Practical Issues of Platelet Glycoprotein IIb/IIIa Receptor Inhibition: Saving Lives and Saving Money

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Abciximab is a monoclonal, human chimeric antibody with unique pharmacodynamics, pharmacokinetics, and receptor-specificity that distinguishes it from the small-molecule platelet glycoprotein IIb/IIIa receptor inhibitors. Abciximab has consistent, well-defined dosing and robust clinical results. Pooled data across abciximab trials comprising 9290 patients at maximum duration of follow-up demonstrates a 19% reduction in the relative risk of mortality (P = .003). There is a misperception of the cost of abciximab that focuses solely on the acquisition price of the drug. Cost-effectiveness analysis models compare the incremental improvement in clinical outcomes related to the increase in cost. Abciximab is extremely cost-effective in cost per life-year saved and is very attractive economically compared to alternative spending of health care dollars.

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Coronary artery disease is a two-compartmental model of chronic low-grade inflammation superimposed with acute thrombotic events.[1] Balloon-dilatation and mechanical disruption of atheromatous coronary plaques leads to a highly thrombogenic milieu and a subsequent robust inflammatory response within the injured vessel.[2] Adjunctive pharmacology during percutaneous coronary intervention (PCI) has evolved to include platelet glycoprotein (GP) IIb/IIIa integrin receptor inhibition as the standard of care to reduce ischemic complications.

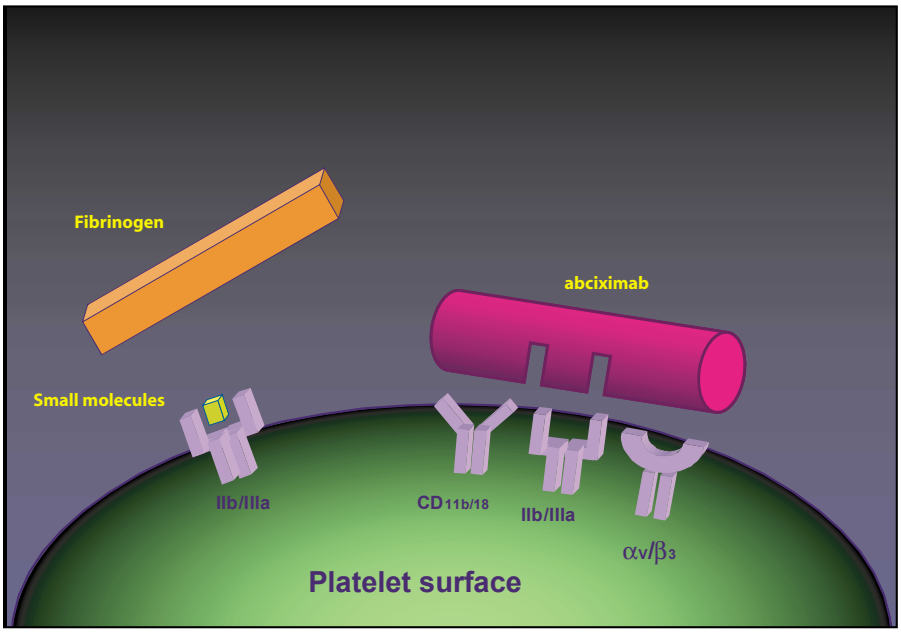

Figure 1. *A conceptual comparison of the physical differences between platelet GP IIb/IIIa antagonists. The small-molecule GP IIb/IIIa inhibitors bind to the active domain of the β_3 subunit, thereby preventing fibrinogen from cross-linking activated GP IIb/IIIa receptors and preventing platelet aggregation. However, the large-molecule abciximab has a molecular weight approximately 100 times that of the small molecules. Not only does abciximab bind to a site-specific domain of the GP IIb/IIIa complex, but it stoichiometrically antagonizes other receptors of the integrin family, such as the $CD_{11b/18}$ (MAC-1) and the α_V/β_3 (vitronectin) receptors.*

More Than Just a "Class Effect"

Abciximab (Centocor, Malvern, PA; Eli Lilly, Indianapolis, IN) became commercially available in the second quarter of 1995, and the small-molecule eptifibatide (Cor Therapeutics, San Francisco, CA) and tirofiban (Merck, West Point, PA) followed within the next couple of years. These three agents antagonize the platelet GP IIb/IIIa integrin receptor, thereby preventing activated platelet aggregation, yet there are a number of differences between the large-molecule abciximab and the small-molecule agents in regard to pharmacokinetics, pharmacodynamics, and receptor-specificity.

