Current Role of Platelet Glycoprotein IIb/IIIa Inhibitors in Acute Coronary Syndromes

Deepak L. Bhatt, MD

Eric J. Topol, MD

ACUTE CORONARY SYNDROMES (ACSs) span the pathological continuum of unstable angina to non–Q-wave myocardial infarction (MI). Each year, in the United States alone, more than 1 million people die of a coronary event.[1] Recurrence of ischemic events is also common in this population, both during the index hospitalization and the subsequent 6 months. Thus, strategies to modify the natural history of ACSs are essential.

Central to an understanding of the pathophysiology of ACSs is an appreciation of the roles of platelet activation, inflammation, and subsequent distal embolization.[2] The persistence of platelet activation up to 30 days after presentation with an ACS highlights the importance of platelets in the origin of the initial ischemic event as well as any recurrent event.[3] Angioscopic findings support the idea that unstable plaque persists for more than a month after an acute MI.[4]

The glycoprotein IIb/IIIa (Gp IIb/IIIa) receptor is critical to the process of platelet thrombus formation, as it serves as the final common pathway for platelet aggregation.[5] The biology of Gp IIb/IIIa receptors is quite sophisticated.[6] Presently, there are 3 commercially available intravenous Gp IIb/IIIa inhibitors that block fibrinogen binding to the receptor. Abciximab is a chimeric monoclonal antibody that binds nonspecifically to the Gp IIb/IIIa receptor. Eptifibatide is a cyclic heptapeptide that selectively binds to the Gp IIb/IIIa receptor. Tirofiban hydrochloride is a nonpeptide derivative of

Context The central role of platelet-rich thrombus in the pathogenesis of acute coronary syndromes (ACSs) is well-known. Glycoprotein IIb/IIIa (Gp IIb/IIIa) receptor antagonists are potent inhibitors of platelet function that may be expected to affect favorably the natural history of ACSs.

Objective To define the optimal role of Gp IIb/IIIa inhibitors in treatment strategies for ACSs.

Data Sources A MEDLINE search was performed to identify all English-language articles regarding use of Gp IIb/IIIa inhibitors in ACSs published between 1966 and June 2000. In addition, relevant abstracts from the annual meetings of the American Heart Association, American College of Cardiology, and the European Society of Cardiology were reviewed.

Study Selection Only studies of 500 or more patients were included. Of 15 studies identified, 10 randomized, placebo-controlled, double-blind trials of Gp IIb/IIIa inhibitors in ACSs were selected for review.

Data Extraction Data quality was determined by publication in the peer-reviewed literature or presentation at an official cardiology society–sponsored meeting, as well as by verification with the primary author.

Data Synthesis Three members of this class of drugs are available for intravenous use. Abciximab, eptifibatide, and tirofiban hydrochloride, each have data demonstrating their value in improving the outcomes of patients presenting with ACSs. Current evidence supports use of these drugs in both conservative and invasive treatment strategies. Glycoprotein IIb/IIIa–blocking therapy is safe, and with proper precautions, bleeding risks can be minimized. Biological differences exist among these agents, but as of yet, no head-to-head comparisons have been made of their clinical efficacy. Unlike intravenous Gp IIb/IIIa inhibitors, available data regarding any role of oral Gp IIb/IIIa inhibitors are not favorable.

Conclusion Current data indicate that intravenous Gp IIb/IIIa inhibitor therapy merits a prominent role in the initial management of patients with ACSs.

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tyrosine that binds selectively to the Gp IIb/IIIa receptor. Lamifiban is not commercially available, but is a nonpeptide derivative of tyrosine and has undergone extensive clinical investigation.

More than 30 000 patients have been randomized to treatment with Gp IIb/ IIIa inhibitors vs placebo.[7] A rigorous examination of the pooled data by Kong et al[7] demonstrated a significant benefit of these agents in reducing ischemic events, producing both an early and sustained benefit. These benefits are seen in patients undergoing percutaneous coro-

Table. Summary of Trials of Glycoprotein IIb/IIIa Inhibitors*

Trial, y	No. of Subjects	End Points	Duration	Percentage With Acute Coronary Syndrome
EPIC,[9] 1994	2099	Death, MI, urgent revascularization, stent or balloon pump placement	3 y	43
IMPACT-II,[10] 1997	4010	Death, MI, urgent revascularization, unplanned stenting	6 mo	41
RESTORE,[11] 1997	2139	Death, MI, urgent revascularization, unplanned stenting	6 mo	100
CAPTURE,[12] 1997	1265	Death, MI, urgent revascularization	6 mo	100
EPILOG,[13] 1997	2792	Death, MI, urgent revascularization	1 y	68
EPISTENT,[14] 1998	2399	Death, MI, urgent revascularization	1 y	33
PARAGON,[15] 1998	2282	Death, MI	6 mo	100
PRISM,[16] 1998	3232	Death, MI, refractory ischemia	30 d	100
PRISM-PLUS,[17] 1998	1915	Death, MI, refractory ischemia	6 mo	100
PURSUIT,[18] 1998	10 948	Death, MI	6 mo	100

*MI indicates myocardial infarction.

nary revascularization and in patients receiving treatment for ACSs.[8]

The purpose of this review is to try to define the optimal role of Gp IIb/IIIa inhibitors in the management of ACSs.

METHODS

We used MEDLINE to identify all published, English-language, randomized, placebo-controlled, double-blind trials of 500 or more patients regarding use of Gp IIb/IIIa inhibitors in ACSs from 1966 through June 2000 (**TABLE**).[9-18] The medical subject headings used were *platelet glycoprotein IIb-IIIa complex*, *unstable angina*, and *myocardial infarction*. Ten of 15 studies identified met the inclusion criteria. Data quality was determined by publication in the peer-reviewed literature. In addition, we reviewed relevant abstracts and presentations from the official 1998 and 1999 annual meetings of the American Heart Association, American College of Cardiology, and the European Society of Cardiology. For studies in which data from abstracts are cited, the information was verified with the author.

