Evolving Antithrombotic Treatment Strategies for Acute ST-Elevation Myocardial Infarction

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The importance of the dissolution and prevention of thrombosis in treating patients with ST-segment elevation myocardial infarction (STEMI) has motivated the development of novel therapies targeting platelet aggregation and thrombus formation. In contemporary practice, the current challenge is the integration of these therapies into reperfusion strategies that may include fibrinolytic therapy or percutaneous coronary revascularization (PCI). Evidence from clinical trials shows that addition of glycoprotein IIb/IIIa inhibition to PCI for treatment of STEMI has substantially lowered the incidence of recurrent ischemic events and improved early survival. In contrast, current trials evaluating a strategy termed facilitated PCI, or planned early PCI after pharmacologic reperfusion therapy, have presently demonstrated an increased risk of bleeding events and mortality. Additional trials have extended the role of antithrombotic agents to STEMI that previously were reserved for patients undergoing elective revascularization or among those treated with non-ST-segment elevation acute coronary syndromes. For example, the recent studies have demonstrated the benefit of clopidogrel treatment among STEMI patients treated with fibrinolysis in reducing the incidence of infarct artery reocclusion and improving early survival. Other anticoagulants under investigation in the management of STEMI include enoxaparin, bivalirudin, and fondaparinux. This review summarizes the current status of pharmacologic and invasive strategies for the treatment of STEMI and describes recent and ongoing directions for clinical investigation.
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Key words: STEMI • Fibrinolysis • Reperfusion • GP IIb/IIIa inhibitors

Despite recent advances in the care of high-risk patients with acute ST-segment elevation myocardial infarction (STEMI), both the therapeutic and logistic limitations of current standard therapies underscore the need for further improvement. Fibrinolytic therapy, for example, is limited by the risk of impaired microvascular flow, reocclusion, and intermittent (or incomplete) patency characterized by incomplete epicardial perfusion or microvascular perfusion, or both.[1] By contrast, successful reperfusion, achieved with primary percutaneous coronary intervention (PCI) in more than 90% of

cases, is associated with improved clinical outcomes compared with fibrinolysis.[2] Unfortunately, a primary angioplasty strategy is limited by the availability of cardiac catheterization laboratories with 24-hour capability to perform revascularization in patients with acute myocardial infarction (ie, laboratories with operators and support staff experienced in the care of these patients). In both types of treatment strategies, however, recent clinical trials evaluating the role of antithrombin and antiplatelet therapies beyond aspirin and unfractionated heparin as adjuncts to either fibrinolysis or primary PCI have further refined the safety and efficacy of reperfusion therapies in STEMI. The purpose of this review is to summarize the status of current pharmacologic and invasive strategies for the treatment of STEMI, report outcomes from recent clinical trials, and describe ongoing and future directions for clinical investigation.

Glycoprotein IIb/IIIa Inhibition and Percutaneous Coronary Intervention for Treatment of STEMI

Several trials have established evidence supporting glycoprotein (GP) IIb/IIIa blockade as adjunctive therapy for primary PCI in patients with STEMI. Addition of GP IIb/IIIa inhibition to PCI in therapies for STEMI has substantially lowered the incidence of recurrent ischemic events and improved early survival, ventricular function, and vessel patency.

Observations from early studies evaluating the use of GP IIb/IIIa inhibitors before primary PCI yielded TIMI (Thrombolysis in Myocardial Infarction) grade 3 (TIMI-3) flow rates that exceeded previously reported rates of reperfusion with aspirin and heparin treatment and were comparable to those with full-dose streptokinase.[3] Based on the clinical observation that abciximab exhibited intrinsic anticoagulant and clot-dissolving activity,[4,5] early investigations showed that rates of reperfusion—the occurrence of TIMI grade 2 or 3 flow—occurred in approximately 40% of patients treated with abciximab before angioplasty.[6] More recently, nearly one-third of patients randomized to abciximab alone in the TIMI 14 trial (32%) and SPEED (Strategies for Patency Enhancement in the Emergency Department) trial (27%) experienced TIMI-3 flow at 90 minutes.[7,8] Although treatment with GP IIb/IIIa inhibitors alone is not ideally suited to achieving early reperfusion, such observations reaffirm the potential of early administration of abciximab to restore infarct-artery patency before mechanical revascularization.

