and in the bone marrow, whether the effect of CPCs is primarily endothelial/vascular or upon the myocardium remains undetermined.

Mesenchymal Stem Cells

Mesenchymal stem cells (MSC) are bone marrow-derived cells with the potential to differentiate into various cell lines depending upon environmental cues:

bone and cartilage [23]; fat, tendon, and muscle [24]; and cardiomyocytes [25]. MSCs are rare, representing only approximately 0.01% of the bone marrow mononuclear cell fraction, but have attractive features for therapy, including the ability to expand many log-fold in vitro; MSC cells also possess unique immune characteristics [26 27] that allow their use as allogeneic graft material.

Probably because they are larger than other cell types studied, intracoronary infusion of MSCs seems problematic. We have noted severe no-reflow in a porcine model with intracoronary MSC infusion, and Vulliet and colleagues found micro infarctions in a canine preparation after coronary infusion [28]. Instead, our laboratory has developed techniques for direct myocardial injection for MSC delivery. In pigs instrumented to allow detailed assessment of myocardial performance, we gave 200×10^6 allogeneic MSCs or placebo by endocardial injection three days following LAD infarction [29]. MSC treatment was associated with improved systolic and diastolic function, and infarct size was significantly reduced. Despite the allogeneic graft without immunosuppression treatment, MSC did not cause inflammatory or rejection responses. Fluoroscopic guidance of endocardial injection catheters is possible with a high degree of spatial accuracy and safety [30], and both the Biocardia system (a helical screw-in needle) and the Boston Scientific Stiletto system have been successfully used in this way.

Delivery strategies for MSC trials have also varied. Intracoronary, endocardial, and intravenous approaches have been proposed [31]. In small pilot studies in humans, intracoronary MSC infusion has been better tolerated than the large animal models might have suggested [32, 33]. In the acute infarct setting, myocardial factors may favor trafficking of cells to the infarct zone, so that intravenous delivery also may be possible, despite preclinical evidence for some filtration by the pulmonary circulation [34, 35].

A phase I, placebo-controlled, double-blind trial sponsored by Osiris Therapeutics tested the intravenous administration of allogeneic MSCs in 53 patients less than 10 days after a first MI [36]. A range of cell doses proved safe; more intriguing was that the cell-treated group experienced reduction in the rate of arrhythmic events (9% vs. 37%, $p = 0.025$), improved pulmonary function (forced expiratory volume (FEV1) % predicted increased 17 percent vs. 6 percent, $p < 0.05$), and improved quality of life. In patients with anterior infarctions, the LVEF improved significantly compared to the placebo group.

Skeletal Myoblasts

Skeletal myoblasts (SK) are found on the basal membrane of striated skeletal muscle, and can also expand in vitro. These cells appear to have the potential for myocardial repair [37] and have been subjected to early clinical testing [38]. Ten patients with MI undergoing coronary bypass grafting (CABG) were treated with intramyocardial injection of 871×10^6 cells at the time of surgery [39]. However,

four patients developed episodes of sustained ventricular tachycardia. In another small and non-randomized study, 30 patients with an ischemic cardiomyopathy received autologous skeletal myoblast injection at the time of CABG or LV assist device (LVAD) implantation [40], and experienced improved contractility in the infarct segments. A novel percutaneous delivery approach via the coronary venous route was used for SK implantation in a series of 9 post-MI patients [41]. Safety concerns related to arrhythmogenicity of SK cells have been further pointed out by comparison with MSCs in a rat model, where SK cells increased arrhythmia inducibility, while MSCs reduced it [42].

Cardiac Stem Cells

Cardiac stem cells have been identified within the heart itself, and are capable of self-replication, differentiation into cardiac myocytes, and post MI myocardial regeneration [43, 44]. Myocardial stem cells have been identified both by antigen panning and by culture techniques. Messina and colleagues cultured myocardial tissue in vitro and observed the growth of self adherent colonies named cardiospheres [45]; under certain conditions, these spheres even exhibited automaticity and contraction. While not subjected to human clinical trials yet, the potential for autologous cell therapy from endomyocardial biopsy is indeed intriguing [46].

Summary and Conclusions

A variety of cell types may prove to influence myocardial repair following MI. The mechanism of benefit remains uncertain, and probably includes angiogenic effects, paracrine influences on endogenous repair mechanisms (including intrinsic cardiac stem cells), and effects on scar formation. Yet to be defined is the optimal cell type or types; optimal timing of cell administration after infarction; and the optimal delivery strategy, whether intravenous, intracoronary, coronary transvenous, transendocardial, or transepicardial. Concerns about pro-arrhythmic effects, particularly noted with skeletal myoblasts, may be ameliorated by the apparent anti-arrhythmic effect of mesenchymal stem cells.