RESULTS
Gp IIb/IIIa Blockade During Percutaneous Coronary Intervention

The effectiveness of Gp IIb/IIIa inhibition was first established for percutaneous coronary intervention (PCI). The

Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial first demonstrated the importance of Gp IIb/IIIa blockade during balloon angioplasty.[9,19] Relatively high-risk patients with unstable angina, evolving MI, or complex angiographic lesion morphologic characteristics were randomized to treatment with abciximab bolus, abciximab bolus and 12-hour infusion, or placebo. A 35% reduction was seen in death, MI, or recurrent ischemia in those patients receiving the bolus and infusion of abciximab (12.8% vs 8.3% for placebo; *P* = .008). The bolus-only regimen was clinically ineffective. Patients treated with abciximab experienced more bleeding and a greater need for transfusion; the rate of major bleeding increased from 7% to 14% (*P* = .001). Three-year follow-up of patients in this trial demonstrated a sustained benefit with abciximab.[20] An analysis of the 489 patients enrolled in EPIC with unstable angina showed a 62% reduction in the rate of 30-day death, MI, and urgent revascularization (*P* = .01).[21] The risk reduction seen in the group with unstable angina was significantly greater than in any other subgroup (*P* = .008 for interaction). Based on these results, Gp IIb/IIIa blockade during PCI appeared to be especially valuable in patients with ACSs.

The Evaluation in PTCA [percutaneous transluminal coronary angioplasty] to Improve Long-Term Out-

come with Abciximab Gp IIb/IIIa Blockade (EPILOG) trial extended the findings of EPIC to lower-risk patients undergoing PCI.[13,22] There was a significant reduction in death, MI, or urgent revascularization at 30 days (from 11.7% to 5.2%; *P*<.001), which persisted through 1 year of follow-up. In addition, EPILOG showed that the increased bleeding rates seen with abciximab in EPIC could be decreased when a lower dose of heparin was used, accompanied by more attentive management of the percutaneous insertion site in the groin. In EPILOG, major bleeding occurred in 3.1% of patients treated with placebo, but only in 2.0% of patients receiving abciximab and low-dose heparin (*P* = .19).

The Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial extended the validity of Gp IIb/IIIa inhibition into the stent era.[14,23] Furthermore, the benefits of stenting, in reducing the need for target vessel revascularization, and abciximab, in reducing death or MI, appeared complementary. At 1 year, mortality was significantly reduced from 2.4% in the stent-placebo arm to 1.0% in the stent-abciximab arm (hazard ratio [HR], 0.43; 95% confidence interval [CI], 0.19-0.97; *P* = .04).[24] Event rates among patients with unstable angina treated with abciximab were reduced compared with patients undergoing elective PCI. Thus, even with contemporary stenting and other interventional strategies, Gp IIb/IIIa inhibition is beneficial.[25,26] The benefit of Gp IIb/IIIa inhibition appears to be independent of baseline lesion morphologic characteristics, although more complex lesions (due to higher event rates) derive a greater absolute risk reduction.[27,28]

Roe et al[29] pooled data from patients with ACSs from EPIC, EPILOG, and EPISTENT. Patients with both unstable angina and chest pain within 48 hours, evolving MI, or acute MI within the past 7 days were included in this analysis. The rate of 1-year death or MI in these 3478 patients was significantly reduced from 13.3% with placebo to 6.7% with abciximab (HR, 0.48; 95% CI, 0.39-0.60). Mortality alone was signifi-

cantly reduced from 2.7% with placebo to 1.7% with abciximab (HR, 0.62; 95% CI, 0.39-0.98). While all patients in these trials, including those without ACSs, showed a significant reduction in death or MI, multivariate regression analysis demonstrated that those with ACSs had an enhanced benefit. Essentially, abciximab administration at the time of PCI converted the risk profile of patients with unstable angina to that of those with stable angina. Furthermore, the sustained benefit of abciximab is noteworthy because the 1-time administration of an agent at the time of percutaneous intervention would not necessarily be expected to affect long-term mortality.[20,30]

In an attempt to improve cost-effectiveness, some operators use provisional abciximab (ie, abciximab given intraprocedurally once difficulty is encountered during PCI). Muhlestein et al[31] found that abciximab given intraprocedurally was effective in dissolving angiographically proven thrombus and in restoring thrombolysis in myocardial infarction (TIMI) flow. Haase et al[32] showed that administration of abciximab after threatened or acute vessel closure prevented vessel occlusion. A reduction in angiographic thrombus was paralleled by an increase in TIMI flow in this analysis also. Certainly, in cases in which a Gp IIb/IIIa antagonist has not been administered prophylactically, these 2 studies support the potential "rescue" use of abciximab during balloon angioplasty when angiographic thrombus is present or vessel closure is imminent. This strategy, however, warrants more extensive prospective evaluation.

Eptifibatide and tirofiban also have been studied as adjuncts during PCI. The Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis-II (IMPACT-II) study enrolled 4010 patients undergoing percutaneous intervention for a broad range of indications.[10] Compared with placebo, the rate of death, MI, urgent revascularization, or "bailout" (unplanned) stent placement was modestly reduced from 11.6% to 9.1% (P=.04) with a 135-μg/kg bolus and a 0.5-μg/kg per minute infusion of epti-fibatide, with no significant increase in bleeding (4.8% for placebo vs 5.1% with therapy), but it was concluded that higher doses would likely be necessary to maximize clinical outcomes. The Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) trial examined 2139 patients with unstable angina or acute MI.[11] There was a significant reduction in early ischemic events at 2 days from 8.7% to 5.4% (P=.005), but by 30 days this reduction was no longer significant. There was no significant difference in major bleeding or the need for transfusion between tirofiban and placebo, 5.3% vs 3.7% (P=.10).