Aside from epicardial coronary artery patency, early pivotal trials demonstrating improved clinical outcomes with abciximab in patients with unstable angina undergoing PCI also led to studies extending the role of GP IIb/IIIa inhibitors in percutaneous revascularization to treatment of acute myocardial infarction (AMI). For the 64 AMI patients undergoing primary or rescue angioplasty, treatment with abciximab resulted in an 83% reduction in 30-day death, reinfarction, or urgent revascularization (26.1% vs 4.5%; $P = .06$). Similarly, in the RAPPORT (ReoPro and Primary PTCA Organization and Randomized Trial) study, patients with AMI receiving abciximab in the catheterization laboratory before primary angioplasty experienced significant reductions in 30-day and 6-month death, reinfarction, or urgent revascularization (5.6% vs 11.2% at 30 days; $P = .03$).[9]

In the ISAR-2 (Second Intracoronary Stenting and Antithrombotic Regimen) trial, 401 patients with AMI within 48 hours of symptom onset for whom rescue or primary PCI was planned were randomized to an abciximab bolus plus infusion or to control.[10] Abciximab as an adjunct to coronary stenting improved 30-day clinical outcomes (a composite of death, reinfarction, and target lesion revascularization; 5.0% vs 10.5%; $P = .038$) (Figure 1). Although the absolute reduction in the composite endpoint was maintained with abciximab therapy at the 1-year follow-up, this early benefit no longer remained statistically significant, largely due to the accrual of restenotic events and the need for repeat revascularization.

On the basis of the promising outcomes with intravenous GP IIb/IIIa inhibition in earlier studies, the ADMIRAL (Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-term Follow-up) study demonstrated that abciximab improved early and late TIMI-3 flow (post-PCI TIMI-3 flow 95.1% for abciximab vs 86.7% for placebo; $P = .04$), was associated with higher left ventricular ejection fraction ($57.0 \pm 10.4\%$ vs $53.9 \pm 10.4\%$; $P < .05$), and more than halved the primary composite endpoint of death, recurrent MI, and urgent target vessel revascularization (TVR) at 30 days after enrollment (14.6% vs 6.0%; $P = .01$) (Figure 2).[11] In this trial, nearly one-fourth of patients received early treatment with abciximab in the emergency room or even in the ambulance. Consistent with prior studies showing improved epicardial TIMI flow with early use of abciximab, a significantly greater proportion of abciximab-treated patients had a patent infarct vessel (TIMI grade 2 or 3 flow) at baseline compared with those receiving placebo (25.8% vs 10.8%; $P = .006$).

In the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trial, 2082 patients with acute