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Chapter 12
Health Economics of Primary PCI

Richard P. Konstance and Russell J. Ivanhoe

Introduction

In 2005, health care spending in the United States reached two trillion dollars, 16 percent of its gross domestic product (GDP) [1, 2]. This is projected to reach 20 percent of the GDP over the next decade, with expenses related to cardiovascular disease being the single largest component [1, 2, 3]. The message is clear that, despite the waning use of the managed care approach, physicians must share the fiscal responsibility of their clinical decisions and they must analyze the economic impact of new therapies or new applications of existing therapies.

Understanding healthcare economics is important for physicians and others who decide among strategies for treating illnesses. However, as the information from such analyses takes increasing prominence in decision-making, the risk for moral hazard rises. For example, recognition of the additional costs of a new treatment, despite proven effectiveness, may delay or even preclude its use. This conflicts with the physician's role as fiduciary for the patient. While such "decisions" have traditionally been ascribed to policy makers, hospital administrators, or health insurers, all parties now face such conflicts.

An evaluation of the economic impact of a treatment cannot be taken out of context. It must be considered in light of the treatment's incremental clinical benefit and it must account for the physician's responsibility for the patients' health. This chapter will discuss some of the basic tools of health economics and their application to clinical studies. The chapter will then evaluate the existing economic data regarding primary PCI and related topics.

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Cost Analysis

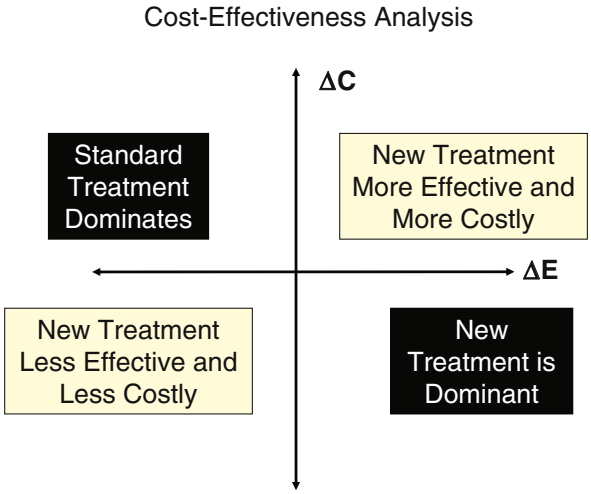
One of the ways economists discuss cost is in the context of lost opportunity. Given a finite amount of resources (e.g., money), commitment of those resources in one way prevents their use in other ways. Thus in healthcare the "opportunity cost" of investing in one treatment strategy may be measured in terms of the benefit of that treatment strategy (e.g., years of life saved) relative to that of the next best alternative.

In addition to understanding the concept of opportunity cost, one who performs or evaluates a cost analysis must take into consideration who incurs the cost. In other words, is it the patient, the insurers, the physician, the hospital, or society? Because of the tremendous difficulty in quantifying many of these costs (e.g., lost productivity, reduced quality of life), most cost analyses attempt only to capture the direct costs incurred by the hospital. Unfortunately, this data is not always accessible.

In the United States, hospitals are reimbursed for inpatient services on the basis of diagnosis related groups (DRG). The amount of payment is intended to reflect the *average* cost per diagnosis and, thus, does not reflect the true per-patient cost of care. If a hospital provides services at a cost below the DRG reimbursement, it generates a profit; whereas if it does so at a cost above the DRG reimbursement, it incurs a loss. If true hospital costs were transparent, reimbursement would equilibrate at a point near these costs. In other words, if insurers learned they were consistently paying a significant margin above the cost of care, they would cut reimbursement.

In an effort to overcome this barrier to cost analysis, a specific methodology has been developed for estimating hospital costs [10]. The UB92 is a widely used billing form employed by all hospitals that treat Medicare patients. The charges on the UB92 are tallied; a Medicare conversion ratio is then applied to arrive at a best estimate of cost. Several factors must be considered in the cost analysis that may not appear on the UB92. For instance, physician professional charges, particularly when several visits occur, are not necessarily accounted for in the cost analysis.