The c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial also studied abciximab during PCI, but had an initial 18- to 24-hour period of treatment, which was continued until 1 hour after the procedure.[12] A total of 1265 patients with unstable angina refractory to conventional medical treatment were enrolled in this trial. The rate of death, MI, or urgent revascularization was significantly decreased at 30 days from 15.9% to 11.3% with abciximab use (P=.01). An angiographic analysis from CAPTURE showed that abciximab facilitated thrombus resolution,[33] and reduced recurrent ischemia as measured by continuous electrocardiogram monitoring.[34] Therefore, abciximab, by virtue of its ability to dissolve existent thrombus and prevent new thrombus, results in a decrease in ischemic events.[31-33]

Importantly, the design of CAPTURE allowed examination of the effect of abciximab prior to intervention. While early percutaneous intervention may prevent intermediate ischemic events, there is an up-front "tax" for such an aggressive approach. Fortunately, Gp IIb/IIIa inhibition can decrease the rates of MI during both the medical treatment phase and the percutaneous treatment of ACSs. The rate of MI was decreased in the group receiving abciximab compared with the placebo group, both before PCI, 0.6% vs 2.1% (P=.03), and after PCI, 2.6% vs 5.5% (P=.009). Importantly, a significant increase in MI occurred due to the PCI itself. Thus, PCI poses a risk of micro-particulate atheromatous embolization, which may lead to microvascular obstruction.[35] This is manifest as varying degrees of creatine kinase elevation and myocardial necrosis. Troponins appear to be an exquisite marker of distal embolization with microvascular obstruction and a sensitive tool to detect myocardial necrosis.[36] In CAPTURE, the benefit of abciximab was confined to patients with elevated serum troponin T levels, in whom abciximab decreased the risk of death or MI at 6 months by two thirds (from 23.9% to 9.5%, P=.002).[37] Troponin status appeared to be a more powerful risk stratification tool than angiography and was better able to identify which patients would benefit from abciximab, raising the possibility that Gp IIb/IIIa therapy should be targeted toward troponin-positive patients.[38]
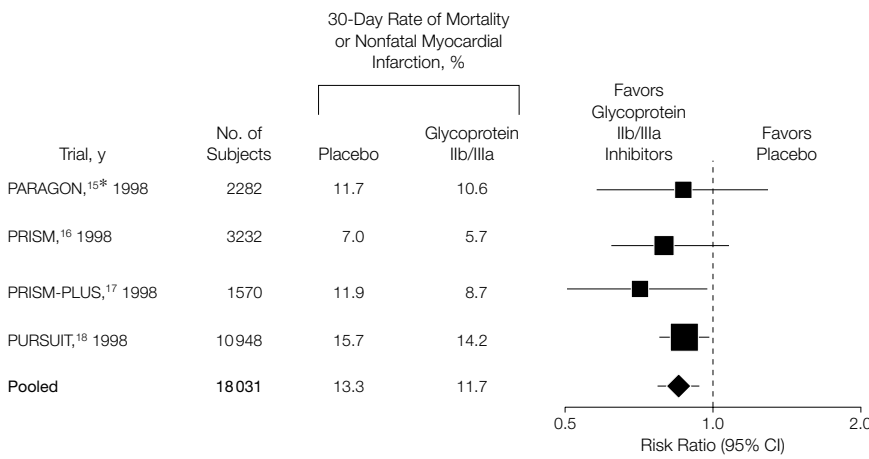
Gp IIb/IIIa Inhibitors for the Medical Management of Unstable Angina and Non–Q-Wave MI

Four trials collectively referred to as "4 P" serve as the foundation for use of Gp IIb/IIIa inhibitors during medical management of ACSs (**FIGURE 1**). The Platelet Glycoprotein IIb/IIIa in Unstable Angina Receptor Suppression Using Integrilin Therapy (PURSUIT) trial enrolled 10 948 patients with unstable angina or non–Q-wave MI and demonstrated a significant 1.5% absolute risk reduction in 30-day death or MI, 15.7% vs 14.2% (P=.04).[18]

Several additional analyses of PURSUIT have been performed that add appreciably to the understanding of Gp IIb/IIIa blockade in ACSs. Eptifibatide reduces the size and incidence of MI in patients who present with ACSs.[39] The beneficial effect of this therapy is durable, with 6-month follow-up showing a preservation of the initial benefit.[40] It remains to be seen whether longer-term follow-up will show a mortality advantage due to prevention of MI.
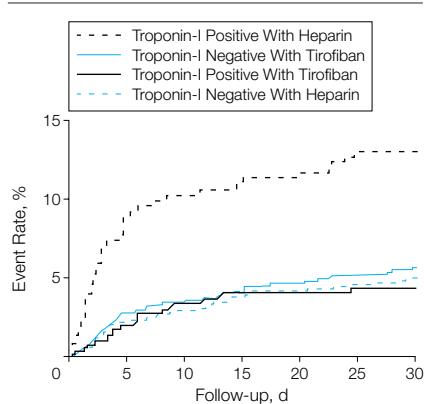
The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) study enrolled 3232 patients with unstable angina and randomized them to treatment with either heparin or tirofiban.[16] The rate of 48-hour death,

Figure 1. Reduction in Death or Nonfatal Myocardial Infarction at 30 Days for the Glycoprotein IIb/IIIa Inhibitor Trials

Trial, y	No. of Subjects	30-Day Rate of Mortality or Nonfatal Myocardial Infarction, %		
		Placebo	Glycoprotein IIb/IIIa	
PARAGON,[15]* 1998	2282	11.7	10.6	
PRISM,[16] 1998	3232	7.0	5.7	
PRISM-PLUS,[17] 1998	1570	11.9	8.7	
PURSUIT,[18] 1998	10948	15.7	14.2	
Pooled	18031	13.3	11.7	

Reproduced with permission from Lefkovits J, Topol EJ. Role of platelet inhibitor agents in coronary artery disease. In: Topol EJ, ed. *Textbook of Interventional Cardiology.* Philadelphia, Pa: WB Saunders Co; 1999:13. Asterisk indicates low dose vs placebo for PARAGON. Size of square data markers indicates sample size.

