Targeting the Use of Platelet IIb/IIIa Inhibitors: Treatment of Acute Myocardial Infarction

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Reperfusion strategies for acute myocardial infarction (MI) have important limitations. As an adjunct to primary angioplasty or stenting, platelet glycoprotein IIb/IIIa inhibition with abciximab has been demonstrated to reduce significantly the incidence of acute ischemic events and improve microvascular tissue level reperfusion. For pharmacologic reperfusion, the combination of abciximab with half-dose fibrinolytic agents does not diminish short-term mortality compared with fibrinolytic monotherapy alone. However, combination reperfusion therapy is associated with lower rates of reinfarction and urgent revascularization procedures, although non-intracranial hemorrhage risk is increased. Strategies to merge combination pharmacotherapy optimally with mechanical revascularization during acute MI are under investigation.
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Notwithstanding efficacy demonstrated in randomized trials, reperfusion strategies for acute myocardial infarction (MI) remain subject to important limitations. The pharmacologic approach with fibrinolytic therapy now appears to have reached a plateau of mortality reduction, with several large-scale studies failing to show incremental benefit with the newer third-generation agents reteplase, tenectoplase, or lanoteplase. Lack of progress in this

regard may be related to an apparent "ceiling" of patency achieved with these drugs, persistent cyclical flow or frank reocclusion in many patients, or impaired microvascular tissue-level reperfusion. Moreover, although mortality reduction is critically dependent upon the time to reperfusion, relatively few patients present within an ideal time window. Finally, a disturbing trend over time toward increasing rates of intracranial hemorrhage has been observed, likely related to broader inclusion criteria for thrombolytic treatment as well as the increasing "aggressiveness" of antithrombotic therapy.

Relatively few patients present within an ideal time window.

Mechanical approaches to revascularization have been advocated as a means to overcome the limitations of fibrinolytic therapy, and randomized trials comparing fibrinolysis to direct percutaneous coronary intervention (PCI) have in general shown immediate intervention to be associated with lower rates of mortality and hemorrhagic complications. But difficulties exist with direct angioplasty as well, including limited catheterization laboratory and staff availability, the requirement for institutional and operator expertise, and logistical barriers to mobilizing catheterization laboratory teams during off-hours. Most important, the treatment effect of direct angioplasty, as with fibrinolytic therapy, is dependent upon the time to reperfusion. Moreover, the quality of tissue-level microvascular reperfusion often remains impaired despite restoration of epicardial infarct vessel patency by mechanical techniques, with an adverse impact on ventricular function and mortality. Although stenting appears to be superior to balloon angioplasty with regard to rates of restenosis and repeat target vessel revascularization (TVR), stents do not improve microvascular flow and have not been shown to lessen mortality or enhance myocardial salvage.

A dichotomy therefore exists between two imperfect approaches to patients with acute MI. Fibrinolytic therapy has the advantages of rapid administration, wide availability, and convenience; direct PCI may be more efficacious at expert institutions, carries less bleeding risk, and allows anatomic-based risk assessment. Until recently, the combination of mechanical and pharmacologic approaches has been hindered by data from trials performed in the 1980s showing higher rates of ischemic and hemorrhagic complications among patients treated with routine adjunctive angioplasty after full-dose thrombolytic therapy. However, the introduction into clinical practice of platelet glycoprotein (GP) IIb/IIIa receptor antagonists provides an opportunity not only to improve the safety and efficacy of PCI during acute infarction but perhaps also to enhance the effectiveness of fibrinolytic therapy and to exploit the strengths of these different approaches in combination.

Stents do not appear to improve microvascular flow.

Given the unequivocal efficacy of aspirin, with or without reperfusion therapy, in improving mortality and reducing reinfarction and recurrent ischemia among patients with acute ST-segment-elevation MI, the potential roles of GP IIb/IIIa inhibitors in this setting have been investigated as 1) adjunctive therapy during primary or direct PCI; 2) a sole means of reperfusion; 3) adjunctive therapy to full-dose fibrinolytic agents; and 4) adjunctive therapy with reduced-dose fibrinolytic agents.