Four types of cost analysis in healthcare have been described: cost-minimization, cost-benefit, cost-effectiveness, and cost-utility [4]. The simplest is cost-minimization. In this type of analysis it is assumed that each treatment option yields an equivalent outcome; thus the least expensive is preferred. Cost-benefit analysis recognizes the potential for differences in outcome. Therefore the cost of each treatment option is calculated relative to the benefit of that treatment option. The cost:benefit ratio of each treatment is calculated separately and then compared. Cost-effectiveness analysis (CEA) and cost-utility analyses aim to simultaneously determine the costs and benefits of two or more treatment options in order to identify the relative benefit of one over another (CEA Figure). A cost utility analysis differs from CEA in that one attempts to assign and incorporate a valuation for quality of life issues. CEA is the most common type of cost analysis and is discussed further below.



Cost-Effectiveness Analysis

There are many instances where two treatments are compared and one of the two established as superior in both effectiveness and cost. For example, if a new treatment is more effective than the standard treatment and is less costly, then the new treatment dominates (CEA Figure). In such a scenario, further analysis is unnecessary. In contradistinction, a new treatment may be found less effective and more costly. Clearly the standard treatment would dominate in that instance. Occasionally, a new treatment may be found less effective than another yet, because it is less costly may be preferred over the standard treatment. This could occur when the perceived severity of illness is low and the demand for the more efficacious treatment is elastic (i.e., willingness to pay is sensitive to and directly related to price). In reality, physicians and administrators are more often faced with deciding on the adoption of new therapies that have proven benefit over an established therapy but at a greater cost. It is in these cases that health economists apply the tool of cost-effectiveness analysis (CEA).

Cost-effectiveness analysis can be simply described by the following relationship:

$$\frac{\Delta Cost}{\Delta Effectiveness}$$

Effectiveness is typically measured by assessing cumulative life years saved (LYS) or, when considering utility, by various quality measures such as quality-adjusted life years (QALY). The measurement of effectiveness usually is derived from randomized trials. In fact, the quality of the clinical trial is the foundation for the quality of the CEA (Table 12.1). However, clinical trials may have restricted entry criteria or short time horizons. In such cases, data may be supplemented

Table 12.1 The relationship between levels of evidence and grades of recommendtions[1]

Level of Evidence		Grade of Recommendation
Level 1	Large randomized trials with clear-cut results and (low risk of error)	Grade A
Level 2	Small randomized trials with uncertian results (and moderate to high risk of error)	Grade B
Level 3	Nonrandomized, contemporaneous controls	Grade B
Level 4	Nonrandomized, historical controls	Grade C
Level 5	No Controls, case series only	Grade C

[1]Adapted from: Cook, Deborah J., Guyatt, Gordon H., Laupacis, Andreas, and Sackett, Danid L. 1992 Rules of Evidence and Clinical Recommendations on the Use of Antithrombotic Agents *Chest* 102(4): 305S–311S

with data derived from epidemiological studies [11]. or by simulation (WS Weintraub [18]) A full discussion can be found in Gold and Califf. [12, 13].

In order for a new treatment to be considered cost effective it must be shown to be an improvement over the current best practice and it must meet generally accepted parameters for cost effectiveness. It is generally accepted that a procedure that has a cost-effectiveness ratio of less than or equal to $50,000 per life year saved is a cost-effective procedure or treatment (Table 12.2). It can be shown that this is an arbitrary cut-off. The *Washington Post* has published a CEA for various safety procedures that are mandated by law (Table 12.3). What actually constitutes a fair value in assessing the cost effectiveness of a medical procedure is complex and beyond the scope of this chapter.

Table 12.2 Cost-effectiveness benchmarks ($/LYS)

CABG for Left Main Disease	$7,000
Cervical Cancer Screening	$12,000
Neonatal ICU	$12,000
Renal Transplant	$19,000
TPA vs. SK for AMI	$32,000
Hemodialysis	$35,000
Heart Transplant	$54,000
Cholesterol Treatment (1° prevention)	$154,000

Table 12.3 Cost effectiveness-safety devices ($/ Life Saved)[1]

Safety sensors-escalators:	$1,600,000
Automobile airbags:	$1,700,000
Automobile seat belts:	$150,000
Automatic Activation Devices:	$125,000

[1]Gary Smedinghoff (Editorial) "Is the Metro too Safe?" Washington Post August 7, 1999 p. A19