Figure 2. Reduction in Death or Myocardial Infarction in Troponin-Positive Patients Who Received Tirofiban

Adapted with permission from Heeschen C, Hamm CW, Goldmann B, et al.[41] Copyright by The Lancet Ltd, 1999. Troponin I was positive if greater than 1.0 µg/L.

MI, or refractory ischemia was reduced from 5.6% to 3.8% with tirofiban compared with heparin (P=.01). There was no significant difference for the composite end point at 30 days, however. In the relatively lower-risk cohort of patients in PRISM, Heeschen et al[41] extended the value of troponin measurement in determining allocation to intravenous Gp IIb/IIIa inhibition (**FIGURE 2**). Furthermore, this benefit was apparent in patients treated either medically or with revascularization.

Thus, troponins serve to identify patients most likely to benefit from Gp IIb/IIIa inhibition and appear to be a more appropriate risk stratification tool for this purpose than angiography. The PRISM in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study randomized 1915 patients with unstable angina and non–Q-wave MI to heparin, tirofiban, or both tirofiban and heparin.[17] The tirofiban-only arm was stopped prematurely because interim analysis revealed an increased rate of mortality compared with the heparin-only arm. The group who received heparin and tirofiban had a significantly decreased rate of 7-day death, MI, or refractory ischemia compared with the group who received only heparin, 17.9% vs 12.9% (P=.004). The observed benefit continued at 30 days and at 6 months. Although the elevated mortality observed in the tirofiban-only arm may have been due to statistical chance, this finding raises the possibility of a prothrombotic effect of Gp IIb/IIIa inhibition without concomitant heparin use.

Lamifiban is another nonpeptide Gp IIb/IIIa inhibitor that was evaluated in the Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON) trial.[15] This randomized trial of 2282 patients com-pared 2 dosages of lamifiban, with or without heparin, with placebo and heparin in patients with unstable angina or non–Q-wave MI. Death or MI at 30 days occurred in 11.7% of patients receiving only heparin, in 10.6% of those receiving low-dose lamifiban, and in 12.0% of those receiving high-dose lamifiban (P=.67). At 6 months, the rate of death or MI was 13.7% for those assigned to low-dose lamifiban (P=.03) and 16.4% for those assigned to high-dose lamifiban (P=.45) compared with 17.9% for the control arm. Thus, low-dose lamifiban appeared efficacious compared with control, but the higher dose was not superior to the lower dose. Assuming that these differences were not due to chance, the possibility that lamifiban, and potentially other Gp IIb/IIIa inhibitors, operate in a narrow therapeutic window must be considered. The recently presented PARAGON B trial showed a weak benefit for lamifiban compared with placebo that was not statistically significant in the overall population.[42] Interestingly, the troponin-positive cohort appeared to derive a marked, and statistically significant, benefit. Nevertheless, it appears that commercial development of this agent will not proceed.

While the 4P trials demonstrate the effectiveness of Gp IIb/IIIa therapy in addition to medical management with heparin, Gp IIb/IIIa therapy also allows a smooth transition from medical management to invasive therapy. Pooled data from the CAPTURE, PURSUIT, and PRISM-PLUS trials reveal a strong benefit of Gp IIb/IIIa inhibition while patients were receiving medical treatment, as well as subsequently after percutaneous intervention (**FIGURE 3**).[43]

Dosing, Concomitant Medications, and Procedures

In the emergency department or medical setting, abciximab is given as an intravenous bolus of 0.25 mg/kg, followed by an infusion of 0.125 µg/kg per minute (up to a maximum of 10 µg/min) for 12 hours. Abciximab is approved for use in ACSs for up to 24 hours, but only if there is a plan for eventual catheterization. Eptifibatide is given as an intravenous bolus

of 180 µg/kg, followed by an infusion of 2 µg/kg per minute. In PURSUIT, epti-fibatide was continued for up to 96 hours. The loading dose of tirofiban is 0.4 µg/kg per minute for 30 minutes, followed by maintenance infusion at a rate of 0.1 µg/kg per minute for up to 108 hours after presentation with an ACS.

In the catheterization laboratory, Gp IIb/IIIa inhibitors are all given as an initial bolus after the arterial sheath is placed, but prior to instrumentation of the artery. While some operators do give these agents only if they encounter technical problems intraprocedurally, this sort of "bailout" administration has not been prospectively studied in a randomized trial. After a bolus of 0.25 mg/kg of abcix-imab, the infusion of 0.125 µg/kg per minute is continued for 12 hours after the PCI. Eptifibatide is given as an intravenous bolus of 180 µg/kg, followed by an infusion of 2 µg/kg per minute that is continued for 20 to 24 hours. A recently reported trial, ESPRIT (Enhanced Suppression of Platelet glycoprotein IIb/IIIa Receptor with Integrilin Therapy), tested a dosing strategy that included a second 180-µg/kg bolus given 10 minutes after the first bolus, with favorable results.[42] While the current bolus dose of tirofiban may be adequate for treatment of ACSs, it may not ensure adequate anti-platelet effect at the beginning of an interventional procedure. Therefore, the dose that is currently being studied for PCI is an intravenous bolus of 10 µg/kg, followed by an infusion of 0.15 µg/kg per minute for 18 to 24 hours after the PCI.
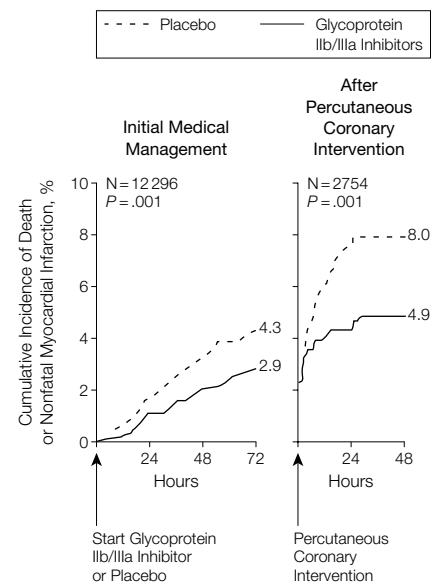
Care must be used in administering Gp IIb/IIIa inhibitors in patients with renal failure. Tirofiban can be used in severe renal impairment with a creatinine clearance of less than 30 mL/min, but the loading dose and the infusion should be halved. In addition, tirofiban is dialyzable. Knowledge of the dosing of eptifibatide in renal failure is more limited, as it has not been well studied in patients with creatinine levels higher than 2 mg/dL. However, a 135-µg/kg bolus, followed by a 0.5 µg/kg per minute infusion has been used in patients with creatinine levels between 2 mg/dL and 4 mg/dL. Abciximab is an antibody that is cleared by the reticuloendothelial system. However, the trials that have studied abciximab have excluded patients with renal failure. Thus, while abcix-imab has been used successfully even in patients receiving dialysis, this is not an approved use.