Glycoprotein IIb/IIIa Blockade as an Adjunct to Primary PCI

Periprocedural administration of intravenous GP IIb/IIIa receptor antagonists has been demonstrated to improve markedly the safety of urgent or elective percutaneous coronary revascularization, with reductions in the risk of ischemic events by as much as 15%–60% in randomized trials.[1] Moreover, at least one agent, abciximab, has been associated with a long-term reduction in mortality following PCI.[2] The efficacy of GP IIb/IIIa blockade in nonemergency situations might logically be expected to extend as well to the setting of acute MI, a hypothesis that has been tested so far only for abciximab. Adjunctive abciximab therapy was evaluated in RAPPORT (ReoPro in Acute Myocardial Infarction and Primary PTCA Organization and Randomized Trial)[3] during primary balloon angioplasty and in the ISAR-2 (Intracoronary Stenting and Antithrombotic Regimen trial),[4] ADMIRAL (Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up),[5] and CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications)[6] trials during stenting. In general, the magnitude of reduction

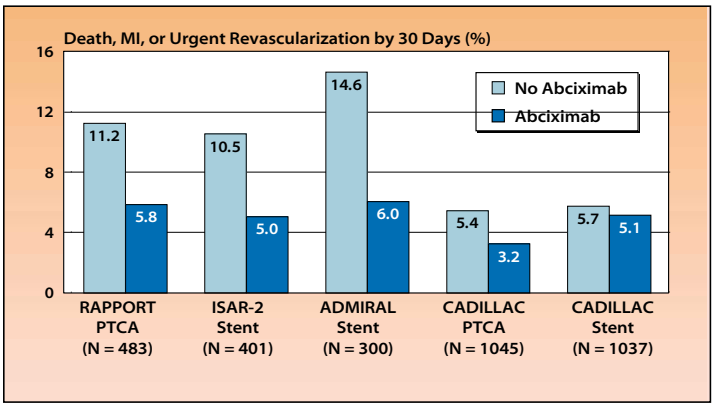


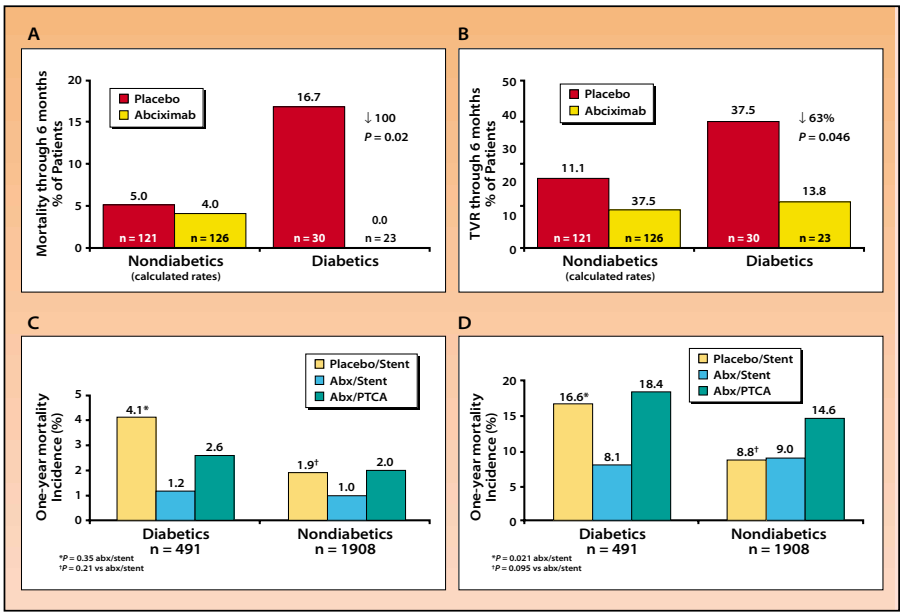
Figure 1. *Composite 30-day ischemic endpoint event rates in placebo-controlled trials of abciximab during primary percutaneous coronary revascularization for acute myocardial infarction (MI). PTCA, percutaneous transluminal coronary angioplasty. Data from Brener et al,[3] Neumann et al,[4] and Montalescot et al.[5]*