Economics of Primary PCI

As randomized clinical trials revealed primary PCI to yield equivalent or better clinical outcomes compared to standard thrombolytic therapy for patients with ST-segment elevation myocardial infarction (STEMI), interest in the economic implications of these two strategies arose. The Primary Angioplasty Registry enrolled 270 patients with STEMI, presenting to one of six medical centers between 1990 and 1992, where reperfusion with primary PCI was pursued. An economic analysis of this study including detailed medical resource utilization patterns and associated medical costs with primary angioplasty was reported [14]. Using hospital and physician billing records, economic outcomes were assessed in terms of both medical costs and medical resource consumption. Charges were converted to costs using cost/charge ratios. The total baseline hospital cost for the primary reperfusion strategy averaged $13,113 (1995 dollar value). Physician fees added another $5,694 to the overall cost of the episode of care. The independent predictors of higher cost were older age, anterior myocardial infarction, higher initial Killip class and greater number of diseased vessels. The need for coronary artery bypass graft (CABG) surgery substantially raised the cost over that of coronary angioplasty alone. Other myocardial infarction complications that contributed to an increase in cost included recurrent ischemia and new or worsened congestive heart failure. Overall, a 10-year difference in age was associated with a 5% increase in adjusted hospital costs, whereas recurrent ischemia was associated a 53% average increase. The need for CABG after angioplasty was associated with a 142% increase in cost.

Primary PCI vs. Thrombolysis

There have been few cost-effectiveness analyses comparing primary angioplasty compared to thrombolytic therapy. Initially there was concern that primary PCI would be prohibitively more costly than thrombolytic therapy despite superior clinical benefit. In the Netherlands, de Boer et al. compared 301 patients randomized to either primary PCI or thrombolytic therapy using streptokinase. Costs for procedures and hospital days were calculated using of hospital administration data and were expressed in 1992 US dollars. The cost-benefit ratios were $25,431 for primary PCI vs. $36,798 for streptokinase. The incremental costs per additional event-free survivor, was estimated at $3,010.

Gibbons et al. [5] were among the first to prospectively evaluate these two treatment strategies and to incorporate a cost analysis in 108 patients randomized to either immediate angioplasty or thrombolytic therapy with a double-chain tissue plasminogen activator called duteplase. (Gibbons) Hospital and professional charges related to cardiac care for the index and subsequent hospitalizations through six months were recorded. Costs were calculated as

80 percent of charges; indirect measures of cost included length of hospital stay, length of coronary care unit stay, readmission within six months, and lost days of work for the patient. A cost benefit analysis was performed such that the mean cumulative six-month cost was compared to mean myocardial salvage for each treatment group. No significant difference was found in cost between the two treatment strategies, yet there was a trend toward lower cost in the primary PCI group. Six-month follow-up costs were lower, initial length of stay was shorter, and there were fewer readmissions in the primary PCI group. There was no difference between groups in return to work parameters.

The Primary Angioplasty in Myocardial Infarction (PAMI) trial was a large-scale multicenter randomized trial of t-PA versus PTCA for STEMI [15, 17]. In this study, compared with thrombolytic therapy, primary PCI resulted in lower rates of in-hospital mortality, reinfarction, recurrent ischemia, and stroke. Hospital length of stay was significantly reduced with primary PCI. The investigators assessed hospital and professional charges from the index admission and post-discharge resource consumption. Hospital and physician bills were obtained from all patients enrolled at U.S. sites. Summary ledger forms (UB 92) and detailed itemized bills were reviewed. Because cost assessment during follow-up was not feasible, late resource consumption was estimated by looking at readmissions and major clinical events during the first two years after discharge. Despite higher initial costs of cardiac catheterization, total mean hospital costs were $3,436 lower in the primary PCI group [16]. The greatest reduction was seen in the "non high risk" patients in whom there was a mean savings of $4,365 per patient, largely due to a reduction in length of stay. In "high risk" patients, PCI reduced in-hospital mortality and stroke rates with only a trend toward lower cost. Variables that correlated with increased hospital charges were advanced age, previous myocardial infarction, and previous heart failure.

The second PAMI study tested the hypothesis that primary PCI with subsequent discharge from the hospital three days later is safe and cost-effective in low risk patients [15, 17]. Overall, patients randomized to accelerated care had a shorter length of stay and lower hospital costs ($9,658± $5,287 vs. $11,604± $6,125). Outcomes at six months were equivalent in both groups.

The GUSTO-IIb study randomized 1138 patients to either primary PTCA or front-loaded t-PA. The immediate results showed a significant benefit for primary PTCA. At six-month follow-up, however, there was no significant difference between treatment arms for the combined endpoint. No economic analysis was deemed necessary because of a failure to show benefit in the primary angioplasty arm [14].

