# Use of Glycoprotein IIb/IIIa Receptor Inhibitors in Acute Coronary Syndromes

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*Percutaneous coronary interventions (PCIs) with intravenous platelet glycoprotein (GP) IIb/IIIa receptor inhibitors have become the standard of care within the higher-risk population of patients with acute coronary syndromes. Three U.S. Food and Drug Administration–approved GP IIb/IIIa inhibitors are available in the marketplace—abciximab (ReoPro), tirofiban (Aggrastat), and eptifibatide (Integrelin)—and a fourth remains in clinical trials (lamifiban). The existence of a "class effect" among all the GP IIb/IIIa receptor inhibitors is hotly debated, but the variance of effectiveness seen even among the small-molecule drugs argues against the "class effect." In patients with acute coronary syndromes, the superiority of the large molecule, abciximab, over the small molecule, tirofiban, has been shown. In diabetic patients with acute coronary syndromes, abciximab is the only GP IIb/IIIa receptor inhibitor to provide a significant mortality advantage in patients undergoing PCI. Abciximab is also the only agent where clinical data support safety in patients with chronic renal insufficiency.*

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**Key words:** Acute coronary syndromes • Glycoprotein IIb/IIIa receptor inhibitors • Abciximab • Tirofiban • Eptifibatide • Lamifiban

The approach to patients with acute coronary syndromes (ACS) has evolved as we have become more astute in identifying higher-risk patients and allocating appropriate resources to treat these patients. What seems clear is that the higher-risk patients seems to benefit from early referral to coronary angiography and, if appropriate, coronary revascularization. Percutaneous coronary interventions (PCI) with intravenous platelet glycoprotein

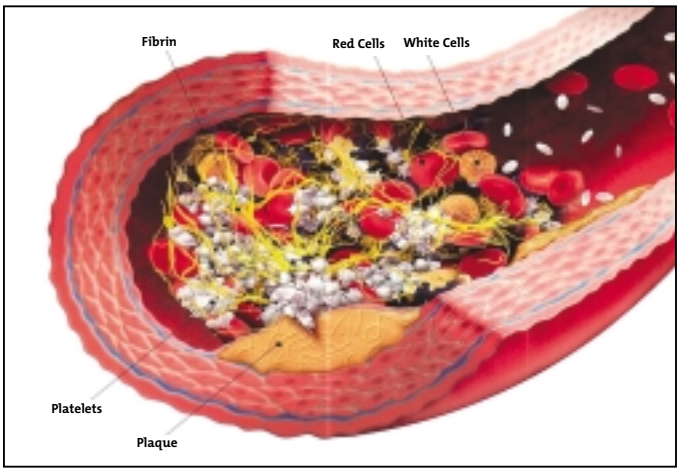


**Figure 1.** *Plaque rupture and the thrombotic cascade.*

(GP) IIb/IIIa receptor inhibitors have become the standard of care within this higher-risk patient population. At the present time three U.S. Food and Drug Administration–approved GP IIb/IIIa inhibitors are available in the marketplace—abciximab (ReoPro), tirofiban (Aggrastat), and eptifibatide (Integrelin)—and a fourth remains in clinical trials (lamifiban). Whether any of these agents provides a clinical advantage in the higher-risk ACS population—by virtue of their different chemical structures, pharmacokinetics, or receptor specificity—will be discussed.

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Over 1,000,000 patients are hospitalized in the United States with an acute coronary syndrome per year.[1] ACS includes a range of conditions from unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI) to ST-segment elevation myocardial infarction. Our focus will be on those patients with ACS who present without ST-segment elevation. Even in this specified patient population, the clinical presentation is heterogeneous and can include a constellation of symptoms consistent with acute myocardial ischemia. The three principal presentations of ACS include new onset of anginal symptoms, an acceleration of anginal symptoms from a previously stable pattern, and rest angina. What distinguishes UA from NSTEMI is the presence of serum markers of myocardial necrosis in NSTEMI.