in 30-day acute ischemic endpoints (death, reinfarction, or urgent repeat revascularization) in these trials of acute MI (50%–60% relative risk reductions) was similar to that observed in other PCI trials for more elective indications (Figure 1). The CADILLAC trial was designed to compare angioplasty with stenting with or without abciximab in patients presenting with acute MI. A reduction of subacute thrombosis and recurrent ischemia leading to repeat revascularization of the target vessel during the first several weeks following stenting or PTCA was observed, though there was no enhancement of Thrombolysis in MI (TIMI) 3 flow rates or reduced late cardiac events. The very low event rate in CADILLAC relative to the other three trials (Figure 1), however, raises important concerns regarding the ascertainment of acute endpoints (the trial was designed primarily to assess the effect of stenting versus angioplasty on late TVR) and the risk profile of patients in that trial. The overall body of randomized trial data from elective and acute MI studies firmly supports the efficacy of abciximab in reducing acute ischemic events during primary PCI.

The influence of abciximab on long-term rates of restenosis or elective TVR following acute PCI, as in the elective setting, is less clear. In RAPPORT, ISAR-2, and CADILLAC, there were no differences between placebo- and abciximab-treated patients with regard to these endpoints at 6 months, whereas elective TVR rates in ADMIRAL were significantly reduced from 17.2% to 9.4% (P = .046) by abciximab. A particularly noteworthy effect in this regard was observed among patients with diabetes (6-month TVR reduced from 37.5% to 13.8%; P = .046), who also enjoyed significant reductions in the risks of mortality (16.7% vs 0%; P = .020) and urgent revascularization (12.5% vs 0%; P = .049).[5] This diabetic protection afforded by abciximab in ADMIRAL is consistent with the significant reduction of mortality and TVR observed in the EPISTENT trial (Figure 2).[7]

In ADMIRAL, the clinical benefit of abciximab was linked in part to observed improvements in infarct-vessel patency.[5] Prior to revascularization, TIMI grade 3 flow (complete epicardial vessel patency) was present in 16.8% versus 5.4% of patients receiving abciximab and placebo (P = .01), respectively. A significant patency advantage persisted in the abciximab group even immediately after the revascularization procedure and at 6-month follow-up. Supportive of the importance of achieving patency prior to revascularization were data regarding treatment effect of abciximab relative to timing of administration. Of the 300 patients in the ADMIRAL trial, 78 (26%) were randomized and administered the study drug in the ambulance or

Figure 2. *Abciximab provided a consistent mortality and target vessel revascularization (TVR) benefit in the* **(A, B)** *ADMIRAL and* **(C, D)** *EPISTENT trials. PTCA, percutaneous transluminal coronary angioplasty. Data in* **A, B** *from Montalescot et al[5]; in* **C** *from Lincoff et al[6]; in* **D** *from Lincoff et al.[7]*



emergency department, and the remainder received placebo or abciximab in the intensive care unit or catheterization laboratory. Early administration was associated with an amplification of the treatment effect of abciximab: the 30-day composite endpoint occurred in 21.1% versus 2.5% of patients receiving early assignment to placebo or abciximab, respectively, compared with rates of 12.4% versus 8.3% among those randomized in the intensive care or catheterization units.

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Further insights into the mechanisms of benefit of abciximab during stenting for acute MI were derived from a placebo-controlled trial of 200 patients by the Munich group.[8] Measurements of Doppler wire flow velocity and left ventricular function were performed immediately after successful stenting and at 14-day follow-up. Although stent placement was successful, with achievement of TIMI 3 patency in nearly all patients, improvements in infarct-vessel peak flow velocity were significantly greater among abciximab-treated patients (18.1 cm/s vs 10.4 cm/s, $P = .024$) and correlated with significantly greater improvements in infarct zone wall motion and higher global left ventricular function. These results suggest that abciximab exerts a beneficial effect beyond that in the epicardial artery, and that intense platelet inhibition by GP IIb/IIIa blockade in this setting may improve tissue-level microvascular reperfusion and thus enhance myocardial salvage. In a separate study, the Munich group also demonstrated that abciximab may reduce platelet-leukocyte interactions and limit microvascular inflammation during reperfusion therapy.[9]