There are estimated to be 80,000–100,000 copies of the platelet GP IIb/IIIa receptor on the surface of the platelet, making this integrin receptor one of the densest receptors per unit area in the body. Abciximab is a monoclonal, human chimeric Fab fragment antibody with a molecular weight approximately 100 times that of eptifibatide and tirofiban. It binds avidly to a site-specific domain on the GP IIb/IIIa receptor and coats the platelet with antibody fragments, thereby stoichiometrically antagonizing other receptors in the integrin family, such as the $CD_{11b/18}$ (MAC-1) and α_V/β_3 (vitronectin) receptors,[3] as depicted in Figure 1. The integrin family of receptors are key adhesion molecules that mediate cell–cell and cell-extracellular interactions between monocytes, platelets, macrophages, and endothelial cells. Antagonizing the MAC-1 receptor with abciximab has been shown in vitro to inhibit monocyte-induced smooth muscle cell apoptosis,[4] potentially stabilizing atheromatous plaque.[5] The vitronectin receptor plays a pivotal role in smooth muscle cell proliferation and migration.[6]

Percutaneous coronary revascularization elicits a robust inflammatory response, partially via microvascular embolization, which persists for days following the intervention.[7] Abciximab suppresses this inflammatory response as measured by a reduction in the inflammatory markers CRP, TNF-α, and IL-6 post-PCI compared to patients treated with placebo.[8]

Abciximab has short plasma half-life kinetics with prolonged biologic activity. It can be detected by immunofluorescence over 15 days after administration, which is longer than the typical life span of a platelet, thus providing a slow tapered recovery of platelet inhibition.[9] These pharmacodynamics also explain why bleeding times can be rapidly normalized with a platelet transfusion in patients treated with abciximab[10] and why no reduction in dose is required in patients with renal insufficiency.

In contradistinction, the small molecules bind to the active domain of the β_3 subunit and have no demonstrable biological activity with other integrin receptors. They have a long serum half-life, but because of their high dissociation constant, have a very short biological effect on the platelet receptor. In addition, the small molecules are renally excreted. This explains why inhibition of the GP IIb/IIIa receptor with eptifibatide or tirofiban cannot be reversed with a platelet transfusion and why there is an obligatory reduction in dose in patients with renal insufficiency.[11]

Do these differences in physical properties, however, translate into differences in clinical outcomes? A meta-analysis of 16 trials, comprising 32,135 patients with ischemic heart disease, compared GP IIb/IIIa inhibitors to placebo and demonstrated a 24% reduction in relative

Figure 2. *The 30-day triple endpoint of death, nonfatal myocardial infarction, or revascularization from a pooled meta-analysis of glycoprotein IIb/IIIa inhibitors trials, comparing all agents combined and separately. There clearly is a "class effect" of improved outcomes compared to that for placebo; however, abciximab appears to produce an incremental improvement in efficacy that exceeds a simple class effect. Data from Kong et al.*[12]

risk (odds ratio, 0.76; 95% confidence interval, 0.66-0.87; $P < .001$), in the 30-day composite endpoints of death, non-fatal myocardial infarction (MI), or revascularization, suggesting a "class effect."[12] However, when these agents were evaluated individually, abciximab demonstrated a significantly better odds ratio in the reduction of major adverse cardiac events than did the two small-molecule agents (Figure 2), suggesting abciximab provides an incremental improvement in clinical outcomes that goes beyond the class effect of simply inhibiting the platelet GP IIb/IIIa receptor. This was proven definitively in the only head-to-head comparison of GP IIb/IIIa inhibitors during PCI; abciximab-treated patients had a significant reduction in the 30-day, major adverse cardiac events of death, MI, and target vessel revascularization (TVR) compared to tirofiban-treated patients.[13]

Saving Lives

Clinical endpoints that occur at a relatively low frequency must be grouped together into a composite endpoint in order to adequately power a trial. Unfortunately, this makes cross-comparison of studies difficult. For example, several different biochemical markers at various levels above the upper limit of normal, new electrocardiographic findings, wall-motion abnormalities on echocardiograms, or perfusion defects on nuclear imaging can define postprocedural MI. Similarly, revascularization and restenosis can be protocol-driven or clinically defined. The only endpoint that has a consistent and reproducible definition is mortality.