ACS results from an acute change in the balance of myocardial cellular perfusion and myocardial cellular metabolic demand. Causes of UA include nonocclusive thrombus on a preexisting plaque, coronary spasm, progressive atherosclerotic narrowing obstruction, arterial inflammation, and precipitating factors extrinsic to the coronary artery bed.[2] The mechanism most often responsible for UA/NSTEMI is atherosclerotic plaque rupture, erosion and/or fissuring, followed by thrombosis.[3] Plaque disruption exposes the lipid core containing tissue factor, collagen, and other substrates that activate the coagulation cascade and accelerate platelet adhesion, activation, and aggregation (Figure 1). Myocardial cell death can occur from either epicardial coronary artery thrombosis or distal embolization into the coronary microcirculation.[4]

## Risk Assessment

The ability to assign relative risk to patients presenting with ACS assists clinicians in determining the approach to an individual patient at presentation. The information required for this assessment is easily derived from the patient's history and physical examination, the electrocardiogram, and serum markers of myocardial necrosis (creatinine phosphokinase or troponin). Patients can then be categorized as high-, intermediate-, or low-level risk for the development of subsequent cardiovascular events (recurrent ischemia, MI, and death) (see Table 1). Characteristics that place a patient at high risk include a presentation with pulmonary edema, ongoing rest pain lasting longer than 20 minutes, angina with an $S_3$ gallop, rales, a new or worsening mitral

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**Table 1**
**Short-Term Risk of Death or Nonfatal MI in Patients with Unstable Angina***

| Feature | High Risk: At Least 1 of the Following Features Must be Present | Intermediate Risk: No High-Risk Feature but Must Have 1 of the Following | Low Risk: No High- or Intermediate-Risk Feature but May Have Any of the Following Features |
|---|---|---|---|
| History | Accelerating tempo of ischemic symptoms in preceding 48 h | Prior MI, peripheral or cerebrovascular disease, or coronary artery bypass grafting, prior aspirin use | |
| Character of pain | Prolonged ongoing (>20 min) rest pain | Prolonged (>20 min) rest angina, now resolved, with moderate or high likelihood of coronary artery disease<br>Rest angina (<20 min) or relieved with rest or sublingual nitroglycerin | New-onset or progressive Canadian Classification System (CCS) Class III or IV angina in previous 2 weeks without prolonged (>20 min) rest pain but with moderate or high likelihood of coronary artery disease |
| Clinical findings | Pulmonary edema, most likely due to ischemia<br>New or worsening MR murmur<br>S5 or new/worsening rales<br>Hypotension, bradycardia, tachycardia | Age > 70 years | |
| Electrocardiogram | Angina at rest with transient ST-segment changes > 0.05 mV<br>Bundle-branch block, new or presumed new<br>Sustained ventricular tachycardia | T-wave inversions > 0.2 mV<br>Pathological Q waves | Normal or unchanged ECG during an episode of chest discomfort |
| Cardiac markers | Elevated (eg, TnT or TnI > 0.1 ng/mL) | Slightly elevated (eg, TnT > 0.01 but < 0.1 ng/mL) | Normal |

* Estimation of the short-term risks of death and nonfatal cardiac ischemic events in unstable angina is a complex multivariable problem that cannot be fully specified in a table such as this; therefore this table is meant to offer general guidance and illustration rather than rigid algorithms.

MI, myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; NTG, nitroglycerin; MR, mitral regurgitation; ECG, electrocardiogram; TnT, Troponin T; TnI, Troponin I.

Adapted from Braunwald E, Mark DB, Jones RH, et al. AHCPR Clinical Practice Guideline No. 10, *Unstable Angina: Diagnosis and Management*. Rockville, MD: Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute, US Public Health Service, US Department of Health and Human Services; 1994. AHCPR Publication No. 94-0602.

insufficiency murmur, hypotension, or dynamic ST-segment changes of 1.0 mm or more.[1] In a prospective analysis of the utility of this risk stratification using these clinical criteria, the low, intermediate, and high-risk population experienced 0%, 1.2%, and 1.7% deaths, respectively, within 30 days of presentation to the emergency department.[5]

