

Defining the role of abciximab for acute coronary syndromes: Lessons from CADILLAC, ADMIRAL, GUSTO IV, GUSTO V, and TARGET

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Acute coronary syndromes (ACS), including those associated with or without ST-segment elevation, share a common pathophysiology mediated by activated platelets and thrombin. It is becoming increasingly appreciated that reperfusion therapies using primary mechanical or pharmacologic strategies result in suboptimal reperfusion at the myocardial tissue level. Complete reperfusion of the coronary microvasculature has recently been shown to be an important predictor for survival following myocardial infarction. Abciximab has well-established clinical benefits in numerous interventional trials. Through its anti-platelet and anti-thrombotic activities, abciximab reduces thrombus formation and hence minimizes risk of thrombotic microvascular embolization and improves tissue-level reperfusion. Several recent landmark trials have evaluated the clinical efficacy of adjunctive abciximab during mechanical or pharmacologic reperfusion therapy in the setting of ACS. This article provides an update of the role of abciximab in the treatment for ACS based on the results of these clinical trials. *Curr Opin Cardiol* 2001, 16:375–383 © 2001 Lippincott Williams & Wilkins, Inc.

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Acute coronary syndromes (ACS) refer to a pathological continuum of clinical presentations including unstable angina, non-ST-segment elevation myocardial infarction (MI), ST-segment elevation MI, and sudden ischemic death [1]. Previously thought to be distinct clinical entities, they share a common pathophysiology, which begins with endothelial erosion, followed by plaque rupture, and subsequent coronary thrombus formation [2,3]. Pivotal 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 thrombus.

The benefits of reperfusion therapy during acute MI include early achievement of arterial patency, limiting the infarct size, decreasing left ventricular dysfunction, and improvement of survival [4–9]. Timely restoration of normal antegrade flow is the key to the mortality reduction 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 ideal reperfusion therapy by itself. The so-called “facilitated PCI” implies an approach in which adjunctive fibrinolytic or platelet glycoprotein (GP) IIb/IIIa receptor blocker is used to optimize patency, reperfusion, and early clinical outcomes of emergent PCI procedures. Indeed, in contrast to the inferior clinical results of the immediate angioplasty post-fibrinolysis strategy [13–15], incorporating GP IIb/IIIa inhibitor into early reperfusion therapy may provide and maintain an anti-thrombotic milieu where pharmacologic or mechanical reperfusion therapy can be performed more safely and effectively.

For non-ST-segment elevation ACS, aspirin plus unfractionated heparin (UFH) or low-molecular-weight-heparin (LMWH) have been recommended in the standard guideline as initial management [16]. However, the antiplatelet effect of aspirin is rather modest. Clopidogrel in addition to aspirin reduces mortality, recurrent MI, and stroke by 20% within a mean duration of 9 months after presentation of ACS [17]. For intermediate and high-risk patients, GP IIb/IIIa inhibitors provide additional protection against recurrent ischemia [18–22]. Over the past decade, with over 16,000 patients enrolled in PCI trials, GP IIb/IIIa inhibitors have been shown to

reduce the risk of death and non-fatal MI by 30-40% [23–29].

Pathophysiological consideration

Central to the acute thromboembolism in ACS is the activated platelets and thrombin. Apart from converting fibrinogen to fibrin, thrombin also causes vasoconstriction, activates platelets, Factors V and VIII, and augments the binding of fibrinogen, von Willebrand factor and collagen to platelets. Adhesion of platelets to inflammatory cells is increased with the number of surface GP IIb/IIIa integrins and P-selectin complex expression on the activated platelets. In addition, activated platelets release pro-coagulants (Factor V, fibrinogen, and Factor XIII), and promote thrombin generation by providing a phospholipid surface that is important for the formation of prothrombinase complex and by GP IIb/IIIa-mediated prothrombin activation.

