The acute coronary syndromes (ACS), with or without ST-segment elevation, share a common pathophysiology of activated platelets and thrombin generation stimulated by plaque erosion and rupture. Both mechanical and pharmacologic treatment strategies have evolved in an attempt to improve reperfusion at the myocardial tissue level. Intracoronary stents have lowered the incidence of abrupt vessel closure and restenosis, while potent platelet inhibition from intravenous glycoprotein IIb/IIIa antagonists has reduced the rate of periprocedural myocardial infarction and late mortality. Abciximab has well-established clinical benefits in percutaneous revascularization trials, and several recent landmark studies have evaluated the efficacy of concomitant abciximab during mechanical reperfusion therapy in the setting of ACS. These trials are reviewed, and an overall perspective is provided. (J Am Coll Cardiol 2003;41:49S–54S) © 2003 by the American College of Cardiology Foundation

The acute coronary syndromes (ACS) refer to a continuum of pathological, clinical, and outcome features associated with unstable angina, non–ST-segment elevation myocardial infarction (MI), and ST-segment elevation MI (1). At the site of an unstable atherosclerotic lesion, endothelial erosion or plaque rupture occurs with subsequent coronary thrombus formation (2,3). Central to the pathogenesis of ACS is platelet activation and aggregation. The interaction between activated platelets and thrombin forms a potent collaborating mechanism leading to the dynamic propagation of a thrombus.

The benefits of reperfusion therapy during acute MI include early achievement of arterial patency, limiting to the size of infarction, a decrease in left ventricular dysfunction, and improved survival (4–9). Timely restoration of normal antegrade flow and tissue-level perfusion are key factors in the reduction of mortality in acute MI (10,11). Both fibrinolytic therapy and emergent percutaneous coronary intervention (PCI) have contributed to improved clinical outcomes (12), but each has its limitations and is not an ideal reperfusion therapy by itself. Facilitated angioplasty is an approach in which adjunctive fibrinolytic therapy or a platelet glycoprotein (GP) IIb/IIIa receptor blocker is given minutes in advance of emergent PCI to optimize patency, reperfusion, and early clinical outcomes. Indeed, by contrast with the inferior clinical results of most immediate-angioplasty post-fibrinolysis strategies (13), the incorporation of GP IIb/IIIa inhibitors into early reperfusion therapy may provide and maintain an anti-thrombotic milieu in which pharmacologic or mechanical reperfusion therapy can be performed more safely and effectively.

Among patients with non–ST-segment elevation ACS, the combinations of aspirin plus either unfractionated heparin or low-molecular-weight heparin have been recommended for initial management by standard guidelines (14). The antiplatelet effect of aspirin, however, is rather modest. Recent trial data, in fact, show that clopidogrel added to aspirin reduces a composite of death, recurrent MI, and stroke by 20% in the early months after presentation with an ACS (15). For intermediate and high-risk patients, especially those with an ACS (16–20), and among patients undergoing PCI (21), GP IIb/IIIa inhibitors provide additional protection against recurrent ischemia. Neither pharmacologic lysis nor primary coronary stenting alone can fully address the issues that affect clinical outcome after ACS: a platelet-rich thrombogenic milieu, residual arterial stenosis, and distal embolization. Although both pharmacologic (aspirin and heparin) and mechanical (PCI) approaches can improve ACS outcome, the vascular injury associated with the syndrome and PCI results in further activation of platelets and thrombus formation, and it increases the risk of re-occlusion. Thus, by inhibiting the GP IIb/IIIa receptors, the final common pathway of platelet aggregation, platelet deposition, thrombin generation, and distal embolization from the disrupted arterial surface can be attenuated. Over the past decade, with over 25,000 patients enrolled in PCI trials testing GP IIb/IIIa inhibitors, these agents have been shown to reduce the risk of death and non-fatal MI by approximately 35% at 30 days (22–30). Abciximab. Abciximab is a monoclonal antibody that strongly binds the GP IIb/IIIa integrin on platelets, thereby blocking the binding of fibrinogen, its primary ligand. Abciximab also binds to $\alpha_{IIb}\beta_{3}$ (vitronectin) receptors on
smooth muscle cells and may inhibit \( \alpha_M\beta_3 \) receptors located on granulocytes and monocytes (31). Thus, in addition to platelet aggregation inhibition and de-thrombosis, abciximab may reduce inflammation and smooth muscle cell proliferation. Although abciximab binds to receptors for an average of 14 days, effective platelet aggregation inhibition lasts for approximately 36 h after cessation of infusion due to redistribution and clearance of the antibody (32). Animal studies correlated 80% GP IIb/IIIa receptor occupancy with efficacy in thrombosis prevention (33), and a subsequent study defined the clinical weight-adjusted dose, correlating this level of occupancy with 80% platelet aggregation inhibition (up to 20 \( \mu M \) adenosine diphosphate) (34).