The electrocardiogram (ECG) and biochemical cardiac markers provide particularly valuable information. Investigators from the Thrombolysis in Myocardial Ischemia III registry reported the 1-year incidence of death or new MI to be 16.3% in patients with 0.05 mV or more ST-segment deviation, 6.8% for patients with isolated T-wave inversions, and 9.2% with no ECG changes.[6] A gradation

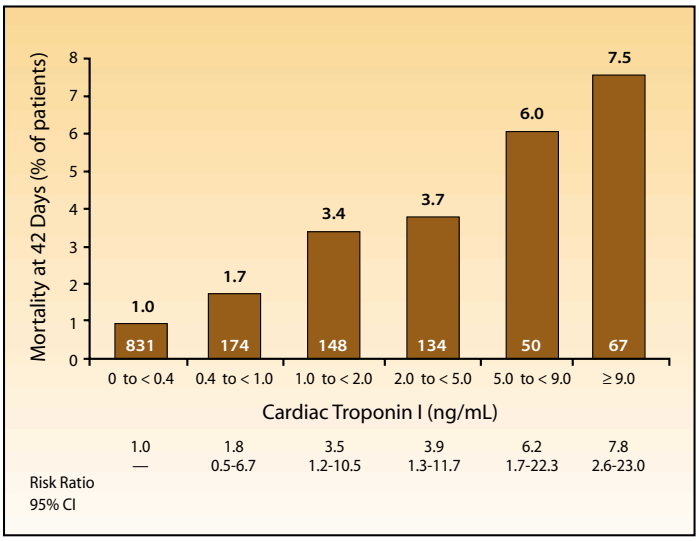


**Figure 2.** *Relationship between cardiac troponin levels and risk of mortality in patients with acute coronary syndromes. Reproduced, with permission, from Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med. 1996;335:1342–1349. Copyright ©1996 Massachusetts Medical Society. All rights reserved.*

of risk was also seen with cardiac troponins, with a 1.0% 42-day mortality in patients with troponin I of less than 0.4 ng/mL up to a 7.5% mortality in patients with troponins over 9.0 ng/mL (Figure 2).

The American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for UA state: "patients who are at intermediate or high risk for adverse outcomes ... should if possible be admitted to a critical care environment with ready access to invasive cardiovascular diagnosis and therapy procedures." The Class I recommendations for an early invasive strategy include patients with any of the following high-risk characteristics[1]:

- Patients with recurrent angina at rest or with low-level activities despite intensive anti-ischemia therapy;
- Elevated Troponin T (TnT) or Troponin I (TnI);
- New or presumably new ST-segment depression;
- Recurrent angina with symptoms of congestive heart failure, $S_3$ gallop, or new or worsening murmur of mitral insufficiency;
- High-risk findings on noninvasive stress testing (left ventricular ejection fraction < 0.35, large stress perfusion defect or multiple moderate-sized defects, stress-induced moderate-sized perfusion defects with left ventricular dilation);
- Hemodynamic instability;
- Sustained ventricular tachycardia;
- PCI within the previous 6 months;
- Prior coronary artery bypass surgery.

Class IIa recommendations include an early invasive strategy in those patients who have repeated presentations for ACS despite therapy and without evidence for ongoing ischemia.

The use of glycoprotein IIb/IIIa receptor antagonists receives a Class I recommendation: "in addition to aspirin and heparin to patients in whom catheterization and PCI are planned. The GP IIb/IIIa antagonist may also be administered just prior to PCI."

## Acute Coronary Syndromes and Glycoprotein IIb/IIIa Receptor Antagonists

The decision on the use of a particular GP IIb/IIIa inhibitor should be driven by scientifically established relevant clinical safety and efficacy endpoints. In this age of budgetary restrictions, a data-based effort to target the use of any pharmacologic agent or device is both appropriate and desirable, and this approach should apply independent of the cost of that therapy. We will now focus on the three available GP IIb/IIIa inhibitors and their use in patients with acute coronary syndromes, particularly those at higher risk of subsequent events (Table 2).