Neither pharmacologic lysis or primary coronary stenting alone can fully address the issues that affect the clinical outcomes following ACS—a platelet-rich thrombogenic milieu, residual stenosis, and distal embolization. Although both fibrinolytic and coronary stenting can achieve recanalization, the vascular injury—either spontaneously (ACS) or iatrogenically (PCI)—results in further activation of platelets and thrombus formation, and increases the risk of reocclusion. Hence, by inhibiting the GP IIb/IIIa receptors, the final common pathway of platelet aggregation, platelet deposition, thrombus generation, and distal embolization on the disrupted arterial surface can be attenuated. It is hoped that these efforts could result in lowering the risk of subsequent ischemia, increased myocardium salvage, and improvement of left ventricular function.

Abciximab

Abciximab strongly binds to the fibrinogen receptor on platelets. It also binds to $\alpha_v\beta_3$ (vitronectin) receptors on smooth muscle cells and may inhibit $\alpha_M\beta_2$ (MAC-1) receptors located on granulocytes and monocytes [30]. Hence, in addition to inhibition of platelet aggregation and thrombosis, abciximab theoretically may reduce inflammation and smooth muscle cell migration and proliferation. Although abciximab binds to receptors for an average of 14 days, the effective aggregation platelet inhibition lasts for 36 hours after cessation of infusion due to redistribution and clearance of the antibody [31]. Animal studies correlate 80% GP IIb/IIIa receptor occupancy with efficacy in thrombosis prevention [32], and studies have defined the clinical weight-adjusted dose, correlating this level of occupancy with 80% platelet aggregation inhibition (up to 20 μ M adenosine diphosphate [ADP]) [33].

Pharmacologic combinations: GUSTO V

The major deficiency of primary PCI strategy for acute MI lies in the inherent delay of the procedure (prolonged door-to-balloon time) [10,11]. On the other hand, the

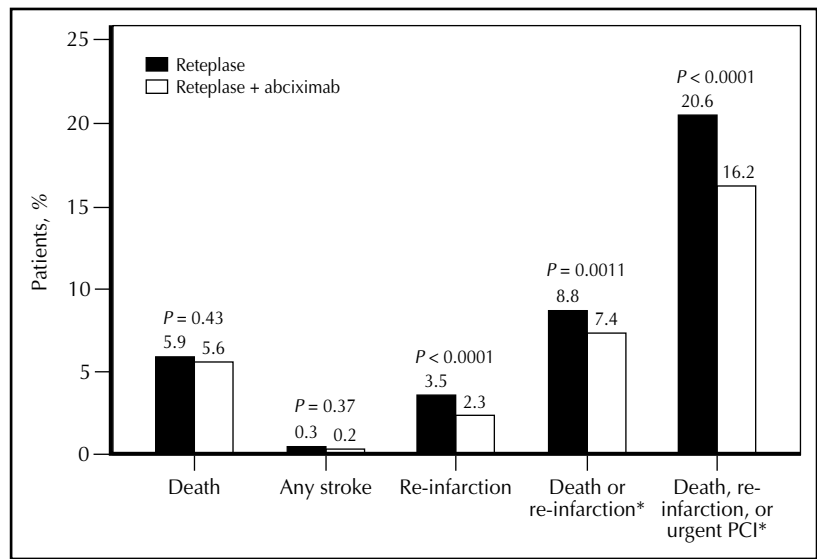
patency rate achieved by thrombolytic therapy alone has been 50 to 60% in most recent trials, and the increased reperfusion efficacy and fibrin specificity of fibrinolytics has not translated into a significant mortality reduction with third generation in large-scale clinical trials [34–36]. As compared with plasminogen activator monotherapy, early studies (GRAPE, SPEED, TIMI-14) [37–39] suggested that a combination of low-dose plasminogen activator (tPA or rPA) and abciximab might provide more rapid and complete myocardial reperfusion based on TIMI flow rates at 60 and 90 minutes.