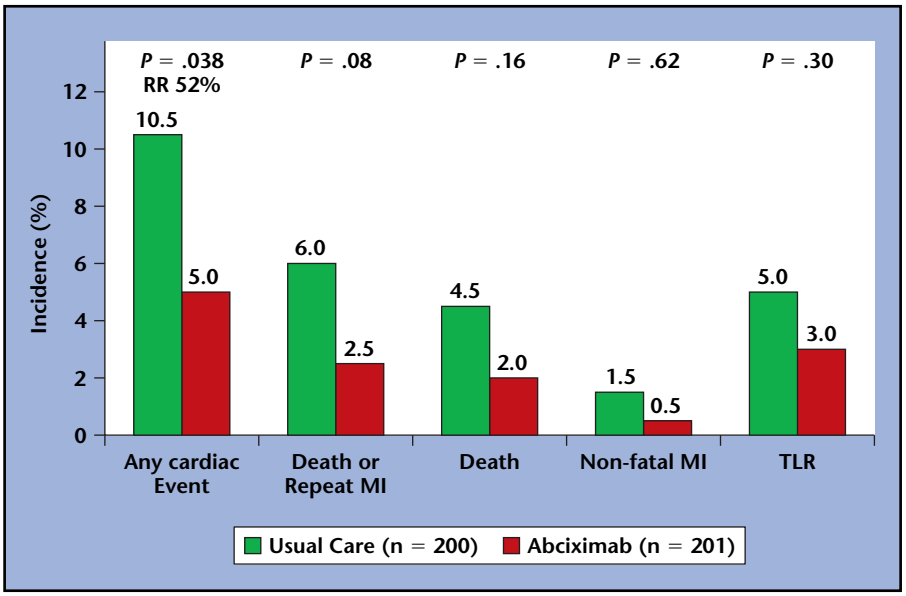


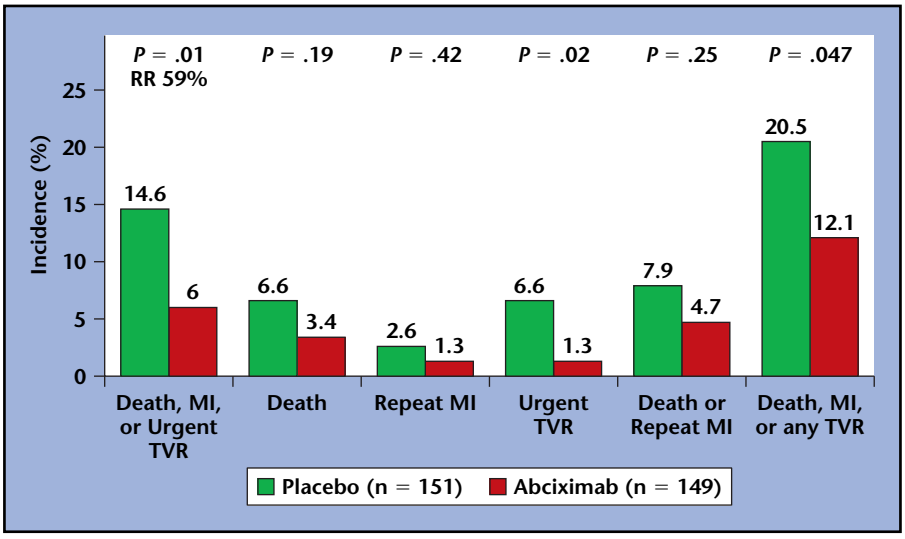
Figure 1. *ISAR-2 trial: 30-day outcome (secondary endpoint). RR, relative risk; MI, myocardial infarction; TLR, target lesion revascularization. Adapted from Neumann FJ et al.*[10]

STEMI were randomized to 1 of 4 treatment strategies: balloon angioplasty alone, balloon angioplasty plus abciximab, stenting alone, or stenting plus abciximab.[12] Unlike the early treatment in the ADMIRAL trial, in CADILLAC, abciximab was administered only in the catheterization laboratory following the diagnostic angiogram, at which time patients were randomized. Among individual treatment groups, event-free survival was greatest in patients assigned to routine stenting (with or without abciximab), intermediate in patients assigned to percutaneous transluminal coronary angioplasty (PTCA) plus abciximab, and lowest in those assigned to PTCA only (30-day composite of death, recurrent myocardial infarction or ischemia-driven repeat revascularization stent plus abciximab, 10.0%; stent alone, 10.9%; PTCA plus abciximab, 16.4%; PTCA alone, 19.4%; $P = .0001$).

In a combined analysis based on randomization to abciximab or no abciximab, patients receiving abciximab tended to have higher baseline infarct-related artery TIMI-3 flow rates. Treatment with abciximab was associated with significantly higher postprocedural coronary flow rates and a significant reduction in the composite endpoint of death, recurrent MI, disabling stroke, and ischemic TVR.[13] At 30 days, subacute thrombosis and length of hospital stay were also significantly decreased. By 6 months, however, restenosis was the predominant clinical event, and event-free survival rates converged, consistent with previous studies demonstrating the lack of effect of abciximab (or any GP IIb/IIIa inhibitor) on angiographic restenosis.[10,14] Thus, although the absolute benefit of abciximab therapy was maintained at 1 year, the benefit remained not statistically significant.