If these agents are administered before diagnostic catheterization that then reveals coronary artery lesions that require surgical intervention, they should be discontinued before surgery. Abcix-imab should be discontinued as soon as coronary artery bypass graft (CABG) surgery is planned. Eptifibatide or tirofiban should be discontinued at least 4 hours before bypass surgery. Randomized clinical trials of patients who had emergency CABG surgery after receiving each of the 3 agents have not shown increased bleeding, but have shown a decreased occurrence of ischemic events.[44,45]

Aspirin was part of standard therapy in all these trials and its use is established in patients with ACSs. In fact, the benefit of Gp IIb/IIIa inhibitor therapy is present in both prior aspirin users and nonusers.[46] Heparin use appears to be necessary during therapy with eptifibatide.[47] Results from the arm of PRISM-PLUS trial that used tirofiban alone, and was terminated prematurely because of a higher rate of mortality compared with heparin, also suggest that concomitant heparin therapy is necessary. It is important, though, not to give too much heparin either, as this increases the rate of bleeding complications, especially in patients undergoing invasive procedures. Heparin dosing should be weight-based, such as a bolus dose of 70 U/kg, aiming for a target-activated partial thromboplastin time of 50 to 70 seconds.[13,48,49] After successful PCI, heparin is generally discontinued, while an infusion of Gp IIb/IIIa inhibitor is maintained. Unlike unfractionated intravenous heparin used alone, there does not appear to be a "rebound effect" due to an increase in thrombin generation when heparin is discontinued in patients also receiving eptifibatide.[50] Neither does there appear to be a rebound effect from discontinuing eptifibatide in patients with

Figure 3. Reduction in Death or Myocardial Infarction in Patients Who Received Glycoprotein IIb/IIIa Inhibitors

A reduction was present both during the initial medical management phase and after percutaneous coronary intervention as well. Adapted with permission from Boersma E, Akkerhuis KM, Theroux P, et al.[43]

unstable angina.[51] This lack of rebound effect is likely applicable to the other Gp IIb/IIIa inhibitors. If the patient is already taking subcutaneous low-molecular-weight heparin (LMWH) prior to catheterization, Gp IIb/IIIa inhibitors may be used in the doses listed above, but how much additional LMWH to give intravenously at the time of PCI would depend on the time of the last subcutaneous dose; these dosing algorithms are only now being formally evaluated.[52]

Adverse Effects

Bleeding is the principal adverse effect from Gp IIb/IIIa inhibitors. As shown in the EPILOG trial, careful management of the percutaneous insertion site in the groin by early sheath removal (3-4 hours after heparin is discontinued and the activated partial thromboplastin time is close to normal) and avoidance of routine venous sheath placement reduces bleeding associated with catheterization procedures. Use of low-dose, weight-adjusted heparin also decreases bleeding complications. Abciximab, unlike fibrinolytic therapy, does not increase

the risk of intracranial hemorrhage.[53] Similarly, the risk of stroke was not increased with eptifibatide therapy in PURSUIT (0.6% vs 0.8% with placebo).[54]

Thrombocytopenia is uncommon with Gp IIb/IIIa inhibitors.[53] Platelet counts lower than 20×10^9/L can develop with abciximab administration about 0.4% to 1% of the time. With readministration of abciximab, this rate is slightly higher at 1.5% to 2%.[51] When thrombocytopenia occurs, it is within 1 to 24 hours of receiving the agent, and the most severe form usually occurs within 1 hour. Platelet counts should recover rapidly after discontinuation at the rate of 20×10^9/L and 30×10^9/L per day. Therefore, when these agents are infused, platelet counts should be measured after 1 to 2 hours and again after 12 hours.

Since abciximab is an antibody, it might be expected to have the potential to induce an allergic response. On initial administration, this does not appear to occur. Information currently is being collecting on readministration of abciximab.[55] Human antichimeric antibody develops in about 5% of patients receiving abciximab within 1 month of administration. However, there have been no reports of anaphylaxis or other serious allergic events with readministration. Furthermore, the presence or absence of human antichimeric antibodies was not predictive of adverse ischemic or bleeding events.

Contraindications

Active bleeding is an absolute contraindication to Gp IIb/IIIa inhibition. Major surgery within the past 3 months, stroke in the past 6 months, and a history of recent trauma are relative contraindications. Uncontrolled hypertension, defined as a systolic blood pressure of 180 mm Hg or higher and/or a diastolic blood pressure of 110 mm Hg or higher, is another relative contraindication. Severe anemia and thrombocytopenia are additional relative contraindications.