With this in mind, the GUSTO V trial [40••] examined the clinical efficacy and safety of half-dose reteplase (5 U, 30 minutes apart) and full-dose abciximab (0.25 mg/kg bolus and 0.125 mg/kg/min for 12 hours) as compared to full-dose reteplase in an open-label design. The inclusion criteria were chest discomfort suggestive of myocardial ischemia, associated with electrocardiographic criteria of ST-segment elevation myocardial injury or new left-bundle branch block. All patients received aspirin and adjusted dose of heparin. Coronary angiography and angioplasty were performed at the discretion of the physicians, and periprocedural abciximab administration was permitted in the reteplase-only group if coronary intervention was done within 24 hours, and was recommended if beyond 24 hours of randomization. At 30 days, the all-cause mortality was similar between the two groups (5.6% for the reteplase+abciximab and 5.9% for the reteplase group, $P = 0.43$) [40••] (Fig. 1). Recurrent ischemia and re-infarction, as well as the need of coronary intervention, were significantly lower in the reteplase+abciximab group at 7 days. The frequencies of major cardiac complications, such as ventricular tachyarrhythmias, asystole, ventricular septal defect or rupture, were in favor of the combination strategy. More encouragingly, there was no significant difference for hemorrhagic stroke in the overall population, although a trend towards more intracranial hemorrhage appears to be associated with elderly patients (for age > 75 years, 2.1% for combination *vs* 1.1% for monotherapy, $P = 0.069$). The incidence of non-intracranial bleeding and thrombocytopenia was higher with the combination.

The most important implication of GUSTO V is that this study opens the door for an alternative to the reperfusion strategy that has been used since the mid-1980's. The “positive” non-inferiority result in the GUSTO V trial reassures the concept of combined fibrinolytic and GP IIb/IIIa strategy in acute MI, and encourages the ongoing effort of testing other combinations (Table 1). The attractiveness of the combination approach is that for patients who fail to achieve prompt reperfusion, such a strategy (“upstream” GP IIb/IIIa inhibition) may facilitate a smooth transition and continuation of GP IIb/IIIa blockade from pharmacotherapy to revascularization. With a large clinical dataset, the true safety pro-

Figure 1. Endpoints at 30 days in GUSTO V trial

Primary and secondary endpoints at 30 days in GUSTO V trial. * Recorded on day 7 or at discharge, whichever was earlier. Adapted from [40].



file of combination strategy, as well as predictors for intracranial hemorrhage, could be formulated. Long-term follow-up may identify the subgroup population who will most benefit, or be at increased risk, with combination therapy. Finally, the Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) study, which compares reteplase+abciximab with abciximab alone before primary stenting, will be another step forward in the examination of facilitated PCI strategy for AMI.

Abciximab as an adjunct for primary PCI for ST-elevation MI

Primary percutaneous coronary angioplasty has been considered as an effective alternative for re-establishing coronary perfusion being successful in >90% of patients [41–43]. With intracoronary stent placement, primary PCI results in larger arterial lumen, less re-occlusion of infarct-related artery, and fewer subsequent ischemic events, as compared with balloon angioplasty PTCA alone [44–49]. Recently, Stone and coworkers [50•] 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 aims to achieve a more effective initial reperfusion and maintain an anti-thrombotic milieu that is more conducive to early PCI. By limiting platelet aggregation and propagation of thrombotic events, the full benefit of early and sustained vessel patency can be achieved.