In the most recent AMI trial evaluating the safety and efficacy of GP IIb/IIIa antagonists, the ACE (Abciximab and Carbostent Evaluation) study randomized 400 patients undergoing primary PCI with stenting to either abciximab or control therapy.[15] Crossover to abciximab occurred in 11% of patients assigned to the control group. At 1 month, abciximab treatment was associated with a significant reduction in the primary endpoint of death, MI, TVR, and stroke (4.5% vs 10.5%; $P = .023$) (Figure 3). Early ST-segment resolution (ie, ≥ 50% ST-segment resolution at 30 minutes) was also achieved more commonly with abciximab (68% with

Figure 2. *ADMIRAL trial: 30-day clinical events. RR, relative risk; MI, myocardial infarction; TVR, target vessel revascularization. Adapted from Montalescot G et al.*[11]



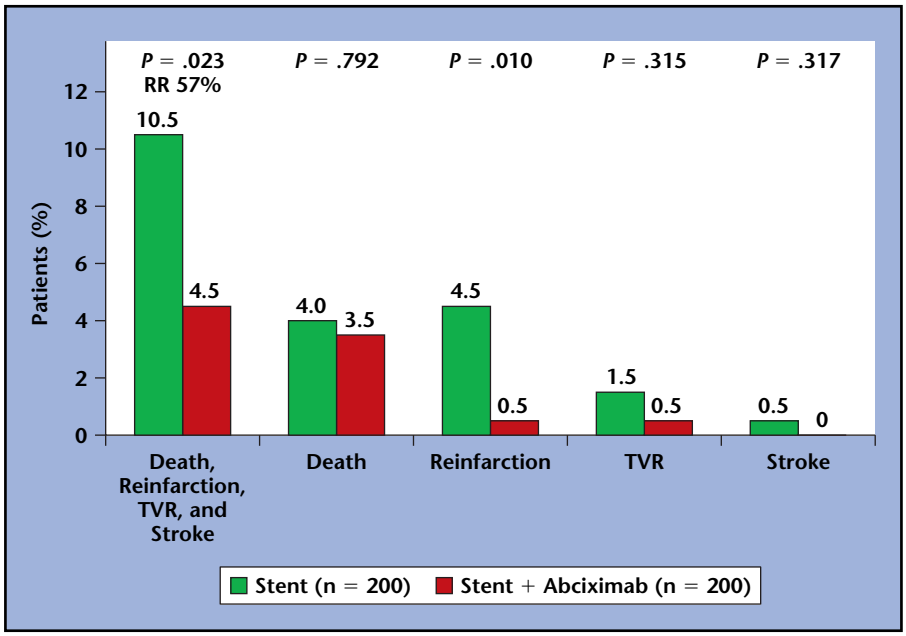


Figure 3. *ACE trial: 30-day outcomes. RR, relative risk; TVR, target vessel revascularization. Adapted from Antoniucci D et al.*[15]

stenting alone vs 85% with abciximab and stenting; $P < .001$). Although the occurrence of restenosis and repeat TVR at 6 months did not significantly differ between the treatment groups, patients randomized to abciximab therapy experienced sustained benefit with regard to reduction in death and MI (5.5% vs 13.5% at 6 months; $P = .006$).

Considering the differences in trial design and study population, it is difficult to reconcile the somewhat divergent results on the relative impact of GP IIb/IIIa inhibition on mortality and ventricular function among the ADMIRAL, ACE, and CADILLAC trials. The apparently greater risk reduction for clinical events observed with abciximab in the ADMIRAL and ACE trials may be due to differences in patient selection, the type of stent used, the lack of abciximab crossover in ADMIRAL, differing endpoint definitions, or the timing of abciximab administration. Collectively, trials evaluating GP IIb/IIIa inhibition as adjunctive therapy to primary angioplasty show benefits consistent with the 2-way (abciximab vs no abciximab) analysis of the CADILLAC results—reductions in early ischemic adverse events that are maintained but no longer statistically significant during longer-term follow-up.

In combined analyses, however, differences in outcome may persist over a longer follow-up. In a recent systematic overview of 4 trials examining treatment with abciximab for primary PCI (ADMIRAL, CADILLAC, ISAR-2, and RAPPORT), treatment with abciximab significantly reduced the 30-day composite endpoint of death, reinfarction, or ischemic or urgent TVR (n = 3266; odds ratio [OR] 0.54, 95% CI 0.40-0.72), with trends toward reduced 30-day death or reinfarction.[16] However, abciximab resulted in an increased likelihood of major bleeding (OR 1.74, 95% CI 1.11-2.72), although differences were not observed among more recent individual trials (ADMIRAL, CADILLAC) with more cautious heparin dosing. By 6 months, abciximab significantly reduced the occurrence of death, reinfarction, or any TVR (OR 0.80, 95% CI 0.67-0.97), and there were positive trends favoring a decrease in mortality alone and in the composite of death or reinfarction.