Combining Therapy With LMWH or Thrombin Inhibition

Along with advances in intravenous antiplatelet therapy, parallel developments have occurred in anticoagulant therapy. The LMWHs have been shown to be superior to unfractionated heparin in patients with ACSs. The Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events (ESSENCE) study showed a significant benefit of enoxaparin over unfractionated heparin in patients with ACSs.[56] The TIMI 11B trial produced similar results.[57] A meta-analysis of ESSENCE and TIMI 11B showed a marked benefit of these agents.[58] The Fragmin Fast Revascularisation during Instability in Coronary Artery Disease II (FRISC II) trial examined dalteparin and found benefit in certain groups.[59] Thus, LMWHs appear to be superior to unfractionated heparins. Pilot studies support the safety of a combination therapy of Gp IIb/IIIa inhibitors and LMWHs. For patients with unstable angina and non–Q-wave MI, tirofiban with enoxaparin appears as safe as tirofiban with unfractionated heparin, with a trend toward greater inhibition of platelet aggregation.[60] Data from the large NICE-4 registry (National Investigators Collaborating on Enoxaparin) further support the safety of the conventional dose of abciximab and 0.75 mg/kg of intravenous enoxaparin at the time of PCI.[61,62]

Direct thrombin inhibition is another promising development in anticoagulation for ACSs. Organization to Assess Strategies for Ischemic Syndromes-2 (OASIS-2) demonstrated the superiority of the direct thrombin inhibitor lepirudin (recombinant hirudin) over unfractionated heparin.[63] Combining lepirudin with Gp IIb/IIIa inhibition may be a promising form of therapy. A meta-analysis of 5674 patients, including 1071 with ACSs, has shown that bivalirudin, another direct thrombin inhibitor, is at least as effective as unfractionated heparin, but is safer.[64] In a pilot study of bivalirudin with backup use of abciximab, the results using this strategy compared favorably with unfractionated heparin and prophylactic abciximab.[65] Larger trials to assess combined use of newer anticoagulants with Gp IIb/IIIa inhibitors are currently in progress.

It is unclear how these concurrent advances in pharmacotherapy will be integrated.[66] Combined therapy may be synergistic with Gp IIb/IIIa inhibition, or alternatively may diminish the need for intravenous antiplatelet therapy. Ongoing trials will evaluate combinations of these various medications and help delineate what the optimal approach to the treatment of ACSs may be.

Comparisons of Gp IIb/IIIa Inhibitors

While Gp IIb/IIIa inhibitors are often discussed as a class, potentially important differences exist among these agents. Both eptifibatide and tirofiban are relatively short-acting, with return of more than 50% of platelet function within 4 hours of cessation of the infusion. In contradistinction, abciximab has a measurable antiplatelet effect that lasts for several days. There are differences in receptor affinity and specificity among the 3 agents. Abciximab binds much more avidly to the Gp IIb/IIIa receptor than do the other 2 agents. Furthermore, abciximab binds to other receptors, such as the vitronectin and Mac-1 receptors, while tirofiban and eptifibatide bind specifically to the Gp IIb/IIIa receptor. These other receptors seem to be important to platelet-leukocyte interactions, but the clinical significance of this is not yet clear. In addition to direct antiplatelet effects, abciximab can act as an anticoagulant.[67,68] This may be due entirely to potent Gp IIb/IIIa inhibition and a subsequent reduction in thrombin generation, but the vitronectin receptor may be involved. To date, only abciximab has long-term mortality-reduction data.[20,30,69] Whether this is due to greater potency, varied biologic effect, or the fact that the abciximab trials have all incorporated PCI has not yet been determined. With the nonplatelet effects of abciximab, comparative studies of platelet aggregation may not be a suitable surrogate for predicting any differences in clinical outcomes.[70]

The costs of each of the 3 therapies are substantial, with differences in pricing among them as well. Abciximab is considerably more expensive than eptifibatide or tirofiban, both of which are similarly priced. The cost of these agents will depend on the patient's weight, spe-

cific dosing regimen, and duration of infusion. However, as an example, the typical cost of an abciximab bolus and 12-hour infusion is $1350 for an 80-kg patient. For the 10-μg/kg bolus and 18- to 24-hour infusion, the price of tirofiban would be $689; for the double bolus and 18- to 24-hour infusion, the price of eptifibatide would be $493. In a cost-effectiveness analysis of EPIC, abciximab was shown to be extremely beneficial.[71] The EPISTENT 1-year data show that abciximab is cost-effective, even in addition to stenting. Compared with stenting and placebo, the combination of stenting and abciximab had a cost-effectiveness ratio of $5291 per added life-year, making abciximab treatment highly cost-effective.[30] A cost-effectiveness analysis of the PURSUIT study also revealed that eptifibatide administration for ACSs was an appropriate use of health care resources.[72]

The first head-to-head comparison between Gp IIb/IIIa inhibitors, the Do Tirofiban And ReoPro Give Similar Efficacy Outcomes Trial (TARGET), is enrolling 4750 patients undergoing PCI, will randomize them to receive either abciximab or tirofiban, and is powered to show noninferiority of tirofiban compared with abciximab. The primary end point will be 30-day death, MI, or urgent revascularization. This study will help determine whether these 2 Gp IIb/IIIa inhibitors are clinically equivalent. If so, the fact that tirofiban is less expensive would probably make it the agent of choice, especially if 1-year mortality is similar, and if the beneficial effect in patients with diabetes is as dramatic as seen with abciximab.[69,73,74]

Monitoring

In current practice, there is no titration of the dose of Gp IIb/IIIa based on measurements of platelet inhibition. However, there is evidence that dose adjustments based on platelet function assays may optimize outcomes. There are several potential methods to measure platelet aggregation.[75] A rapid, bedside platelet function assay that uses a sample of whole blood to determine Gp IIb/IIIa activity is now available.[76] In PARAGON,

the beneficial effect of lamifiban in reduction in death or MI was seen in patients with plasma levels of drug that resulted in 80% to 90% platelet inhibition. In healthy volunteers, both eptifibatide and tirofiban can have a wide range of inhibition of fibrinogen binding.[77] One study found substantial variability in platelet inhibition with abciximab (N=100).[78] Furthermore, in this study, patients with less than 80% inhibition had an almost 50% rate of adverse events. The GOLD study used the rapid assay to correlate platelet inhibition, measured at different times during therapy, with ischemic events or major bleeding in 500 patients undergoing PCI with any of the 3 approved Gp IIb/IIIa inhibitors.[79] It appears that a level of platelet inhibition greater than 80% is optimal. Additionally, platelet assays may allow more appropriate dosing in conditions such as renal failure. A measurement of platelet inhibition would also serve the practical purpose of ensuring systemic delivery of the agent, as opposed to undetected infiltration of an intravenous line.