Because abciximab reduces the composite endpoint of death, MI, and urgent revascularization during balloon angioplasty for acute MI [51], and stenting reduces repeat revascularization [52], the combination of stent and abciximab appears to be logical. In the Stent-PAMI trial

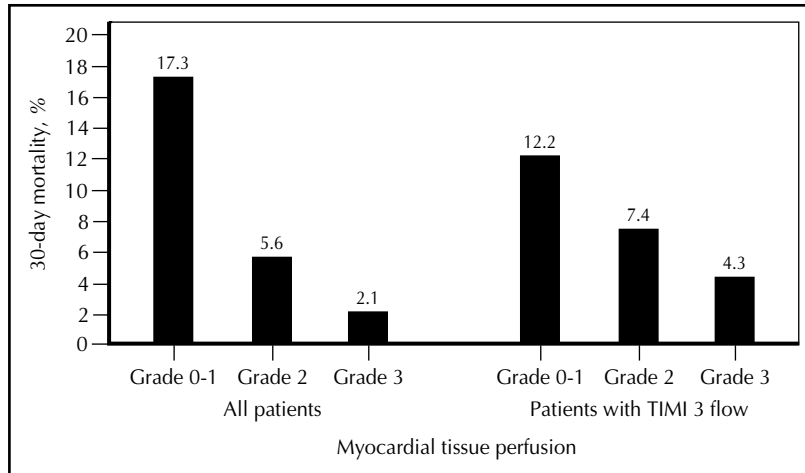
[52], stent placement was associated with lower clinical and angiographic restenosis rates. However, among patients treated with stents, there tended to be lower incidences of TIMI grade 3 flow (89.4 vs 92.7%, $P = 0.10$), absence of improvement of LVEF, and more importantly, a suggestion of increased mortality at 6 months (4.3% vs 3.5%) and at 1 year (5.8 vs 3.1%). In a randomized trial of 200 acute MI patients undergoing stent placement, Neumann *et al.* [53] reported significant improvement in peak flow velocity, regional wall motion, and overall left ventricular function at 14 days among abciximab-treated patients as compared with placebo. In the STOPAMI trial [54•], which randomized 140 acute MI patients to stent + abciximab or alteplase, stent + abciximab was associated with improved myocardial salvage based on follow-up nuclear scintigraphic studies. In addition, post-hoc analysis revealed a trend of lower mortality and target vessel revascularization with stent + abciximab. This reassures that mechanical reperfusion strategy with abciximab is a reasonable approach for acute MI.

Table 1. Planned or ongoing trials testing the combination strategy with fibrinolytic and glycoprotein IIb/IIIa inhibitors for acute MI

Study acronym	Fibrinolytic	Glycoprotein IIb/IIIa blocker
ASSENT 3	Tenecteplase	Abciximab
INTEGRITI/TIMI 20	Tenecteplase	Eptifibatide
ENTIRE/TIMI 23	Tenecteplase	Abciximab
FASTER/TIMI 24	Tenecteplase	Tirofiban
TIGER	Tenecteplase	Eptifibatide

ASSENT 3, Third Assessment of Safety and Efficacy of a New Thrombolytic; ENTIRE, Enoxaparin and TNK-tPA With or Without GP IIb/IIIa Inhibitor as Reperfusion Strategy in ST-Elevation MI; FASTER, Fibrinolytics and Aggrastat ST-Elevation Resolution; INTEGRITI, Integrilin and Tenecteplase in Acute Myocardial Infarction; TIGER, Tenecteplase and Integrelin Given for Event Reduction.

Figure 2. Association of myocardial blush and mortality



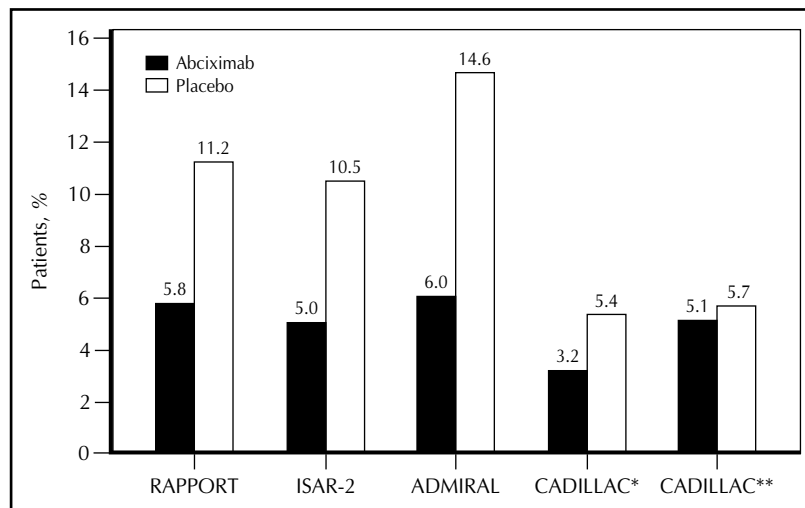
Association of myocardial blush (microvascular perfusion) and mortality among 173 acute MI patients undergoing emergent PTCA. Adapted from [50].