Stenting revolutionized PCI by significantly lowering acute vessel closure and target-vessel revascularization. But stenting has not been shown to reduce mortality compared to plain balloon angioplasty. In fact, the results of the Stent Primary Angioplasty in Myocardial Infarction (Stent-PAMI) study showed a non-significant increase in mortality in patients treated with a stent during an acute MI, compared to patients treated with angioplasty without stenting.[14] Of course, Stent-PAMI also demonstrated an overall benefit of stenting, primarily by an overwhelming reduction in urgent TVR that powerfully drove the primary endpoint of death, MI, or urgent TVR to statistical significance.

Among the oral GP IIb/IIIa inhibitors, which have virtually the identical pharmacodynamics as the intravenous small molecules, there has been a consistent increase in mortality in clinical trials.[15–18] Thus, there is yet to be a U.S. Food and Drug Administration–approved oral GP IIb/IIIa inhibitor.

Abciximab, however, has consistently demonstrated a trend in the reduction of mortality that increases over the long-term follow-up. In a pooled analysis of eight abciximab trials involving 9290 patients at the maximum duration of follow-up with analysis based on an intention-to-treat, there was a 19% reduction in the relative risk of mortality ($P = .003$).[19] The hazard ratios are shown in Figure 3. Although an explanation for this observation

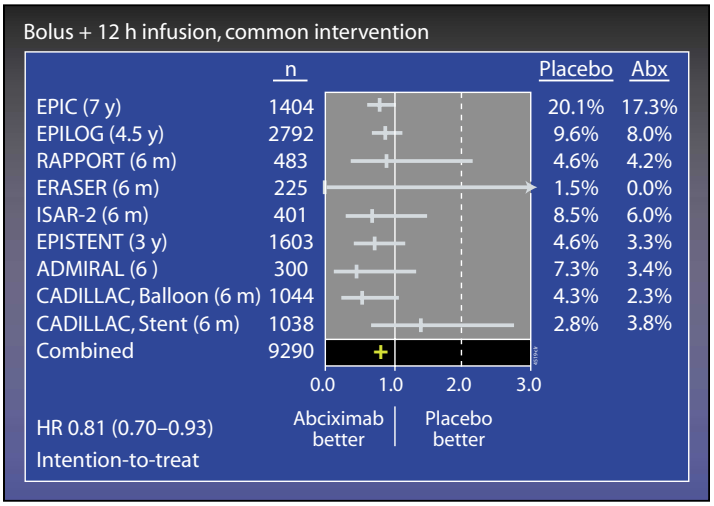

Figure 3. *Hazard ratio (HR) plot of 8 abciximab (Abx) trials involving 9290 patients at the maximum duration of follow-up showing an overall 19% reduction in relative risk of mortality seen on an intention-to-treat analysis (HR, 0.81; 95% CI, 0.70-0.93; P = .003). Data from Eli Lilly.*[19]

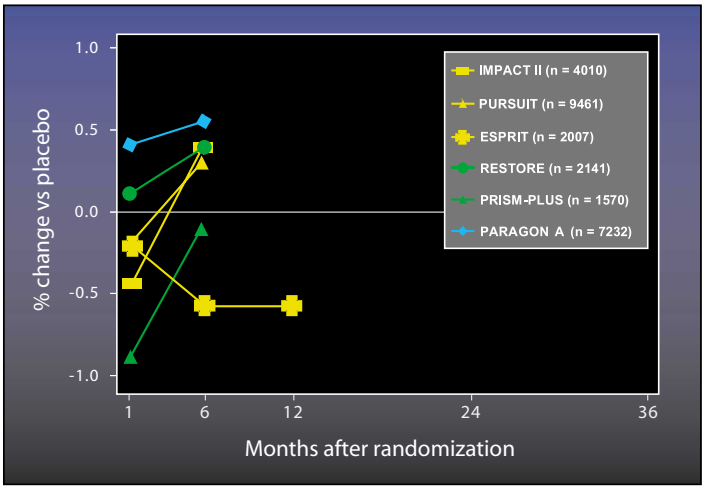

Figure 4. *Absolute differences in mortality trends over time in trials with the small-molecule GP IIb/IIIa inhibitors have failed to demonstrate a consistent reduction in death. Although these studies were not powered to detect a difference in mortality, the trends are unfavorable. IMPACT II, Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis; PURSUIT, The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; ESPRIT, Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy; RESTORE, Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis; PRISM-PLUS, Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms; PARAGON A, Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organized Network.*