### *Abciximab: ReoPro*

Abciximab is a recombinant human-murine chimeric Fab fragment that binds nonselectively and irreversibly to the platelet GP IIb/IIIa receptor. Because of noncompetitive findings and rapid clearance of free drug from the circulation by the reticuloendothelial system, there is a very short plasma half-life of 10 minutes. As a result of its high affinity for the receptor, abciximab has a long biologic half-life of 12–24 hours. Maximum receptor blockade and inhibition of aggregation occur about 2 hours after bolus injection. Abciximab can redistribute itself from the originally bound platelet to newly produced platelets. This acts to prolong the antiplatelet effect.[7] GP IIb/IIIa receptor occupancy by abciximab exceeds 30% at 8 days following the completion of the infusion and 10% at 15 days, with residual binding seen out as late as 21 days.[8] Whether this characteristic plays a role in the efficacy of abciximab is not clear, but it is speculated that prolonged platelet inhibition during the post-PCI period of vessel passivation may be desirable.

The ability of abciximab to bind to the $\alpha_v\beta_3$ (vitronectin) receptor and the leukocyte receptor MAC-1 may be of more than academic interest. The vitronectin receptor is found on platelets, endothelial cells, monocytes, smooth muscle cells, and

**Table 2**
**Major Differences Among GP IIb/IIIa Inhibitors**

| | Abciximab | Eptifibatide | Tirofiban |
|---|---|---|---|
| Platelet-bound half-life | Long (hours) | Short (seconds) | Short (seconds) |
| Plasma half-life | Short (minutes) | Long (2.5 h) | Long (1.8 h) |
| Drug-to-receptor ratio | 1.5–2.0 | 250–2,500* | >250† |
| % Dose in bolus | ~75%‡ | <2%–5% | <2%–5% |
| Dosage adjustment in renal insuffiency | None | Yes | Yes |
| Specificity/Selectivity | | | |
| IIb/IIIa | xxx | xxx | xxx |
| $\alpha_v\beta_3$ | xxx | | |
| Mac-1 | x | | |
| Anticoagulant properties | | | |
| ↓ Thrombin generation | + + | + | + |
| ↑ Activated clotting time | +35 sec | +25 sec | N/A |
| Reversibility§ | 12 h | 4–6 h | >4 h |
| Reversibility with platelets | Yes | No | No |

*IMPACT-II trial and PURSUIT trial doses.
† RESTORE trial and PRISM-PLUS trial doses.
‡ For any individual receiving a weight-adjusted, 12-hour infusion.
§ Fifty percent return of platelet function without platelet transfusion.

polymorphonuclear leukocytes The vitronectin receptors on smooth muscle cells have been associated with the intimal hyperplasia that occurs following vascular injury from coronary interventions and may contribute to restenosis. The MAC-1 receptor accelerates the inflammatory response following vascular injury, perhaps by enhancing the leukocyte accumulation and binding to device-damaged blood vessel walls.[9]

In a subgroup analysis of 489 patients with UA in the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) study, abciximab bolus with infusion was associated with a 62% reduction in the 30-day composite endpoint of death, MI, or urgent revascularization (4.8% vs 12.8%; $P = .012$).[10] Even at 3-year follow-up, abciximab was associated with a 60% reduction in mortality among patients with UA or NSTEMI (5.1% vs 12.7%; $P = .01$).[11] The Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade (EPILOG) study included 1328 patients with UA and found a reduction of that same composite endpoint from 12.2% in the placebo group to 4.8% in patients receiving abciximab plus low-dose heparin.[12] In the c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial, 1265 patients with refractory UA were studied to determine the ability of abciximab to stabilize patients prior to angioplasty. Following diagnostic catheterization demonstrating a culprit lesion amenable to angioplasty, patients were randomized to either placebo or abciximab for 18–24 hours prior to the planned angioplasty and then for 1 hour following completion of the intervention. Abciximab was associated with a 71% reduction in the incidence of MI (0.6% vs 2.1%; $P = .029$) prior to the intervention. This would suggest a benefit from the upstream use of abciximab for patients presenting with acute coronary syndromes. In addition, a 29% reduction in the 30-day composite endpoint of death, MI, or urgent revascularization was seen in the abciximab-treated group (11.3% vs 15.9%; $P = .012$).[13]