In another systematic overview of trials evaluating use of abciximab in treating STEMI, GP IIb/IIIa inhibition was associated with significant reductions in 30-day death and recurrent infarction. In another systematic overview of clinical trials evaluating use of abciximab in primary PCI, GP IIb/IIIa inhibition, abciximab was not associated with benefit as an adjunctive therapy to fibrinolysis.[17] In this meta-analysis of 8 randomized trials involving 3949 patients, abciximab treatment as an adjunct to primary PCI was associated with a reduction in mortality at both 30 days (2.4% abciximab vs 3.4% no abciximab, $P = 0.047$) and at 6 to 12 month follow-up (4.4% abciximab vs 6.2% no abciximab; $P = 0.01$). Furthermore, no increase in major hemorrhage (4.7% abciximab vs 4.1% no abciximab; P = NS) was observed.

Facilitated Primary PCI: Combination Fibrinolysis and GP IIb/IIIa Inhibition

Facilitated PCI, or the strategy of planned early PCI after pharmacologic reperfusion therapy, is intended to combine the reperfusion benefits of fibrinolysis and primary angioplasty in the management of STEMI. For example, fibrinolysis can result in TIMI-3 flow as early as 60 minutes after administration. Alternatively, primary angioplasty achieves higher rates of normal epicardial artery blood flow, but generally at later time points. Thus, as a

combined approach, facilitated PCI could theoretically provide the best outcomes based on TIMI flow and clinical events.

The rationale for facilitated PCI is derived from observations of the clinical benefit associated with a patent infarct artery prior to the performance of catheter-based revascularization. As described above, in the ADMIRAL trial, nearly one-fourth of patients received early administration of abciximab in either the emergency room or the ambulance.[11] Baseline TIMI-3 flow was significantly more common among patients receiving abciximab both immediately before and after revascularization, a finding consonant with earlier studies showing a 25% to 35% rate of TIMI-3 flow with abciximab given 60 to 90 minutes before angiography.[7,18] Although some of the marked benefit in the early-treatment group in the ADMIRAL study may be due to chance alone, resulting in an inexplicably high rate of adverse events in the placebo-treated patients, these data support ongoing trials of pharmacologic reperfusion before mechanical revascularization. These data are also consistent with 3 other reports. Among the 2507 patients in the PAMI (Primary Angioplasty in Myocardial Infarction) trials, early and late mortality were strikingly reduced for patients with spontaneous recovery of TIMI-3 flow before the procedure, independent of their final TIMI flow grade.[19] In the randomized PACT (Primary Angioplasty Compatibility Trial) study, early reperfusion with reduced-dose alteplase resulted in greater early recovery of left ventricular function.[21] Finally, a meta-analysis showed that mortality is reduced when thrombolytic therapy is started before arrival at the hospital rather than in the emergency room.[22]

The investigators of the Strategies for Patency Enhancement in the Emergency Department (SPEED) trial, described the outcomes of 323 patients who underwent PCI approximately 1 hour after reperfusion therapy, and compared these with outcomes for a similar cohort that did not undergo early revascularization.[18] In this trial, a facilitated treatment strategy was associated with significant reductions in the composite 30-day endpoint of death, reinfarction, and urgent repeat target vessel revascularization compared with patients not undergoing early revascularization (5.6% vs 16.0%, $P < 0.001$). Although these findings were more descriptive than comparative, they were encouraging because earlier trials had consistently shown lower immediate procedural success rates, higher mortality, and higher rates of reinfarction, bypass surgery, and bleeding than with a conservative approach. In contrast, the more recent ASSENT (Assessment of the Safety and Efficacy of a New Treatment for Acute Myocardial Infarction)–4 PCI trial was halted prematurely following enrollment of 1667 patients, because of higher 30-day mortality among patients randomized to full-dose tPA-TNK (tenecteplase) and facilitated PCI compared with primary PCI alone (6.0% vs 3.8%; $P = .04$).[22] By 90 days, the primary composite endpoint of death, heart failure, or cardiogenic shock was also significantly higher in the fibrinolytic PCI group (18.8% vs 13.7%; $P = .0055$), although the individual endpoints did not statistically vary.