To re-address the issue of complementary role of abciximab and stenting in acute MI, the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial randomized 2665 acute MI patients from 92 centers in North and South America and Europe using a 2x2 factorial study design: stent + abciximab, PTCA + abciximab, stent + placebo, and PTCA alone. At 6 months, the primary composite endpoint (death, re-infarction, urgent target vessel revascularization, or stroke) was halved with stent placement as compared with PTCA (10.9% vs 19.3%, $P = 0.008$). At 30 days, the cumulative subacute thrombosis was lower with abciximab after either PTCA (reduced from 1.7% to 0.6%, $p = 0.07$) or stent placement (1.0 to 0%, $P = 0.03$). Notably, abciximab was noted to offer no clinical benefit among stent-recipients (Fig. 3), nor was the post-procedural TIMI grade 3 flow improved with abciximab. This finding may have been affected by the relatively low-risk population enrolled in this study, as reflected by

the much lower mortality rate when compared with other primary PCI trials.

The Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-term Follow-up (ADMIRAL) study [55••] examined the effect of abciximab in primary stenting for acute MI. The 30-day composite endpoint of death, MI, or urgent target-vessel revascularization was reduced from 14.6% to 6.0% with adjunctive abciximab as compared with placebo (relative risk = 0.41, 95% confidence interval = 0.18–0.93, P value = 0.01). This benefit was sustained at 6 months. Importantly, the investigators linked the relationship of TIMI 3 flow with clinical outcome among acute MI patients undergoing primary stenting. The incidence of TIMI 3 flow was significantly higher among the abciximab group prior to (16.8 vs 5.4%, $P = 0.01$), and at the end of the procedure (95.1 vs 86.7%, $P = 0.04$) (Fig. 4). The presence of post-procedural TIMI 3 flow

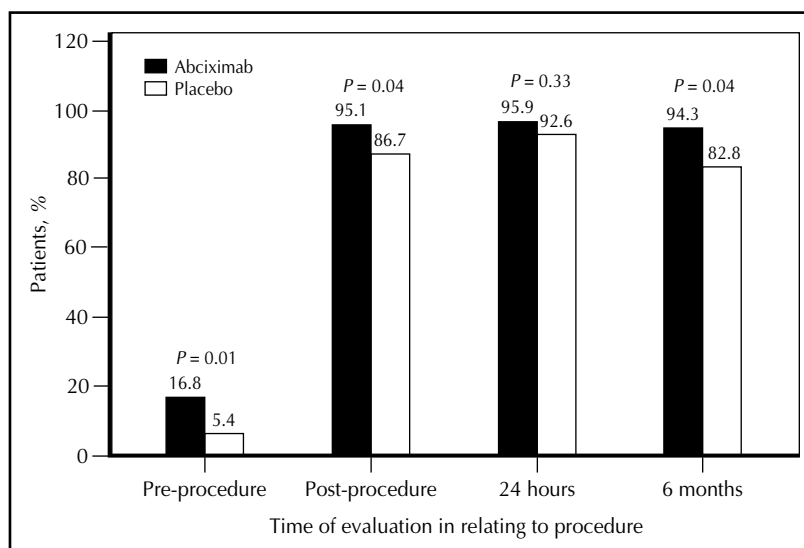
Figure 3. Results using adjunctive abciximab for PCI in acute MI trials



Death, re-infarction, or urgent target vessel revascularization at 30-days using adjunctive abciximab for PCI in acute MI trials. CADILLAC* = PTCA arm; CADILLAC** = Stent arm.