*Tirofiban: Aggrastat*

This low-molecular-weight nonpeptide compound differs in many respects from abciximab. Tirofiban has a longer physiologic half-life of 1.8 hours and a shorter biologic half-life of seconds as a result of reversible binding kinetics to the IIb/IIIa receptor. Renal elimination of tirofiban requires dosing adjustments in patients with mild renal insufficiency. Tirofiban binds selectively to the IIb/IIIa receptor and has no interaction with the vitronectin or MAC-1 receptor. Patients with ACS were evaluated in the Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study and the Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE).[14,15]

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The PRISM-PLUS trial evaluated the effects of tirofiban, heparin, or both as medical treatments in 1915 high-risk patients with ACS. Study drug infusion averaged 71.3 hours, with angiography and angioplasty performed at the discretion of the investigator. The tirofiban-only arm was discontinued after excess mortality was observed during the first 7 days. In the subgroup of 475 patients undergoing PCI during the course of this trial, tirofiban with heparin was associated with a significant reduction of the composite endpoint of death, MI, refractory ischemia, or rehospitalization for UA, compared to heparin alone at 30 days (8.8% vs 15.3%). The reduction in the endpoints of death and MI with tirofiban did not achieve statistical significance.

The RESTORE trial evaluated the effect of a 36-hour infusion of tirofiban compared to heparin in 2139 high-risk patients undergoing PCI. The primary endpoint was a composite of death, MI, coronary artery bypass surgery due to failed angioplasty or recurrent ischemia, repeat target-vessel revascularization for recurrent ischemia, and stenting due to threatened or abrupt closure within 30 days. This occurred in 10.3% of the tirofiban-with-heparin group and 12.2% in the placebo group ($P$ = .160). Study design may have played a role in the negative result seen in the RESTORE trial, as biochemical markers of cardiac necrosis were not mandated to be measured frequently during the study, leading to possible underestimation of the non-Q-wave MI endpoint.

The Do Tirofiban and ReoPro Give Similar Efficacy Trial (TARGET) is the only head-to-head trial comparing a "small molecule" to the "large molecule."[16] In this randomized trial, the ability of tirofiban was compared with that of abciximab to prevent ischemic events associated with PCI. Though patients with acute coronary syndromes were not a prespecified subgroup, the primary endpoint of death or nonfatal MI at 30 days occurred in 9.3% of patients in the tirofiban group and 6.3% in the abciximab group of ACS patients. This relative increased event rate of 49% seen in the tirofiban group over the abciximab group achieved statistical significance. Besides the inferiority of this small molecule in ACS patients undergoing PCI, other explanations for the results of the TARGET trial include the potential underinhibition of the IIb/IIIa receptor in this trial with the dose of tirofiban used. An ex vivo evaluation of the effect of this dose (10 μg/kg bolus followed by a 0.15 μg/kg/min infusion) revealed 90% inhibition of platelet aggregation in response to 5μM adenosine diphosphate.[17] In a pharmacodynamic study by Swierkosz and colleagues, they report that the dose of tirofiban used in RESTORE results in less than the goal of 80% platelet aggregation inhibition when assessed by light transmission aggregometry using the PPACK assay and 20μM adenosine diphosphate.[18]

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*Eptifibatide: Integrilin*

Eptifibatide is a peptide that, like tirofiban, competitively and specifically inhibits the RGD sequence of the GP IIb/IIIa receptor. This results in a long plasma half-life (150 minutes) and short biologic half-life (2.5 hours). Like tirofiban, eptifibatide undergoes renal clearance with appropriate dosing adjustments needed in patients with renal insufficiency. Tirofiban and eptifibatide do not affect the vitronectin and MAC-1 receptors, and in vitro experiments have shown that, unlike abciximab, they enhance leukocyte-platelet aggregation in whole blood.[11] Because leukocyte-platelet interactions affect reperfusion injury and restenosis, the advantage of these agents derived from IIb/IIIa receptor blockade may be counterbalanced by the potential negative effects of this additional interaction.