Data from the following sources: IMPACT II: Lancet. *1997;349:1422–1428; American College of Cardiology, oral presentation, 1999; PURSUIT:* N Engl J Med. *1998;339:436–443; European Society of Cardiology, oral presentation, 1998; ESPRIT: Society of Cardiac Angiography and Intervention, oral presentation, 2000;* JAMA. *2001;285:2468–2473;* JAMA. *2002;287:618-621. RESTORE:* Circulation. *1997;96:1445–1453; J* Am Coll Cardiol. *1998;32:28–34. PRISM-PLUS:* N Engl J Med. *1998;338:1488–1497. PARAGON A:* Circulation. *1998;97:2386–2395.*

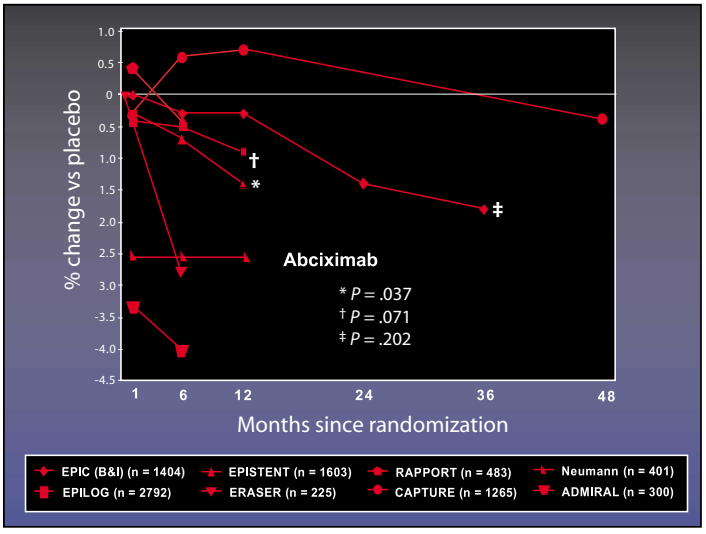

Figure 5. *Absolute differences in mortality trends over time in trials with the GP IIb/IIIa inhibitor abciximab have demonstrated a consistent reduction in death. These studies similarly were not powered to detect a difference in mortality, and not all the individual results reach statistical significance. Clearly, however, the trends are favorable. Furthermore, most of these curves have a negative slope, which implies that the reduction in mortality seems to increase over time. EPIC, Evaluation of 7E3 for the Prevention of Ischemic Complications; EPILOG, Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade; EPISTENT, Evaluation of Platelet IIb/IIIa Inhibition in Stenting; ERASER, Acute Platelet Inhibition with Abciximab does not Reduce In-stent Restenosis; RAPPORT, ReoPro and Primary PTCA Organization and Randomized Trial; CAPTURE, c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina; ADMIRAL, Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-term Follow-up.*

Data from the following studies: EPIC: N Engl J Med. *1994;330:956–961; Lancet. 1994;343:881–886;* JAMA. *1997;278:479–484; EPILOG: Internal data, Centocor, Malvern, PA; EPISTENT:* Lancet. *1998;352:87–92;* N Engl J Med. *1999;341:319–327;* Lancet. *1999;354:2019–2024; ERASER:* Circulation. *1999;100:799–806; RAPPORT:* Circulation. *1998;98:734–741; CAPTURE:* Lancet. *1997;349:1429–1435; American College of Cardiology, oral presentation, 2000; Neumann:* J Am Coll Cardiol. *2000;35:915–921; ADMIRAL: European Society of Cardiology, oral presentation, 2000.*

may not be readily available, this phenomenon cannot be explained simply by a reduction in early in-hospital events[20] or by the degree of platelet inhibition.[21] The small-molecule agents have yet to demonstrate a similarly consistent reduction in long-term mortality (Figures 4 and 5).

Cost-Efficiency Versus Cost-Effectiveness

New therapies are required to show that they are safe and efficacious compared to the current standard of care. A secondary consideration should be the cost of therapy. In assessing the value of new technology over the current standard, the overall benefit should be a balance between clinical outcomes and cost. There are three potential scenarios to be considered: 1) If the outcomes of the new therapy are better and the cost is the same or lower, then utilize the new, better therapy; 2) If the outcomes of two therapies are the same, then utilize the less expensive therapy; and 3) If the outcomes of a new therapy are better, but the cost is greater, then a cost-effectiveness analysis should be performed to determine if the added expense is worth the improved outcomes. A classic example is the addition of airbags and antilock brakes to automobiles: both are an added cost, both improve safety outcomes.[22]

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Cost-efficiency focuses solely on reducing cost at any given outcome;

this is analogous to cost-minimization. Cost-effectiveness, however, relates the cost of therapy to health benefits in determining if the added cost is economically attractive, given the incremental improvement in clinical outcomes. The clinical outcomes that are most tangible and important to patients include living longer, reducing hospitalizations, and reducing symptoms, which roughly translates into the common triple endpoint measured clinically of death, MI, and revascularization.