Glycoprotein IIb/IIIa Blockade as Sole Reperfusion Therapy

Based upon evidence of platelet disaggregatory properties of abciximab, it has been suggested that coronary reperfusion may be achieved by potent GP IIb/IIIa inhibition alone, without administration of exogenous plasminogen activators (or percutaneous coronary revascularization). In Phase II studies of patients treated with only abciximab, rates of TIMI 3 reperfusion 45–90 minutes have ranged from 18% to 32%,[10–12] comparable to patency rates achieved with streptokinase. Similarly, TIMI 3 patency rates of approximately 30% were observed in a small study of patients with acute infarction receiving eptifibatide an average of 51 minutes prior to angiography.[13] Thus, although GP IIb/IIIa antagonists may have modest thrombolytic properties, their optimal role in these patients will likely be as adjuncts to traditional reperfusion therapies.

Glycoprotein IIb/IIIa Blockade as an Adjunct to Full-Dose Fibrinolytic Therapy

Preclinical studies have demonstrated that GP IIb/IIIa antagonists accelerate reperfusion and potently inhibit reocclusion and cyclic flow variations in animal models of coronary thrombolysis. Four phase II clinical trials tested various doses of abciximab, eptifibatide, or lamifiban administered in either a delayed fashion or concurrently with full-dose fibrinolytic therapy in patients with acute MI.[14–17] Although details of the study designs, dose ranging, and endpoints varied, consistent trends toward improved early[15] and late[14] angiographic infarct vessel patency were observed with administration of GP IIb/IIIa antagonists with fibrinolytic agents.

Moreover, combination therapy was associated with improvements in the speed and stability of reperfusion, as assessed by continuous electrocardiographic monitoring[15,16]; in one study, for example, the median time to ST-segment recovery was reduced from 116 to 65 minutes ($P = .05$) by the addition of eptifibatide to alteplase.[15] Bleeding complications, however, tended to be increased by combination therapy in these studies; with streptokinase, excess hemorrhagic risk was marked, and led to early termination of one trial.[16,17]

Glycoprotein IIb/IIIa Blockade as an Adjunct to Reduced-Dose Fibrinolytic Therapy

Recent trials have focused on the hypothesis that by inhibiting platelet activation induced by exogenous plasminogen activators and directly disaggregating the platelet thrombus, adjunctive use of GP IIb/IIIa antagonists may allow administration of *reduced* doses of fibrinolytic agents during acute MI. It was hoped that such an approach might accelerate and enhance early patency, improve tissue-level microvascular reperfusion, prevent reocclusion, diminish bleeding complications, and/or reduce the need for "rescue" (for failed reperfusion) PCI while facilitating early PCI performed for other clinical indications.

Six phase II angiographic trials have evaluated or are currently underway to test various dose combinations of fibrinolytic agents, GP IIb/IIIa inhibitors, and heparin (or

enoxaparin) in patients with acute MI. Within the limits of relatively small sample sizes and multiple dosing groups, these trials have, in general, suggested improvements in early epicardial vessel patency with a half-dose fibrinolytic agent plus a full-dose GP IIb/IIIa antagonist compared with standard full-dose fibrinolytic monotherapy.[11,12,18] Improvements in TIMI 3 flow rates at 60 minutes have ranged from 10 to 20 absolute percentage points. Patency rates tended to decline when concomitant heparin doses were reduced below approximately 50–60 U/kg. Additionally, the proportion of patients with resolution of electrocardiographic ST-segment elevations has been greater with combination therapy, suggesting enhanced microvascular tissue-level reperfusion beyond epicardial vessel recanalization. In the TIMI 14 trial, for example, even among patients who had achieved full angiographic infarct vessel patency by 90 minutes, only 44% treated with alteplase monotherapy exhibited complete electrocardiographic ST-segment resolution; this rate was increased to 69% ($P = .0004$) in patients receiving abciximab plus reduced-dose alteplase.[19] Differences in clinical endpoints (ischemic and hemorrhage events) were not typically detected in these small studies, although the combination of abciximab and streptokinase was associated with increased bleeding (mirroring the experience in earlier trials) and has not been investigated further.[12]