**Pharmacologic combinations.** The key limitations to the widespread use of primary PCI strategies for acute MI are attributable to the lack of available catheterization laboratories and the inherent time delays in initiating the procedure (prolonged door-to-balloon time) (10,11). These limitations have led to the continued search for an ideal thrombolytic strategy that would provide a high rate of early Thrombolysis In Myocardial Infarction grade 3 (TIMI-3) flow. Several trials have been performed assessing a combination pharmacologic approach, and although these were designed as medical therapy trials and not with an intent-to-stent approach, they do provide mechanistic insight into the benefit of abciximab for patients with ST-elevation MI. Compared with plasminogen activator monotherapy, early studies (Glycoprotein Receptor Antagonist Patency Evaluation [GRAPE], Strategies for Patency Enhancement in the Emergency Department [SPEED], TIMI-14) (35–37) demonstrated that a combination of low-dose plasminogen activator (tPA or rPA) and abciximab provided more rapid and complete myocardial reperfusion based on TIMI flow rates at 60 to 90 min. The GUSTO V trial (38) studied half-dose reteplase plus full-dose abciximab compared with full-dose reteplase in an open-label design among patients presenting with ST-elevation MI. At 30 days, the all-cause mortality was similar between the two groups (5.6% for the reteplase plus abciximab group, 5.9% for the reteplase group; \( p = 0.43 \)) (38) (Fig. 1). However, recurrent ischemia and re-infarction, as well as the need for coronary intervention, were significantly lower in the reteplase plus abciximab group. The reduction of vessel re-occlusion (recurrent ischemia or re-infarction) demonstrates the importance of activated platelets in acute MI, despite successful initial recanalization and the benefit of platelet IIb/IIIa blockade. The results are likely to be applicable to the facilitated PCI or intent-to-stent approach.

**Abciximab as an adjunct to primary PCI in ST-segment elevation MI.** Primary PCI has been considered an effective alternative for re-establishing coronary perfusion, being successful in >90% of patients (39–41). With intracoronary stent placement, primary PCI results in larger arterial lumen, less re-occlusion of the infarct-related artery, and fewer subsequent ischemic events, compared with balloon angioplasty alone (42–47). Recently, Stone et al. (48) reported the predictive value of myocardial blush score for 30-day mortality after PCI (Fig. 2), which highlights the importance of perfusion at the myocardial tissue level. The strategy of incorporating abciximab with PCI is designed to achieve a more effective initial reperfusion and to maintain an anti-thrombotic milieu, even downstream at the tissue level.

**Figure 1.** Primary and secondary end points at 30 days in the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes V trial. Recorded on day 7 or at discharge, whichever was earlier. MI = myocardial infarction; PCI = percutaneous coronary intervention. Reprinted with permission from Elsevier Science (Lancet 2001;357:1905–14).