Oral Gp IIb/IIIa Inhibitors

The results of the first large trials of the oral Gp IIb/IIIa inhibitors xemilofiban hydrochloride, orbofiban acetate, and sibrafiban, have been disappointing. The Evaluation of Oral Xemilofiban in Controlling Thrombotic Events (EXCITE) trial evaluated the effect of xemilofiban in patients undergoing PCI.[80] There was no significant difference in the rate of death or MI at 6 months, although there was excess bleeding in the patients who were receiving xemilofiban compared with placebo. Mortality was higher in those patients receiving xemilofiban, 0.3% vs 0.7% with placebo (P=.048).

The Orbofiban in Patients with Unstable Coronary Syndromes (OPUS) trial of patients with ACSs was stopped due to excessive mortality in the group receiving orbofiban 2.0% compared with placebo 1.4% (P=.049).[81] The Sibrafiban Versus Aspirin to Yield Maximum Protection from Ischemic Heart Events Post-Acute Coronary Syndromes (SYMPHONY) trial also enrolled patients with ACSs and random-
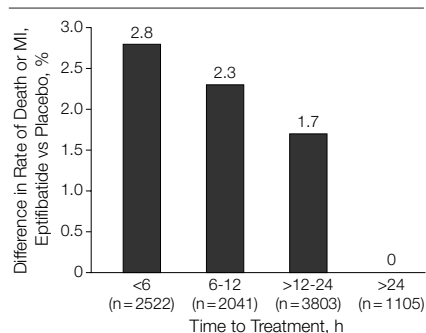
ized them to either sibrafiban or placebo, finding a greater rate of mortality with sibrafiban, 2.0% vs 1.8%.[82] The recently presented SYMPHONY 2 trials showed a similar increase in mortality.[42] A pooled analysis of these 4 large trials of oral Gp IIb/IIIa inhibitors in 33 340 patients by Chew et al[83] shows a statistically significant 37% increase in mortality with the oral Gp IIb/IIIa inhibitors from 1.3% to 1.7% (P=.001). This disturbing finding raises the possibility that oral Gp IIb/IIIa inhibitors may have a prothrombotic effect. Further studies of newer oral agents are ongoing, and the results of additional trials will determine the ultimate fate of this class of agents.

Treatment Strategy for Unstable Angina or Non–Q-Wave MI

The benefits of Gp IIb/IIIa inhibitors in stabilizing patients with ACSs has yet to be fully realized.[84] Abundant data support the importance of early treatment with fibrinolytic therapy for acute ST-segment-elevation MI. In an analogous fashion, early treatment with Gp IIb/IIIa in patients with non–ST-segment elevation ACSs would be expected to improve outcomes. An analysis from the PURSUIT trial shows that this may indeed be the case.[85] Patients who were randomized to therapy with eptifibatide who were within 24 hours of symptom onset had a significant 2.2% absolute reduction in death or MI (P=.003), while those treated after 24 hours derived no benefit. Furthermore, there appeared to be a gradient of effect, with patients treated the earliest after symptom onset having a greater benefit from therapy (FIGURE 4). An ongoing trial will prospectively examine the benefit of early, empiric administration of eptifibatide vs placebo in patients with unstable angina or non–Q-wave MI. Patients are randomized to administration of eptifibatide either at presentation or at the time of percutaneous intervention.

Administration of Gp IIb/IIIa inhibitors to patients with ACSs at the time of percutaneous intervention is beneficial. The data regarding the use of periprocedural abciximab in ACSs, equalizing the risk to that of patients with stable

Figure 4. Importance of Time to Treatment in Unstable Angina and Non–Q-Wave Myocardial Infarction (MI)

There is a greater reduction in 30-day death or nonfatal myocardial infarction vs placebo when patients are treated early after symptom onset. Data from Bhatt DL, Marso SP, Houghtaling P, et al.[85]

angina, is compelling.[29] Thus, many cardiologists prefer to wait until after a diagnostic catheterization to decide on initiation of Gp IIb/IIIa inhibition. This appears to be an excellent strategy, especially if catheterization facilities are readily available and the procedure can be performed in a timely fashion. However, the early empiric administration of Gp IIb/IIIa inhibitors before coronary anatomy is delineated may also be justified.[86] In an analysis of the PURSUIT trial, Roe et al[86] found that, among patients who underwent coronary angiography, even those with less than 50% angiographic stenosis appeared to derive a modest benefit from eptifibatide therapy, though this was not statistically significant in the relatively small number of patients studied. Perhaps, this effect is due to eptifibatide preventing platelet aggregation and thrombus progression in an otherwise nonocclusive coronary stenosis. Potentially, another operative mechanism would be prevention of platelet embolization and microvascular obstruction. More important, therapy with eptifibatide in this low-risk cohort of patients was extremely safe. Thus, unlike the situation of misdirected administration of a fibrinolytic agent to a patient without ST-segment-elevation MI, which can be catastrophic, therapy with eptifibatide in patients ultimately found to have minimal coronary artery atherosclerosis does not appear to pose a liability.