In the second Integrelin to Minimize Platelet Aggregation and Prevent Coronary Thrombosis (IMPACT II) trial, 4010 patients from all risk strata undergoing PCI were evaluated in a placebo-arm, low-dose eptifibatide (135 μg/kg bolus + 0.5 μg/kg/min) arm, and high-dose (135 μg/kg bolus + 0.75 μg/kg/min) arm for 20–24 hours. Based on an intention-to-treat analysis, there was no significant difference observed between the placebo group and those receiving eptifibatide in the 30-day composite endpoint of death, MI, or urgent revascularization.[19] The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial assessed the role of up to a 72-hour infusion of 2 doses of eptifibatide in patients with ACS; patients underwent PCI at the discretion of the investigator. In patients undergoing early PCI, a 30% event reduction was observed (16.7% vs 11.6%; $P$ = .01).[20]

The more recently reported Enhanced Suppression of the Platelet Receptor IIb/IIIa with Eptifibatide Therapy (ESPRIT) study evaluated the efficacy of this agent as an adjunct to coronary stenting. A significant reduction in 30-day cumulative event rates of 35% was seen in this relatively low-risk elective PCI patient population. Though a 21% cumulative event reduction was seen at 1 year in the overall study population, in patients presenting with ACS at a higher risk within 2 days of study, no significant reduction of death or MI occurred at the 1-year mark.[21]

The Evaluation of Platelet IIb/IIIa Inhibition for Stenting (EPISTENT) trial, which evaluated the efficacy of abciximab compared to placebo in patients undergoing stent implantation, showed a clinically and statistically significant mortality reduction at 1 year not seen with eptifibatide in the ESPRIT trial.[22] It is difficult to extrapolate the results of the ESPRIT trial where no mortality benefit was found to the population of patients in EPISTENT, as that study population consisted of nonacute PCI patients with planned stent implantation and excluded these higher-risk patients. Major exclusions for the ESPRIT trial included acute MI within the previous 24 hours, ongoing chest pain leading to urgent referral for PCI, and severe renal dysfunction.

*Lamifiban*

Lamifiban is a peptidomimetic, highly specific inhibitor of the GP IIb/IIIa platelet receptor. As is the case with the other "small molecules," lamifiban targets the RGD sequence on the IIb/IIIa receptor and is eliminated by renal clearance. The Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON-B) study was recently reported. In this trial, the lamifiban infusion was titrated to achieve a steady-state concentration of 18–42 ng/mL and was given for up to 72 hours. In patients who underwent a PCI, the drug was infused for an additional 18–48 hours postprocedure. There was no difference between the placebo and lamifiban groups for the primary composite endpoint of death, MI, or severe recurrent ischemia at 30 days (11.8% vs 12.8%; $P = .329$). In the subgroup of patients undergoing PCI during the study period, no significant benefit from the use of lamifiban accrued despite an increase risk of hemorrhage.[23]

*The ACC/AHA 2002 ACS Practice Guidelines make an important distinction among the available GP IIb/IIIa receptors for use in diabetic patients with the following Class IIa recommendation: "Abciximab for diabetics treated with coronary stenting."*

## Special Populations

*Diabetic Patients with Non-ST-Segment Elevation MI Acute Coronary Syndromes*

Diabetic patients have increased mortality in the setting of NSTEMI-ACS and have more extensive coronary atherosclerosis at presentation.[24] A comprehensive discussion of the mechanism responsible for this is provided in the article by Drs. Meier-Ewert and Nesto in this supplement, "Targeting the Use of Glycoprotein IIb/IIIa Antagonists—The Diabetic Patient." Diabetic patients have poorer results from either percutaneous or surgical interventions than nondiabetic patients do. The specific role of GP IIb/IIIa receptor blockers in this patient population awaits further study, though overwhelming clinical trial evidence does show a special role for abciximab. In a recent meta-analysis of diabetic patients that included the PRISM, PRISM-PLUS, PARAGON A and B, PURSUIT, and GUSTO IV (Global Utilization of strategies To Open Occluded Coronary Arteries IV) trials, the pooled analysis revealed a significant 26% reduction in 30-day mortality when treated with GP IIb/IIIa receptors. However, within this pooled analysis, the only agent that on its own achieved a significant mortality advantage was abciximab in the GUSTO IV trial. This same meta-analysis revealed a 70% reduction in 30-day mortality ($P = .002$) in the pooled analysis of diabetic patients undergoing PCI. Within that pooled analysis, again, the only trial that on its own achieved a significant mortality benefit in diabetic patients undergoing PCI was the GUSTO IV study with abciximab.[25]

Without inclusion of the GUSTO IV data with abciximab, it is likely that the meta-analysis including only the small molecules would have failed to show this mortality advantage.