Combination therapy has thus far been evaluated in only one large-scale mortality trial, Global Use of Strategies to Open Occluded Arteries in Acute Myocardial Infarction (GUSTO V), in which 16,588 patients were randomized to receive either abciximab plus half-dose reteplase or conventional full-dose reteplase.[20] Planned primary PCI was an exclusion criterion, but emergency angiography and revascularization were permitted for clinical indications of failed pharmacologic reperfusion. Combination therapy was associated with only a nonsignificant reduction in mortality at 30 days, from 5.91% to 5.62% ($P = .45$). Younger patients, those presenting later after the onset of symptoms, and patients with anterior infarction tended to have greater treatment effect. Moreover, there was evidence of more complete and stable reperfusion among patients treated with abciximab plus half-dose reteplase, with significant reductions in rates of reinfarction (3.5% vs 2.3%; $P < .0001$) and recurrent ischemia (12.8% vs 11.3%; $P = .004$) and less frequent need for urgent (largely "rescue") PCI within the first 6 hours (8.6% vs 5.6%; $P < .0001$). The incidence of intracranial hemorrhage was the same in the two treatment groups (0.6%), although combination therapy was associated with nearly a doubling in rates of non-intracranial bleeding complications.

Additional support for the findings of GUSTO V were derived from ASSENT-3 (Assessment of Safety and Efficacy of a New Thrombolytic Regimen), a "large exploratory trial" in which two different combination regimens were compared with tenectoplase monotherapy.[21] A total of 6095 patients were randomized to tenectoplase with unfractionated heparin, tenectoplase with enoxaparin (low-molecular-weight heparin), or half-dose tenectoplase with abciximab. The sample size was too small to assess mortality differences, but both experimental regimens significantly reduced the primary composite endpoint relative to tenectoplase with heparin. The magnitude of treatment effect of abciximab on reinfarction and

Figure 3. *Comparison of in-hospital rates of reinfarction and urgent percutaneous coronary intervention (PCI) in patients randomized to fibrinolytic monotherapy (Lysis) or abciximab plus half-dose fibrinolytic (Abciximab + Lysis) in the GUSTO V and ASSENT-3 trials. All* P < .05 *for the differences between treatment groups. Data from the GUSTO V Investigators[20] and the ASSENT-3 Investigators.[21]*

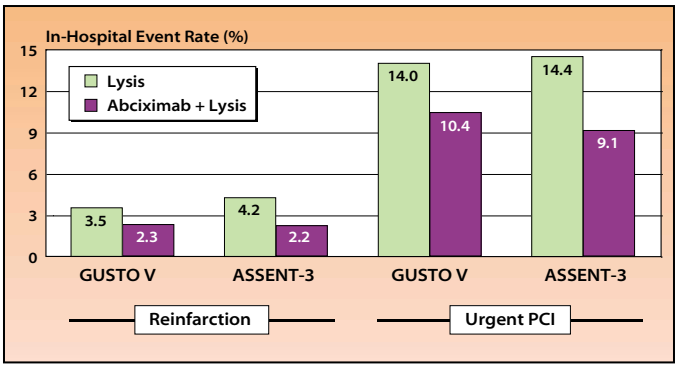
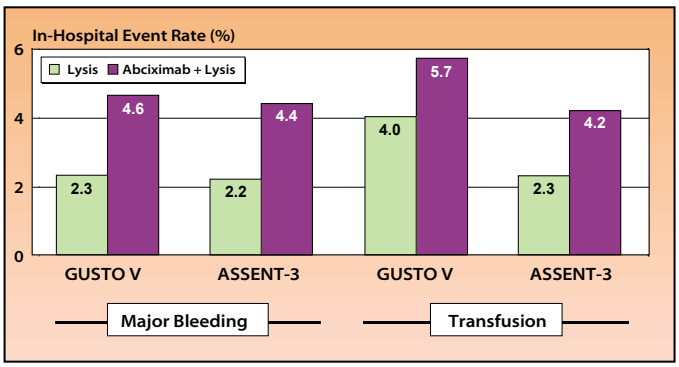


Figure 4. *Comparison of in-hospital rates of major bleeding and blood transfusion in the GUSTO V and ASSENT-3 trials. All* P < .05 *for the differences between treatment groups. Data from the GUSTO V Investigators[20] and the ASSENT-3 Investigators.[21]*



urgent PCI rates was similar to that observed in GUSTO V (Figure 3). As with GUSTO V, however, bleeding complications were increased with combination therapy (Figure 4). In both GUSTO V and ASSENT-3, the clinical benefit of GP IIb/IIIa inhibition with low-dose fibrinolytic was less in elderly patients, due at least in part to an interaction between hemorrhagic risk and advanced age. Among patients over 75 years old in GUSTO V, the intracranial bleeding rate nearly doubled with combination therapy relative to reteplase monotherapy, from 1.1% to 2.1%. Similarly, in ASSENT-3, major bleeding rates in patients over 75 years old with tenectoplase monotherapy and tenectoplase plus abciximab were 4.1% and 13.3%, respectively.