**Figure 2.** Association of myocardial blush (microvascular perfusion) and mortality among myocardial infarction patients with Thrombolysis In Myocardial Infarction grade 3 flow undergoing emergent percutaneous transluminal coronary angioplasty. Adapted with permission from the American College of Cardiology Foundation, J Am Coll Cardiol 2000;35:403A.
Because abciximab reduces the 30-day composite end point of death, MI, and urgent revascularization with balloon angioplasty for acute MI (49), and stenting reduces abrupt vessel closure and restenosis (50), the combination of stent and abciximab is logical. In the Stent-Primary Angioplasty in Myocardial Infarction (Stent-PAMI) trial (50), stent placement was associated with lower clinical and angiographic restenosis rates. However, among patients treated with stents, there tended to be a lower incidence of TIMI grade 3 flow (89.4% vs. 92.7%; \(p = 0.10\)), absence of improvement of left ventricular ejection fraction, and more importantly, a suggestion of increased mortality at six months (4.3% vs. 3.5%) and at one year (5.8% vs. 3.1%).

To consider the complementary role of abciximab and stenting in acute MI, the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) (51) trial randomized 2,665 acute MI patients from 92 centers in North America, South America, and Europe, using a 2x2 factorial study design: stent plus abciximab, percutaneous transluminal coronary angioplasty plus abciximab, stent plus placebo, and angioplasty alone. At six months, the primary composite end point (death, re-MI, urgent target vessel revascularization [TVR], or stroke) was reduced by half with stent placement, compared with angioplasty (10.9% vs. 19.3%; \(p = 0.008\)). At 30 days, cumulative subacute thrombosis was lower with abciximab after either angioplasty (reduced from 1.7% to 0.6%; \(p = 0.07\)) or stent placement (1.0% to 0%; \(p = 0.03\)). Notably, abciximab did not offer a clinical benefit among stent recipients (Fig. 3), nor was the post-procedural TIMI grade 0.07) or stent placement (1.0% to 0%; \(p = 0.04\)) (Fig. 4). The presence of post-procedural TIMI 3 flow was strongly associated with a lower incidence of composite end points at 30 days (7.4% with TIMI 3 vs. 35.3% for TIMI 0 to 2; \(p < 0.001\)), similar to the observations from the Stent-PAMI trial (50), SPEED trial (53), and Stone et al. (48). Mortality at six months was also significantly correlated with post-procedural TIMI 3 flow (2.3% with TIMI 3 vs. 17.6% with TIMI 0 to 2; \(p = 0.001\)).

The use of abciximab in PCI-stent for non–ST-segment elevation ACS: EPISTENT and TARGET. There are differences among the three commercially available GP IIb/IIIa inhibitors and in the extent of relative risk reduction of ischemic events provided by these agents in PCI trials. For example, approximately 75% of the abciximab dose is in the bolus given immediately before PCI, whereas <10% of the dose of small-molecule agents is given as...
bolus. This may affect the consistency and extent of platelet aggregation inhibition in the early minutes after drug administration and during the PCI. Eptifibatide, like abciximab, provides inhibition of both αIIbβ3 and αβ3 receptors; (54) tirofiban, on the other hand, demonstrates exclusive specificity toward αIIbβ3 receptor and has a shorter biological half-life.

In the Evaluation of Platelet IIb/IIIa Inhibition in Stenting (EPISTENT) trial (28), the first large-scale clinical study to evaluate a combination of stent placement and abciximab administration, 2,399 patients were enrolled; 782 had unstable angina or an MI within the previous several days. Patients were randomized to abciximab plus balloon angioplasty, stent plus placebo, or stent plus abciximab. At 30-day follow-up, compared with placebo, abciximab had reduced by more than half the composite of death, MI, and urgent TVR among the recent ACS subgroup receiving a stent. At six-month follow-up, the composite rate of death or MI was 12.6% in the stent plus placebo group and 5.0% in the stent plus abciximab group (p = 0.002). As impressive, at one-year follow-up, abciximab reduced mortality in this ACS-stent cohort by 61% (2.3% vs. 0.9%).