The ACC/AHA 2002 ACS Practice Guidelines make an important distinction among the available GP IIb/IIIa receptors for use in diabetic patients with the following Class IIa recommendation: "Abciximab for diabetics treated with coronary stenting."[1]

*Patients with Prior Coronary Artery Bypass Grafting*

Little is known about the outcome of prior coronary artery bypass grafting (CABG) patients with ACS. In the PURSUIT trial, 12% of

patients had a history of prior CABG. These patients had more adverse clinical characteristics at baseline, including diabetes, prior MI, peripheral vascular disease, and history of congestive heart failure (CHF). Baseline angiographic data showed these patients to have more multivessel disease and lower ejection fractions. The adjusted 30-day death rate is 45% greater in patients with prior CABG versus patients with no history of CABG. The 30-day rate of death or MI was 18.9% in the placebo group when the culprit vessel was a bypass graft and 20.2% in the eptifibatide group.[26]

The EPIC trial with abciximab included 114 patients undergoing revascularization of saphenous vein grafts. The 30-day composite endpoint rate was 7.5% in patients receiving the abciximab bolus and infusion and 12.9% in patients in the placebo group.[27]

*Patients with Chronic Renal Insufficiency*

Even less is known about the impact of glycoprotein IIb/IIIa receptor inhibition in patients with chronic renal insufficiency (CRF). Patients with CRF have over 3 times higher in-hospital mortality following PCI than patients with normal renal function and over 5 times in-hospital mortality if they are also diabetic.

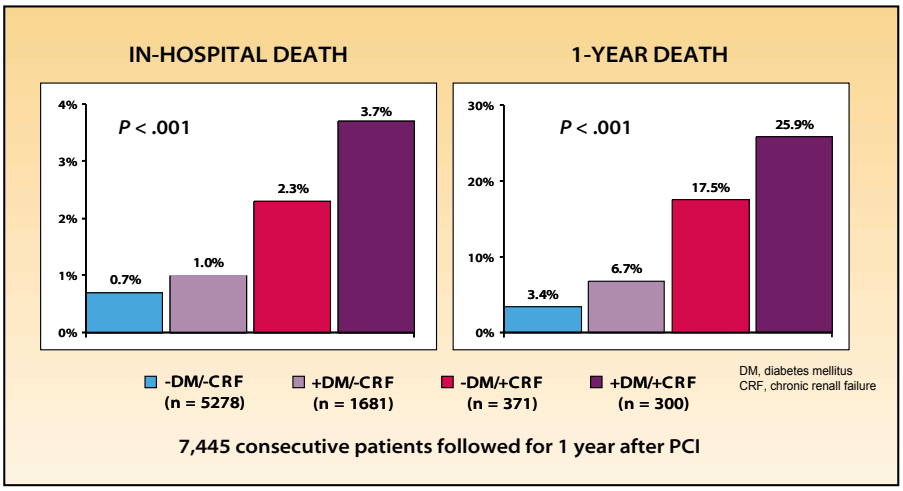


**Figure 3.** *Prognosis post-percutaneous coronary intervention (PCI) in patients with chronic renal insufficiency. A direct relationship exists between renal dysfunction and mortality following PCI. Data from Mehran et al.* J Am Coll Cardiol. *2000;35:1878–886.*

One-year mortality in patients with CRF is also 5 times higher than patients with normal renal function and 7 times higher if they are also diabetic. Thus CRF would seem to identify a population of patients undergoing PCI who are at high risk and could be considered candidates for use of GP IIb/IIIa receptor inhibitor (Figure 3).