One concern with a strategy of empiric administration of Gp IIb/IIIa therapy before coronary angiography is the potential for need of CABG surgery. An analysis of the PURSUIT trial by Marso et al[87] showed that CABG not only is safe in these patients who initially received eptifibatide therapy, but it also resulted in improved outcomes. The reduction in rates of 6-month death or MI was from 35.3% to 23.8% with eptifibatide therapy in patients undergoing CABG within 72 hours of initiation of the study drug ($P = .009$). There was no difference in the risk of major bleeding (56.7% with placebo vs 58.2% with eptifibatide, $P = .70$). Furthermore, platelet transfusions can reverse any excess bleeding that may occur after surgery.[88] In addition, abciximab may even protect platelets from being destroyed by the cardiopulmonary bypass pump.[89] In a pooled analysis of EPIC, EPILOG, and CAPTURE data, patients who underwent CABG after unsuccessful PCI had a decrease in the rate of 30-day MI, including post-CABG MI (from 73% to 45%, $P = .01$).[44] The situation appears similar for tirofiban. A post-randomization analysis of the data from PRISM-PLUS demonstrates that a strategy of tirofiban and heparin is superior to heparin alone regardless of whether the patient is managed medically, with PCI, or with CABG. Rates of 30-day death, MI, refractory ischemia, or rehospitalization for unstable angina were decreased with the addition of tirofiban.[45] Thus, early empiric administration of Gp IIb/IIIa therapy in ACSs appears to be beneficial regardless of whether patients have insignificant coronary artery disease, lesions amenable to percutaneous intervention, or surgical anatomy.

Positive troponin status appears to identify patients who derive maximal benefit from Gp IIb/IIIa inhibitors. In addition to troponin positivity, prior aspirin use serves as a marker for an increased risk of adverse outcomes.[46,90,91] This may be because prior aspirin users are "aspirin-resistant," experiencing an ischemic event despite antiplatelet therapy with aspirin.[92] Many patients are taking aspirin at the time of presentation with an ACS; thus, prior aspirin use is an important and prevalent risk factor. Compared with unfractionated heparin, eptifibatide and tirofiban have each been shown to have significant benefit in prior aspirin users, while these agents did not appear to have substantial benefit in those not already taking aspirin.[46,91] Importantly, prior aspirin use does not attenuate the benefits of Gp IIb/IIIa inhibition, but instead serves as a marker for augmented effect.

While early use of these agents in ACSs is recommended, these agents are often used as "rescue" therapy. Patients who have breakthrough ischemic pain or electrocardiogram changes despite therapy with aspirin, heparin, nitroglycerin, and β-blockers can be given Gp IIb/IIIa inhibitors. Clinically, this strategy can postpone, and perhaps even obviate, the need for urgent catheterization. In high-risk patients, who are to be transferred to a tertiary care center, initiation of eptifibatide therapy before transfer improved outcomes compared with patients receiving placebo.[93] Therefore, Gp IIb/IIIa blockade may be able to serve as a bridge to revascularization. In circumstances in which these agents are not started on initial presentation, they may be useful to help stabilize patients who have symptom progression despite conventional medical therapy. If ready access to catheterization and interventional facilities exists, Gp IIb/IIIa inhibitor therapy can begin at the time of the procedure, with excellent results. However, in total, these various analyses support the concept of early initiation of therapy soon after presentation, guided by troponin status, electrocardiographic data, and a history of prior aspirin use. In many cases, this would involve initiation of therapy in the emergency department,[94] regardless of whether eventual treatment will include percutaneous intervention or surgical revascularization.

CONCLUSION

Intravenous platelet Gp IIb/IIIa inhibitor therapy has greatly enriched the therapeutic armamentarium for patients with ACSs. Administered either at the time of urgent angiography with percutaneous

coronary revascularization, or empirically in the emergency department at presentation, these agents build on the precedent antithrombotic template of aspirin and heparin. The incidence of MI has been substantially reduced, and in the case of abciximab, survival has been enhanced. Key issues that need to be resolved include differentiation among agents and the coadministration with more potent anticoagulants, such as LMWHs or direct thrombin inhibitors. Nevertheless, based on current data, intravenous glycoprotein IIb/IIIa inhibitors merit a prominent role in the management of ACSs, either medically or in conjunction with PCI.

ADDENDUM

Results of the Global Use of Strategies To Open Occluded Coronary Arteries (GUSTO) IV ACS trial were recently presented at the European Society of Cardiology annual meeting in August. In addition to the presence of chest pain for longer than 5 minutes, entry criteria for this trial were either a positive troponin level or electrocardiographic changes, with early revascularization strongly discouraged. Unexpectedly, this trial of 7800 patients did not show a benefit of abciximab therapy compared with placebo, which appears to be due, in part, to the lower-risk population that was included vs that in other ACS trials. When the GUSTO IV trial was designed, it was powered for an expected 30-day rate of death or MI of 11%, as opposed to the observed 8% rate. Potentially, troponin-positive status in the absence of electrocardiographic or angiographic data does not identify a high-risk group and is not as powerful at stratifying patients for Gp IIb/IIIa therapy as previous retrospective analyses of the outcomes of troponin-positive patients implied. These other ACS trials enrolled patients based on electrocardiographic criteria, not troponin positivity, thus identifying a much higher-risk profile than many GUSTO IV patients. An alternative explanation for the GUSTO IV findings is that the duration of abciximab use (24 or 48 hours) may have untoward results. More critical analysis of the GUSTO IV ACS trial

is needed before any definite conclusions can be reached. Nevertheless, the value of abciximab in the treatment of ACS in conjunction with PCI remains unchanged. Furthermore, the substantial amount of data supporting the use of eptifibatide and tirofiban in the medical management of high-risk ACS patients with ST-segment depression and positive troponins remain valid. Importantly, when data from all 6 trials (PURSUIT, PRISM, PRISM-PLUS, PARAGON A, PARAGON B, and GUSTO IV ACS) that have used Gp IIb/IIIa inhibitors for treatment of ACSs are pooled, the benefit of Gp IIb/IIIa blockade over placebo remains significant, with the rate of 30-day death or MI reduced from 11.5% to 10.7% ($P = .04$).

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