While a relatively shorter transit time may be one potential explanation for the absence of benefit with this strategy, still more trials are underway, including the FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) trial (abciximab/reteplase followed by early PCI). However, in a systematic overview of 17 trials in which patients with STEMI were treated with either facilitated (n = 2237) or primary (n = 2267) PCI, initial TIMI-3 flow was approximately 2-fold higher in the facilitated PCI group, yet individual rates of death, recurrent MI, urgent TVR, and major bleeding were significantly higher with the facilitated PCI strategy.[23] Given that trials to date have not demonstrated improved survival and have raised safety concerns with a facilitated PCI strategy, this approach cannot at present be considered a standard of care.

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Antithrombin Therapies as Adjuncts to Fibrinolysis

Compared with the treatment of patients with non-ST-segment elevation acute coronary syndromes, in which treatment with enoxaparin may be equivalent, but not superior, to unfractionated heparin (UFH), therapy with enoxaparin in combination with fibrinolytic therapy for STEMI may be superior to adjunctive use of UFH. In the ExTRACT (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment) TIMI 25 trial, 20,506 patients with STEMI treated with fibrinolytic therapy were randomized to receive either UFH or enoxaparin.[24]

Importantly, this trial did not evaluate a facilitated PCI strategy, nor was early cardiac catheterization mandated. At 30 days, treatment with enoxaparin was associated with a significant reduction in the composite endpoint of death or MI (12.0% vs 9.9%; $P < .0001$). Although rates of intracranial hemorrhage did not differ between treatment groups, the occurrence of nonfatal major bleeding was significantly more common with enoxaparin (2.1% vs 1.4%; $P < .0001$).

In addition to enoxaparin, other novel anticoagulants are under investigation in the management of STEMI. Fondaparinux is a synthetic pentasaccharide that indirectly inhibits factor Xa through highly selective binding to antithrombin III. Against the background of numerous trials establishing the efficacy of fondaparinux in preventing venous thromboembolism,[25,26] the OASIS-6 (Organization to Assess Strategies in Acute Ischemic Syndromes–6) trial was conducted to evaluate treatment with fondaparinux, heparin, or placebo in 12,092 patients with STEMI to reduce early ischemic adverse events.[27] Specifically, patients were randomized to treatment with fondaparinux or either UFH or placebo, depending on whether heparin therapy was indicated. Treatment with fondaparinux was associated with a significant reduction in the primary endpoint of death or recurrent MI at 30 days (11.2% vs 9.7%; $P = .008$). The individual endpoint of mortality was also significantly reduced with fondaparinux at both 9 and 30 days (8.9% vs 7.8% at 30 days; $P = .03$). In addition, the occurrence of severe bleeding also tended to be lower with fondaparinux (1.3% vs 1.0%; $P = .13$). In subgroup analysis, significant benefit with fondaparinux was observed among patients receiving thrombolytic therapy and those not receiving any reperfusion therapy; however, no benefit was identified for patients undergoing primary PCI. Specifically, although the 30-day outcome of death or MI did not significantly differ between primary PCI patients receiving heparin or fondaparinux, guiding catheter–related thrombotic complications (eg, abrupt closure, new angiographic thrombus, catheter thrombus, no reflow) were significantly more common in the fondaparinux group (22 vs 0 events; $P < .001$). Given the increased risk of catheter-related thrombotic events, the relatively brief required duration of anticoagulation for patients undergoing primary PCI, and the long half-life of fondaparinux (potentially complicating vascular sheath removal), there is probably little advantage for treatment with fondaparinux as initial therapy for patients undergoing primary PCI.

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Thienopyridine Therapy in Treatment of STEMI

Recently, orally administered antiplatelet agents not active through the cyclooxygenase pathway have been evaluated in patients with non-ST-segment elevation acute coronary syndromes and patients undergoing PCI, as alternatives to or in combination with aspirin, to prevent ischemic complications. Clopidogrel is a thienopyridine derivative that decreases ADP (adenosine diphosphate)–induced platelet aggregation. Formulated as an inactive prodrug, clopidogrel requires in vivo conversion by hepatic cytochrome P450 3A4 to an active metabolite, resulting in noncompetitive inhibition of the platelet ADP receptor subtype $P2Y_{12}$.