With eptifibatide, there are no clinical data available for patients with serum creatinine above 4.0 mg/dL. In the PURSUIT study, a major exclusion criterion was a serum creatinine above 2.0 mg/dL. With tirofiban, the major trials evaluating efficacy and safety excluded patients with serum creatinines above 2.5 mg/dL.

Pooled data from the EPIC, CAPTURE, EPILOG, and EPISTENT trials included only 63 patients out of 7562 in these studies who had a serum creatinine above 2 mg/dL. Abciximab was safely administered to patients with renal insufficiency, as there was no difference in the rates of all major bleeding between the abciximab and placebo groups. There was no difference between the abciximab and placebo groups in this meta-analysis in the 30-day primary endpoint of death, MI, or urgent intervention in these patients with renal insufficiency.[28] An analysis

## Main Points

- Patients presenting with acute coronary syndromes (ACS) can be risk stratified using the history, physical examination, electrocardiogram, and biochemical markers for myocardial necrosis.
- ACC/AHA guidelines recommend an early invasive strategy for patients who are at higher risk for adverse outcomes.
- Glycoprotein (GP) IIb/IIIa receptor inhibitors have become accepted therapy for patients presenting with ACS undergoing percutaneous coronary intervention.
- There is significant heterogeneity in the efficacy of the various GP IIb/IIIa inhibitors, with the only head-head trial (TARGET) showing the superior performance of abciximab over the small molecule tirofiban in the subgroup of patients presenting with ACS.
- The 2002 ACC/AHA guidelines specify the recommend use of abciximab in diabetic patients undergoing stent implantation.

of all patients who had received abciximab at the Mayo Clinic between 1995 and 1998 revealed that patients with renal insufficiency derived the same benefit in reduction of death or MI as did patients with normal renal function.[29] The GUSTO-IV ACS study was a multinational, multicenter, randomized, double-blind, placebo-controlled trial in patients with ACS. In the patients with a serum creatinine over 2 mg/dL who received placebo (178 patients), the incidence of the combined endpoint of death or MI was 26.8% versus 7.6% in those with normal renal function. In patients who received the abciximab infusion for 48 hours, the combined endpoint occurred in 15.1% of patients versus 26.8% in the placebo group.[30] Abciximab does not require any dosing adjustment in patients with CRF because of the rapid removal of free drug from the circulation by the reticuloendothelial system.[31] Trials designed to specifically evaluate the efficacy and safety of GP IIb/IIIa receptor inhibitors will be needed to provide clearer answers on their role in patients with CRF.

*Abciximab does not require any dosing adjustment in patients with CRF because of the rapid removal of free drug from the circulation by the reticuloendothelial system.*

## Summary

The use of GP IIb/IIIa receptor inhibitors has become accepted therapy for patients presenting with higher-risk ACS undergoing PCI. Whether a "class effect" exists amongst all of the GP IIb/IIIa receptor inhibitors is a question that is hotly debated. The variance of effectiveness seen even among the small-molecule drugs would seem to argue against the "class effect." The efficacy of tirofiban and eptifibatide is established, whereas another small molecule, lamifiban, has been found to be ineffective. In terms of patients presenting with ACS, the TARGET trial, the only head-to-head trial of a small and large molecule, showed the superiority of the large molecule, abciximab, over the small molecule, tirofiban. In diabetic patients with ACS, abciximab was the only GP IIb/IIIa receptor inhibitor shown to provide a significant mortality advantage in patients undergoing PCI and is singled out in the most recent ACC/AHA guidelines as the agent of choice for use in diabetic patients undergoing stent implantation. Abciximab is also the only agent where clinical data support safety in patients with chronic renal insufficiency.

Sound clinical practice in this era of budgetary constraints dictates the need for a thoughtful, data-based approach to patient care. Targeting the use of the GP IIb/IIIa receptor inhibitor abciximab using this data-based approach is therefore prudent. Based on the accumulation of data, abciximab seems to be the superior agent for patients with ACS undergoing percutaneous coronary interventions. ■

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