Summary

At present, primary PCI remains the preferred means of reperfusion among most patients with acute MI. As with more elective indications, adjunctive abciximab confers substantial clinical benefit in this setting and should be considered the standard of care. Placebo-controlled data do not exist for eptifibatide and tirofiban during primary PCI. Moreover, given the apparent superiority of abciximab during PCI for non-ST-segment-elevation ischemic syndromes,[22] interchangeability between the different GP IIb/IIIa inhibitors cannot be assumed for patients with acute MI.

For pharmacologic reperfusion, the combination of abciximab and a half-dose fibrinolytic agent has not been shown to fulfill the hopes of a regimen that would improve early mortality while reducing bleeding complications. Nevertheless, this strategy does represent an incremental improvement over fibrinolytic monotherapy, with clear reductions in ischemic morbidity. Assessments of hemorrhagic risk versus clinical benefit must be considered for individual patients, and combination therapy may be best focused on those at higher risk by virtue of larger infarctions or late presentation. In particular, the current body of clinical data suggests that bleeding risk in patients over 75 years of age may be excessive with the combination of GP IIb/IIIa blockade and a fibrinolytic agent, and highlights the need for better therapies in this growing high-risk segment of the population.

Strategies to optimally merge combination pharmacotherapy with mechanical revascularization during acute MI remain to be developed. The GUSTO V and ASSENT-3 trials did not test such an approach; early PCI was reserved for clinical indications of failed reperfusion and was not employed in a routine fashion. The rationale for pretreatment with the combination of a reduced-dose fibrinolytic with a GP IIb/IIIa inhibitor in patients undergoing primary PCI would be to achieve epicardial vessel patency and perhaps enhanced microvascular reperfusion during the time delay inherent in mobilizing the cardiac catheterization laboratory. Trials are currently underway specifically to evaluate this concept of "facilitated PCI." ■

References

1. Lincoff AM, Califf RM, Topol EJ. Platelet glycoprotein IIb/IIIa blockade in coronary artery disease. *J Am Coll Cardiol*. 2000;35:1103–1115.
2. Anderson KM, Califf RM, Stone GW, et al. Long-term mortality benefit with abciximab in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol*. 2001;37:2059–2065.
3. Brener SJ, Barr LA, Burchenal JEB, et al. A randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. *Circulation*. 1998;98:734–741.
4. Neumann F, Kastrati A, Schmitt C, et al. Effect of glycoprotein IIb/IIIa receptor blockade with abciximab on clinical and angiographic restenosis rate after the placement of coronary stents following acute myocardial infarction. *J Am Coll Cardiol*. 2000;35:915–921.
5. Montalescot G, Barragan P, Wittenberg O, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Eng J Med*. 2001;344:1895–1903.
6. Stone G, Grines C, Cox D, et al. Comparison

Main Points

- Fibrinolytic therapy now appears to have reached a plateau of mortality reduction, with several large-scale studies failing to show incremental benefit with the newer third-generation agents reteplase, tenectoplase, or lanoteplase.
- Adjunctive administration of abciximab during primary percutaneous coronary intervention (angioplasty or stenting) for acute myocardial infarction reduces the risk of acute ischemic complications by as much as 50%, improves tissue-level reperfusion, and may diminish microvascular inflammation.
- Administration of GP IIb/IIIa inhibitors as sole reperfusion therapy (without a fibrinolytic agent) results in coronary patency rates similar to that achieved with streptokinase, likely due to platelet disaggregatory properties.
- Pharmacologic reperfusion with the combination of abciximab and half-dose of a fibrinolytic agent does not significantly reduce short-term mortality beyond that of fibrinolytic monotherapy.
- Combination therapy is associated with improved stability of patency, as shown by lower rates of reinfarction, recurrent ischemia, and emergency revascularization. Non-intracranial bleeding rates are increased by combination therapy, and intracranial bleeding rates are increased in elderly patients.