The success of primary PCI and whether or not it should be used as the first approach to treating acute myocardial infarction may depend on operator experience and local success rates. Lieu et al. [19] created a decision analytic model to compare three approaches to treating acute myocardial infarction: primary angioplasty, intravenous thrombolysis, or no intervention [19]. Outcomes were derived from published randomized studies and meta-analyses. The

parameter of QALY was used as the outcome measure. For a hypothetical cohort of 10,000 patients with an acute myocardial infarction, primary angioplasty improved outcomes by 741 undiscounted QALYs relative to thrombolysis (514 discounted QALYs). When a hospital met efficacy assumptions and a volume of >200 cases/year, there was a substantial cost-effectiveness benefit for primary PTCA. This benefit was lost when the hypothetical hospital was inexperienced or redundant in the community. The authors concluded that consideration should be given to regionalization of primary angioplasty services.

Economics of Primary PCI vs. thrombolysis in the current era

It is important to point out that the aforementioned cost analyses comparing primary PCI to thrombolysis were done largely in the pre-stent, pre-GP IIb/IIIa inhibitor era. Therefore it is arguable that such analyses are no longer valid. The cost-effectiveness of primary stenting has been compared to that of primary balloon angioplasty [7,8]. In the Stent PAMI trial, one-year costs were higher with stenting ($20,571 vs. $19,595) and in CADILLAC trial one-year costs were the following: $18,021 for primary PCI alone, $19,331 for PCI plus abciximab, $18,278 for stenting alone, and $19,466 for stenting plus abciximab. Le May et al. [6] reported a cost analysis of the Canadian STAT trial which randomized 123 STEMI patients presenting to a single center between August 1997 and June 1999 to primary stenting or thrombolytic therapy with accelerated tPA [6]. Costs were reported in 1999 U.S. dollars based on U.S.-to-Canadian exchange rate of 0.67. In patients assigned to primary PCI, 81% had successful deployment of stents; abciximab was used in 12 patients (19.4%). Compared to the thrombolytic group, fewer patients in the primary PCI group reached the combined endpoint of death, reinfarction, stroke, or repeat revascularization at six months (24.2% versus 55.7%; a difference that persisted for two years). Length of stay was shorter for the primary PCI group (6.7 $\pm$ 11.3) than in the tPA group (8.7 $\pm$ 6.7) and hospitalization costs were lower $6354 $\pm$ 6382 versus $7893 $\pm$ 4429. At six months, these costs were $7100 $\pm$ 7111 versus $9559 $\pm$ 6933.

In CAPTIM, a French trial which compared primary PCI to pre-hospital thrombolytic therapy, a cost-effectiveness sub-study was performed in 299 STEMI patients between June 1997 and September 2000 [9]. Direct costs through one year were assessed and expressed in U.S. dollars using the 2000 exchange rate for the franc. In the primary PCI group, stents, and GP IIb/IIIa inhibitors were used in 72% and 30% of cases respectively. Mean costs of the initial hospitalization were $883 lower in the primary PCI group, largely due to longer length of stay in the thrombolytic group. In the primary PCI group, catheterization and angioplasty were more costly than in the thrombolytic group, however the additional cost of the thrombolytic agent in the thrombolytic group offset this higher cost. At one-year, costs remained $1,224 lower in the primary PCI group. Results did not differ on the basis of gender, age, or location of the AMI. However, primary PCI was less costly only for non-high-risk patients.

Conclusions

The aggregate data suggest improved outcomes with primary PCI for acute MI at a cost equal to or lower than thrombolytic therapy. This therapy qualifies as an approach where better outcomes are achieved at the same or lower cost, diminishing the impetus for justification of primary PCI on a cost-effectiveness basis. The resource constraints (of more widespread availability of emergency catheterization facilities) notwithstanding, a discussion of whether the data support regionalization of services for primary PCI in the setting of acute myocardial infarction is not in the purview of this chapter. Well-designed clinical trials that include an economic analysis should help cardiologists sort through the issues of how best to treat acute myocardial infarction in the era of drug-eluting stents and direct thrombin inhibitors as well as the more expeditious use of thrombolytic therapy. Moreover, economic analysis should be a key feature in optimizing the widespread delivery of primary PCI services, specifically with regard to the debate of "hub and spoke" rapid transport versus primary PCI in the smaller community hospital without on-site surgical backup.

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