The most recent large-scale clinical trial among intent-to-stent patients, the do Tirofiban And Reopro Give similar Efficacy outcome Trial (TARGET) (55) randomized 4,809 patients to either tirofiban (10 μg/kg bolus plus 0.15 μg/kg/min for 18 to 24 h) or abciximab (0.25 μg/kg plus 0.125 μg/kg/min). This study included 3,025 patients who underwent PCI-stent as treatment for an ACS. While this trial was designed as a non-inferiority trial for tirofiban, a significant increase of the composite end point of death, MI, or urgent TVR was associated with tirofiban at 30 days (7.6% vs. 6.0%; hazard ratio [HR], 1.26; p = 0.038). The benefit of abciximab was most profound among the ACS patients (death/MI/TVR at 30 days, 6.3% for abciximab vs. 9.3% for tirofiban; HR, 1.49; 95% CI, 1.15 to 1.93), and this was sustained at six months. Considering the composite of death, MI, and any TVR at six months, the HR for tirofiban tended to be higher (HR; 1.19, p = 0.054). These results from TARGET, especially considering the results of the upstream benefit of tirofiban among ACS-PCI patients in Platelet Receptor inhibition for Ischemic Syndrome Management in Patients Limited to very Unstable Signs and Symptoms (PRISM-PLUS) (17) and Treat Angina with Aggrastat and determine Cost of Therapy with Intensive or Conservative Strategy-Thrombolysis In Myocardial Infarction (TACTICS TIMI)-18 trials (56), raise more questions about the appropriate choice of GP IIb/IIIa agents for management of ACS and the timing coordination for subsequent PCI. The results of published trials in non–ST-segment elevation ACS indicate that, among intermediate-to-high-risk patients who are not proceeding without delay to the catheterization laboratory for urgent PCI, upstream therapy with a small molecule GP IIb/IIIa agent (tirofiban or eptifibatide) should be initiated. For high-risk, non–ST-segment elevation ACS patients who are proceeding to catheter-based intervention immediately with the intent to stent, abciximab appears to confer greater clinical benefit when combined with early PCI.

Conclusions. Large-scale clinical trial evidence over the last decade has demonstrated, unquestionably, that abciximab plays an important and beneficial role in PCI patients, and this is evident among ACS subgroups in intent-to-stent trials. For ST-segment elevation MI, a strategy of interventional procedure with stents and adjunctive abciximab has been shown to be the reperfusion modality of choice when experienced operators and laboratory personnel are available in a timely manner. This approach was shown to be superior to standard thrombolytic therapy in STOP-AMI and superior to direct PCI-stent without abciximab in ADMIRAL. Dual therapy of low-dose reteplase and abciximab is safe and effective as shown in GUSTO-V, but because mortality rates did not differ from standard thrombolytic strategies, this approach is not likely to be competitive with a direct PCI strategy. Abciximab added to combination lytic approaches should be avoided in the elderly (age >75 years) and among patients who are being treated with streptokinase.

The current standard of therapy for moderate-to-high-risk non–ST-segment elevation ACS should include the administration of tirofiban or eptifibatide beginning soon after hospitalization, if immediate PCI is not planned. Because most of the benefits shown in the clinical trials were derived from the complementary use of PCI and intravenous GP IIb/IIIa antagonists, all but low-risk patients should undergo early cardiac catheterization for further risk stratification and possible revascularization while receiving the GP IIb/IIIa inhibitor infusion. Abciximab should be administered to ACS patients who are taken immediately to the catheterization laboratory or who are not already receiving an IIb/IIIa inhibitor before a planned PCI. Among patients undergoing primary coronary intervention, abciximab remains the reference standard of GP IIb/IIIa inhibitor initiated in the catheterization laboratory, though with an increased cost.

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REFERENCES