of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med*. 2002;346:957–966.
7. Lincoff AM, Califf RM, Moliterno DJ, et al. Complementary clinical benefits of coronary-artery stenting and blockade of platelet glycoprotein IIb/IIIa receptors. *N Engl J Med*. 1999;341:319–327.
8. Neumann FJ, Blasini R, Schmitt C, et al. Effect of glycoprotein IIb/IIIa receptor blockade on recovery of coronary flow and left ventricular function after the placement of coronary artery stents in acute myocardial infarction. *Circulation*. 1999;98:2695–2701.
9. Neumann FJ, Zohlnhofer D, Fakhoury L, et al. Effect of glycoprotein IIb/IIIa receptor blockade on platelet-leukocyte interaction and surface expression of the leukocyte integrin Mac-1 in acute myocardial infarction. *J Am Coll Cardiol*. 1999;34:1420–1426.
10. van den Merkhof LF, Zijlstra F, Olsson H, et al. Abciximab in the treatment of acute myocardial infarction eligible for primary percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol*. 1999;33:1528–1532.
11. SPEED Trial Investigators. Randomized trial of abciximab with and without low-dose reteplase for acute myocardial infarction. *Circulation*. 2000;101:2788–2794.
12. Antman E, Guigliano R, Gibson C, et al. Abciximab facilitates the rate and extent of thrombolysis: results of the thrombolysis in myocardial infarction (TIMI) 14 trial. *Circulation*. 1999;99:2720–2732.
13. Cutlip DE, Cove CJ, Irons D, et al. Emergency room administration of eptifibatide before primary angioplasty for ST elevation acute myocardial infarction and its effect on baseline coronary flow and procedure outcomes. *Am J Cardiol*. 2001;88:62–64.
14. Kleiman NS, Ohman EM, Kereiakes DJ, et al. Profound platelet inactivation with 7E3 shortly after thrombolytic therapy for acute myocardial infarction: preliminary results of the TAMI 8 trial [abstract]. *Circulation*. 1991;84:II–522.
15. Ohman EM, Kleiman NS, Gacioch G, et al. Combined accelerated tissue-plasminogen activator and platelet glycoprotein IIb/IIIa integrin receptor blockade with Integrilin in acute myocardial infarction. Results of a randomized, placebo-controlled, dose-ranging trial. *Circulation*. 1997;95:846–854.
16. PARADIGM Investigators. Combining thrombolysis with the platelet glycoprotein IIb/IIIa inhibitor lamifiban: results of the platelet aggregation receptor antagonist dose investigation and reperfusion gain in myocardial infarction (PARADIGM) trial. *J Am Coll Cardiol*. 1998;32:2003–2010.
17. Ronner E, Kesteren HA, Zijnen P, et al. Safety and efficacy of eptifibatide versus placebo in patients receiving thrombolytic therapy with streptokinase for acute myocardial infarction. A phase II dose escalation, randomized, double-blind study. *Eur Heart J*. 2000;21:1530–1536.
18. Brener SJ, Zeymer W, Adgey AAJ, et al. Eptifibatide and low-dose tissue plasminogen activator in acute myocardial infarction. The Integrilin and Low-Dose Thrombolysis in Acute Myocardial Infarction (INTRO AMI) trial. *J Am Coll Cardiol*. 2002;39:377–386.
19. de Lemos JA, Antman EM, Gibson CM, et al. Abciximab improves both epicardial flow and myocardial reperfusion in ST-elevation myocardial infarction: observations from the TIMI 14 trial. *Circulation*. 2000;101:239–243.
20. GUSTO V Investigators. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. *Lancet*. 2001;357:1905–1914.
21. ASSENT-3 (Assessment of Safety and Efficacy of a New Thrombolytic Regimen) Investigators. Efficacy and safety of tenectoplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet*. 2001;358:605–613.
22. TARGET Investigators. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Eng J Med*. 2001;344:1888–1894.