Figure 4. Achievement of TIMI 3 flow

Achievement of TIMI 3 flow with abciximab in ADMIRAL trial. Adapted from [55••].



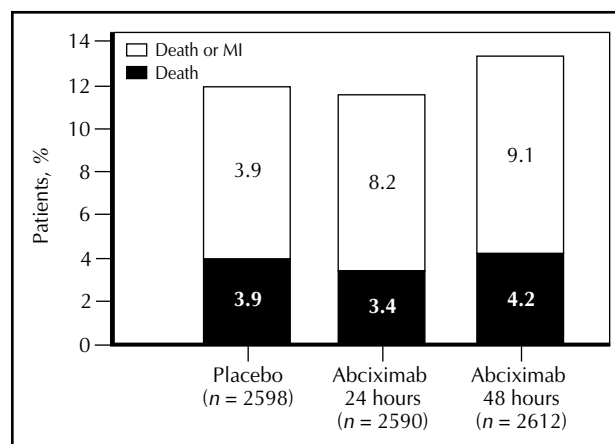
was strongly associated with a lower incidence of composite endpoints at 30 days (7.4% with TIMI 3 vs 35.3% for TIMI 0-2, $P < 0.001$), similar to the observations from the Stent-PAMI trial [52], SPEED trial [38], and Stone et al [50]. Mortality at 6 months was also significantly correlated with post-procedural TIMI 3 flow (2.3% with TIMI 3 vs 17.6% with TIMI 0-2, $P = 0.001$). Interestingly, within the diabetic subgroup, abciximab resulted in a significant reduction in death (0 vs 16.7%, $P = 0.02$), and composite endpoints of death, reinfarction, or any revascularization (20.7 vs 50.0%, $P = 0.02$), as compared with placebo.

The use of abciximab in Non-ST-segment elevation ACS: GUSTO IV and TARGET

Individual variability exists among the 3 commercially available GP IIb/IIIa inhibitors. Different from the small molecule agents, most of abciximab's dose is in the bolus given immediately prior to PCI. Besides, it is non-renal excreted and hence dose adjustment for renal insufficiency is not required. The decline of anti-thrombotic effect occurs gradually over 24-48 hours after cessation of infusion. Eptifibatid, like abciximab, provides inhibition to both $\alpha_{IIb}\beta_3$ and $\alpha_v\beta_3$ receptors; the latter may inhibit the binding of smooth muscle cells and thrombospondin [56]. Tirofiban, on the other hand, demonstrates exclusive specificity towards $\alpha_{IIb}\beta_3$ receptor, and has a shorter duration of biological half-life.

The benefits of eptifibatid and tirofiban seen in the ACS trials prompted a study of abciximab as primary medical therapy for ACS. The GUSTO-IV trial [57••] randomized 7800 patients who were believed to have ACS based on anginal symptom, plus elevation of troponin T or ischemic electrocardiographic changes, to 3 treatment arms: abciximab bolus plus 48-hour infusion,

abciximab bolus plus 24-hour infusion, or placebo. Aspirin and UFH were given to all patients. As compared with the 5 P's (PRISM, PRISM-PLUS, PURSUIT, PARAGON-A, and PARAGON-B) [18,19,21,22,27], the study protocol discouraged early PCI unless severe refractory ischemia occurred [57••]. In fact, less than 5% patients underwent PCI within the first month after enrollment. At 30 days, the composite endpoint of death and MI was not different across the three groups (48-hour abciximab 9.1%, 24-hour abciximab 8.2%, placebo 8.0%, $p = ns$) (Fig. 5). Even within the troponin-positive subgroup (a cohort shown to benefit most from GP IIb/IIIa inhibition in the other ACS trials), clinical benefit was not observed among patients given abciximab (death or MI at 30 days: 11.7% for 48-hour abciximab, 10.2% for 24-hour abciximab, and 9.7% for placebo).