Beyond the clinical settings of PCI or unstable angina, more recent study with clopidogrel has been extended to patients with STEMI, leading to the US Food and Drug Administration's approval of this agent for STEMI patients not treated with primary angioplasty.[28] In the CLARITY (Clopidogrel as Adjunctive Reperfusion Therapy) TIMI 28 trial, 3491 patients with STEMI treated with aspirin, heparin, and fibrinolysis were randomized to treatment with clopidogrel (300 mg loading dose followed by 75 mg/day) or placebo to evaluate the primary endpoint of either an angiographically documented occluded infarct artery, or death or MI by the time of angiography, performed 2 to 8 days following initial treatment.[29] Important exclusion criteria were age above 75 years, cardiogenic shock, and planned early (< 48 hours) cardiac catheterization or primary angioplasty. Treatment with clopidogrel was associated with a 36% relative reduction in the trial's primary endpoint (21.7% vs 15.0%; $P < .001$). Angiographic measures of TIMI-3 flow and grade 3 myocardial blush were also significantly improved in the clopidogrel treatment group. Bleeding outcomes and stroke did not statistically vary between treatment groups, and by 30 days, clopidogrel therapy was associated with a 20% relative reduction in the occurrence of death, recurrent MI, or

ischemia-driven urgent TVR (OR 0.80, 95% CI 0.65-0.97, $P = .026$).

The COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) study randomized 45,852 STEMI patients at 1250 centers in China to treatment with clopidogrel (75 mg/day) or placebo to examine the co-primary endpoints of death and composite occurrence of death, recurrent MI, or stroke by 4 weeks or hospital discharge.[30] All patients were treated with aspirin, yet only approximately one-half received fibrinolytic therapy. Clopidogrel treatment was associated with significant reductions in both in-hospital death (7.5% vs 8.1%; $P = .03$) and the composite endpoint of death, recurrent MI, or stroke (9.2% vs 10.1%; $P = .002$). Overall, there were no significant differences in the occurrence of major bleeding, intracranial hemorrhage, or blood product transfusions between the treatment groups.

Conclusion

The recognition that thrombosis is fundamental to STEMI and that its dissolution and prevention is essential in patients treated with either fibrinolysis or primary angioplasty has motivated the development of novel therapies targeting platelet aggregation and thrombus formation and their integration into treatment strategies. Among patients undergoing primary PCI, for instance, evidence from clinical trials supports the benefit of treatment with abciximab in reducing early and late ischemic adverse events. Accordingly, treatment with abciximab started as early as possible before primary PCI is a level IIa recommendation according to the American College of Cardiology/American Heart Association guidelines.[31] Further ongoing study is examining whether similar benefit may be achieved with alternative antithrombin therapy alone. The multinational, randomized HORIZONS (Harmonizing Outcomes with Revascularization and Stents) trial, for example, is presently enrolling 3400 STEMI patients undergoing primary PCI to treatment with either abciximab or bivalirudin against background treatment with aspirin and clopidogrel. Similarly, other recently completed trials have provided insight into the role of antithrombotic therapies that have been applied earlier in clinical indications other than STEMI or were hypothesized to be effective as part of a combined pharmacologic and invasive reperfusion strategy. For patients treated with fibrinolytic therapy, the addition of clopidogrel—previously reserved for treatment of patients undergoing PCI—is associated with a reduced incidence of infarct artery reocclusion and improved early survival. Alternatively, combination of full-dose GP IIb/IIIa inhibition with reduced-dose fibrinolysis followed by planned PCI ("facilitated PCI") may be associated with increased mortality and bleeding complications.

While recent clinical trials have provided clarity to some of the ongoing uncertainties in the care of STEMI patients, many patients do not receive any reperfusion therapy, and others are not treated with fibrinolysis or primary PCI within recommended timelines.