An incremental cost-effectiveness ratio (ICER) can be defined as

$$\text{ICER} = \frac{C_{\text{new}} - C_{\text{standard}}}{E_{\text{new}} - E_{\text{standard}}}$$

where C = costs and E = effectiveness. An ICER provides an objective measurement of health care cost and clinical efficacy. Although an ICER cannot determine whether or not a therapy is worthwhile, it can be used to determine whether or not a therapy is economically attractive.

Benchmarks

In order to compare the cost-effectiveness of therapies there must be a benchmark. Public law 92-603 (1972) established Federal responsibility to cover the cost of medical care and provide dialysis for all patients with renal failure. This is a crude assumption, but sets a rough estimate of how the Federal government defines the cost per life-year saved. One year of dialysis currently costs approximately $30,000–$50,000.

A therapy that produces an additional life-year for a patient for less than $20,000 is commonly considered highly cost efficient, whereas a therapy of more than $100,000 per life-year saved is felt to be economically unattractive. For example, treating a patient with congestive heart failure and a left ventricular ejection fraction of <35% with enalapril is estimated to be a cost savings per life-year saved. Coronary artery bypass surgery for a patient with angina and two-vessel coronary artery disease is estimated to cost $72,900 per life-year saved. The same procedure, however, in a patient with left main coronary artery disease and severe angina is estimated to cost $9200 per life-year saved.[23–25] Several common cardiovascular diseases and their estimated cost per life-year saved are shown in Table 1.

Abciximab has demonstrated clinical efficacy with a consistent infusion length of 12 hours. Because of its pharmacokinetics, a relatively short 12-hour infusion provides a long duration of action.

Abciximab is frequently criticized as being expensive compared to the cost of the small-molecule agents. Although the actual acquisition cost of abciximab is higher than that of the small-molecule agents, the overall cost for GP IIb/IIIa inhibitors can be deceiving to calculate, thus making direct head-to-head comparison difficult. The cost of these drugs is directly related to the patient's weight and the duration of infusion. Frequently, the focus is solely on the acquisition price of the drug, and the not-so-insignificant hospital costs, such as the length of stay and the cost of repeat revascularization, are ignored. Abciximab has demonstrated clinical efficacy with a consistent infusion length of 12 hours. Because of its pharmacokinetics, a relatively short 12-hour infusion provides a long duration of action. On the other hand, the drug-infusion time in studies using eptifibatide and tirofiban ranges from 16 to 96 hours, and they have yet to show the same magnitude of beneficial results. In fact, an infusion length of eptifibatide of less than 16 hours in the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial[26] was associated with a higher hazard ratio of 3.1 (HR, 2.0-4.8; $P < .001$) for 30-day death, MI, and revascularization, compared to an infusion length of 16 to 18 hours.[27] It is simply erroneous to compare the cost of a 12-hour infusion of abciximab to a 12-hour infusion of eptifibatide or tirofiban.

Making Cost-Effective Choices

To more closely determine actual costs saved, results were pooled from three multicenter trials: Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC),[28] Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade (EPILOG),[29] and Evaluation of Platelet IIb/IIIa Inhibition in Stenting (EPISTENT).[30] At the maximum duration of follow-up, the cost per life-year saved in patients treated with abciximab was $4,891,[19] which is clearly very attractive economically. However, as interventional cardiologists, we are

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Table 1
Common Cardiovascular Therapies: Their Estimated Cost Per Life-Year Saved and Relative Cost-Effectiveness