Figure 5. Primary endpoints in GUSTO IV

The primary endpoints of death or MI at 30 days in GUSTO IV trial. Adapted from [57••].

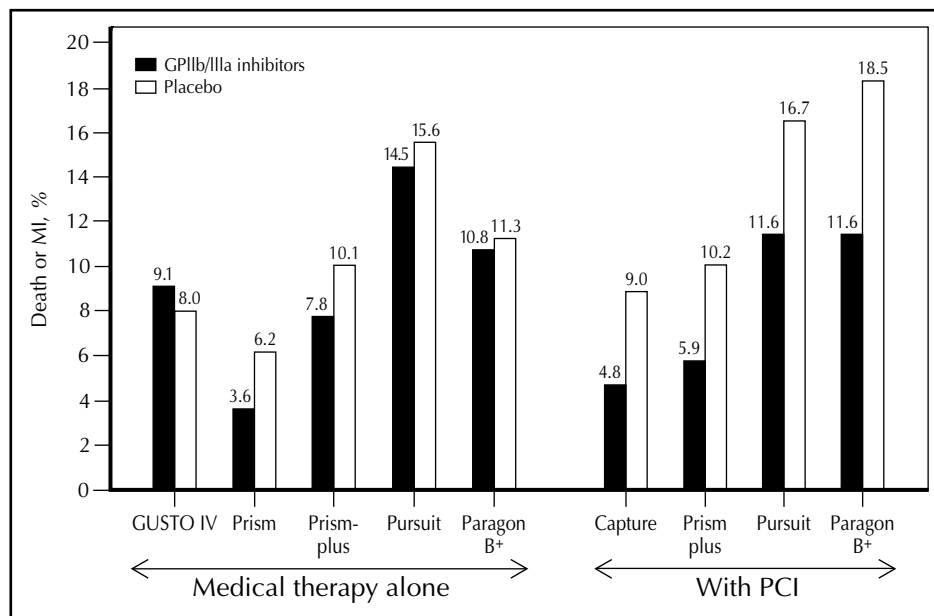
Some of the postulated explanations for the negative results from GUSTO IV include enrollment of a relatively low-risk population, identified by positive troponin alone without electrocardiographic manifestations of ischemia, uncertainty regarding appropriate dosing, the possibility of untoward “toxic” effect with prolonged platelet inhibition with abciximab, and the lack of PCI. The difference in the efficacy of abciximab in GUSTO IV and in CAPTURE, EPIC, EPILOG, and EPISTENT trials [23–26] underscores the complementary relationship of GP IIb/IIIa inhibitor administration during PCI. In fact, when stratifying the data from other GP IIb/IIIa inhibitor-ACS trials into those with and without PCI, the clinical benefits are mainly observed among patients who have received PCI (Fig. 6).

Of equal importance in examining the role of abciximab in non-ST-segment elevation ACS is the Do Tirofiban And Reopro Give Similar Efficacy Trial (TARGET) [58••]. With the routine use of GP IIb/IIIa inhibitors in PCI, efforts to find a less expensive platelet inhibitor with similar efficacy as abciximab would be ideal. The TARGET trial randomized 4809 patients undergoing elective or urgent PCI with an intention-to-stent to receive either tirofiban (10 µg/kg bolus plus 0.15 µg/kg/min for 18 to 24 hours) or abciximab (0.25 µg/kg plus 0.125 µg/kg/min). Although this trial was initially designed as a non-inferiority trial for tirofiban, a significant increase of composite endpoint of death, MI, or urgent target-vessel revascularization was associated with tirofiban at 30 days (7.6 vs 6.0%, hazard ratio=1.26, $P = 0.038$), with the difference largely explained by significantly