While recent clinical trials have provided clarity to some of the ongoing uncertainties in the care of STEMI patients, many patients do not receive any reperfusion therapy, and others are not treated with fibrinolysis or primary PCI within recommended timelines.[32] In spite of significant reductions in death or MI with contemporary therapies, the observation that in-hospital mortality among patients in clinical practice with acute coronary syndromes is nearly 3-fold higher when compared indirectly with randomized clinical trials underscores the need to better understand the reasons for this gap between health care achievements in clinical trials and contemporary "real world" practice.[33] Despite guidelines and recommendations for early triage and administration of reperfusion therapy within 90 minutes of presentation,[31] only a minority are treated within a short time interval after symptom onset, and delayed treatment is associated not just with reduced epicardial (eg, TIMI flow) and myocardial (eg, ST-segment resolution and myocardial blush) perfusion but also with higher mortality.[34] Not only do these delays in reperfusion adversely affect mortality for all patients, but the effect is most pronounced in patients with high-risk features (eg, cardiogenic shock, anterior MI) and those with recent presentation. In the CADILLAC trial, early (< 3 hours) primary PCI was associated with significant improvements in survival and left ventricular function, yet less than one-third of patients were treated within 3 hours of symptom onset.[35] Thus, in patients presenting early, for whom long delays until primary PCI are expected, alternative strategies may be considered. Alternatively, for patients with low-risk characteristics or those presenting later, withholding fibrinolytic therapy in favor of transfer to a center capable of performing primary PCI may be preferred to minimize potential bleeding risks. Such findings not only underscore the need for health care providers to reexamine

regional processes for treatment strategies and established policies for the care of patients with MI, but they also emphasize the need for public education to broaden patients' awareness and symptom recognition.

Thus, despite remarkable achievements in the care of patients with STEMI, we remain ever more reliant on the results of evaluations from clinical trials seeking to refine treatment strategies relative to individual risk presentation, the availability of facilities for invasive procedures, and the timing of revascularization. To this purpose, ongoing trials are designed to tailor antiplatelet and anticoagulant treatment for high-risk STEMI patients and to better understand the interactions with presenting characteristics, the timing of revascularization, and even with drug-eluting stents. Such trials may clarify the complementary—rather than exclusionary—benefits of presently available antiplatelet and antithrombin therapies to maintain efficacy (reducing death and recurrent MI) while improving safety (eg, decreasing bleeding and thrombocytopenia). While unresolved issues inform the need for further clinical trials to refine the place of antithrombotic therapies in a treatment algorithm for STEMI, clinicians can apply the available evidence to select current therapies associated with clinical benefit. ■

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Main Points

- Addition of glycoprotein (GP) IIb/IIIa inhibition to percutaneous coronary intervention (PCI) for treatment of ST-segment elevation myocardial infarction (STEMI) has substantially lowered the incidence of recurrent ischemic events and improved early survival.
- In a meta-analysis of 8 randomized trials evaluating treatment with abciximab in STEMI, GP IIb/IIIa inhibition was associated with significant reductions in 30-day death and recurrent infarction.
- Facilitated PCI is intended to combine the benefits of pharmacologic reperfusion with primary angioplasty in the management of STEMI; overall, trials to date have not demonstrated improved survival and have raised safety concerns, and this approach cannot at present be considered a standard of care.
- In the ExTRACT TIMI 25 trial of enoxaparin (vs unfractionated heparin) in patients with STEMI treated with fibrinolytic therapy, at 30 days enoxaparin was associated with a significant reduction in the composite endpoint of death or recurrent MI.
- Other novel anticoagulants under investigation in the management of STEMI include fondaparinux, but there is probably little advantage for treatment with fondaparinux as initial therapy for patients undergoing primary PCI.
- The US Food and Drug Administration has approved clopidogrel as an adjunct treatment for STEMI patients receiving thrombolysis as a primary reperfusion therapy.
- In the CLARITY-TIMI 28 trial of clopidogrel (vs placebo) in patients with STEMI treated with aspirin, heparin, and fibrinolysis, clopidogrel reduced the occurrence of death, recurrent MI, or ischemia-driven urgent target vessel revascularization TVR at 30 days.
- In the COMMIT study of STEMI patients, clopidogrel treatment was associated with significant reductions in in-hospital death and the composite endpoint of death, recurrent MI, and stroke.

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