Strategy	Condition	Cost Per Life-Year Saved (US $)	Cost Effective
Enalapril	CHF/LVEF < 35%	Cost savings	Highly
Anticoagulant	Mitral stenosis/AF	$4,200	Highly
β-blocker	Post-MI/medium risk	$5,600	Highly
CABG	LMCAD/severe angina	$9,200	Highly
Hypertensive Rx	HBP/diastolic ≥ 105 mm Hg	$20,600	Borderline
rt-PA	Acute MI	$32,700	Borderline
CCU	r/o MI/50% probability	$35,000	Borderline
GXT	Asymptomatic male > 60 years; 1 + RF	$37,700	Borderline
Hypertensive Rx	HBP/diastolic 95-104 mm Hg	$41,900	Borderline
Lovastatin 20 mg/dy	1° prevention, chol > 300, 3 + RF, aged 55–64 years	$45,900	Borderline
CABG	Angina, 2V CAD	$72,900	Marginal

CHF, congestive heart failure; LVEF, left ventricular ejection fraction; AF, atrial fibrillation; MI, myocardial infarction; LMCAD, left main coronary artery disease; HBP, high blood pressue; rt-PA, recombinant tissue plasminogen activator; CCU, coronary care unit; GXT, grade exercise treadmill; RF, risk factors; CABG, coronary artery bypass graft.

driven by immediate results; this is exemplified by the angiographic appearance of a stented artery and the subsequent explosion in the use of stents. We do not hesitate to place "just one more" stent when an artery does not look "quite right." Yet, we hesitate to start someone on abciximab, because of the perception that this is such an expensive drug. This dichotomy in perception is directly related to the instant visual gratification of placing a stent in a vessel versus the intangible reduction in long-term mortality.

Ironically, the cost of abciximab is roughly the same as the cost of a stent. In fact, in a cost-effectiveness analysis from EPISTENT, the incremental cost-effectiveness per life-year saved in adding a stent to a patient treated with plain balloon angioplasty and abciximab was $6213. On the other hand, the incremental cost-effectiveness per life year saved of adding abciximab to a patient treated with a stent was $5291.[31] Thus, in terms of cost per life-year saved, it is more cost effective to treat a patient with abciximab than to place a stent. Compared to alternative spending of health care dollars, as shown in Table 1, this would appear to be a very attractive alternative.

Stenting has never been shown to reduce mortality over time; mechanical intervention is simply a temporizing therapy.

Conclusion

Abciximab has demonstrated a superior, consistent reduction in clinical endpoints in patients undergoing percutaneous intervention and shown a strong trend in the reduction of mortality over time that cannot be explained by a decrease in early in-hospital events. It possesses unique pharmacodynamics, pharmacokinetics, and receptor-occupancy properties that distinguish it from simply the class effect of the small-molecule glycoprotein IIb/IIIa antagonists.

Abciximab is often perceived to be an expensive therapy. Cost-effectiveness analysis, however, has demonstrated that it is more affordable than stenting in terms of cost per life-year saved. Cost-efficiency focuses on minimizing cost despite clinical outcomes, whereas cost-effectiveness takes into account the incremental improvement in clinical outcomes at a given increase in cost.

Coronary artery disease is a lifetime condition that is unrelenting. Stenting has never been shown to reduce mortality over time; mechanical intervention is simply a temporizing therapy. We must look beyond the eye-appealing, acute, angiographic results of a stented vessel and begin to focus on therapy that improves mortality and is cost effective—saving lives and saving money. ■

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Main Points

- Percutaneous coronary intervention includes platelet glycoprotein (GP) IIb/IIIa integrin receptor inhibition as the standard of care to reduce ischemic complications.
- Abciximab, eptifibatide, and tirofiban antagonize the platelet GP IIb/IIIa receptor, thereby preventing activated platelet aggregation; however, there are important differences between the large-molecule abciximab and the small-molecule agents regarding their pharmacokinetics, pharmacodynamics, and receptor-specificity.
- A meta-analysis of 16 trials suggests that abciximab demonstrates an incremental improvement in clinical outcomes that distinguishes it from the class effect of simply inhibiting the platelet GP IIb/IIIa receptor.
- Abciximab has short plasma half-life kinetics with prolonged biologic activity, providing a slow, tapered recovery of platelet inhibition. Bleeding times can be rapidly normalized with a platelet transfusion in patients treated with abciximab, and no reduction in dose is required in patients with renal insufficiency.
- Abciximab has shown a strong trend in the reduction of mortality over time that cannot be explained by a decrease in early in-hospital events.
- Abciximab is often perceived to be an expensive therapy; but cost-effectiveness analysis, which takes into account the incremental improvement in clinical outcomes at a given increase in cost, has demonstrated that it is more affordable than stenting in terms of cost per life-year saved.