fewer peri-procedural MI with abciximab (5.4% vs 6.9%, $P = 0.04$). Superiority of abciximab at 30 days was consistent across individual ischemic endpoints. However, the composite endpoint was no longer different at 6 months [59]. The initial reduction of peri-procedural MI was not translated into a 6-month mortality reduction. The benefit of abciximab was most profound among the 3,025 ACS patients (death/MI/TVR at 30 days, 6.3% for abciximab vs 9.3% for tirofiban, hazard ratio=1.49, 95% confidence interval 1.15-1.93) and this was sustained at 6 months. Since the two drugs provided nearly identical 6-month outcomes, these data suggest that the non-antiplatelet effects of abciximab, vitronectin and MAC-1 inhibition, have no benefit on survival or restenosis.

The results of GUSTO IV and TARGET trials raised more questions about the appropriate choice of GP IIb/IIIa agent for management of ACS. By summarizing the results from GUSTO IV and TARGET, medium- or high-risk ACS patients should be started on tirofiban while being triaged for early catheterization within 48 hours, followed by revascularization by either PCI or CABG. Based on TACTICS-TIMI 18 trial led by Cannon and co-investigators [60••], an early invasive strategy with tirofiban is an ideal approach, especially in the subgroup with troponin elevation. On the other hand, if PCI is planned within the first few hours from admission, abciximab could be started in advance or in the catheterization laboratory, given the superior 30-day and 6-month outcome with abciximab as compared to tirofiban within the ACS population in TARGET.

Figure 6. Results with medical therapy alone and using PCI



The incidence of death or MI at 30 days after the administration of GP IIb/IIIa inhibitors for ACS, stratified by invasive and non-invasive strategies. This contrasts the benefits gained by PCI with adjunctive GP IIb/IIIa antagonist as compared with GP IIb/IIIa antagonist used as a medical therapeutic alone. The results of PARAGON B presented include composite endpoint of death, MI, or refractory ischemia.

Conclusions

Based on the evidence accumulated over the last decade, abciximab undoubtedly plays a key role in ACS patients undergoing PCI, or combined with fibrinolytic for reperfusion. The current standard of therapy for moderate to high-risk non-ST-elevation ACS should include the administration of tirofiban or eptifibatide, beginning soon after hospitalization if immediate PCI is not planned. Since most of the benefits shown in the clinical trials were derived from the complementary usage 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 GP IIb/IIIa inhibitor infusion. Abciximab should be reserved for patients who are taken immediately to the catheterization laboratory and have not been treated with other agents, or have a planned PCI. Among patients undergoing primary coronary intervention, abciximab remains the reference standard of GP IIb/IIIa inhibitors within the catheterization laboratory based on the results of long-term follow-up in the EPI trials (EPIC, EPILOG, EPISTENT) and the TARGET, though with an increased cost.

For ST-elevation MI, an interventional procedure with stents and adjunctive abciximab is the reperfusion modality of choice, provided experienced operators and laboratory personnel are available in a timely manner. Dual therapy of low-dose reteplase and abciximab is safe and effective, and study results of various combination strategies of fibrinolytic and GP IIb/IIIa inhibitors will continue to emerge. Because combined strategy is associated with a trend towards higher risk of intracranial hemorrhage in elderly population (age > 75 years), monotherapy may be more suitable as a pharmacotherapy for acute MI in these patients. On the other hand, for patients undergoing early PCI (within 12 hours of therapy), the combined strategy appears to be attractive due to the benefits associated with GP IIb/IIIa blockade during PCI. The variation in the pharmacokinetics between different GP IIb/IIIa inhibitors may highlight the importance of platelet monitoring in this situation. If trials show similar efficacy between a combined strategy and monotherapy immediately prior to PCI, the issue of cost will be a key factor determining the optimal pharmacologic therapy for acute MI.

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