Platelet Glycoprotein IIb/IIIa Receptor Antagonists in Cardiovascular Disease

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Atherosclerotic heart disease is the most common cause of death in developed countries.1 Thrombosis with platelet deposition and fibrin formation begins immediately (within 1-24 hours) after spontaneous or mechanical injury and is usually mural and subocclusive.2 Plaque disruption activates the coagulation cascade leading to thrombin generation. Exposure of deeper components of atherosclerotic plaques (collagen, tissue factor) and thrombin generated by arterial injury are powerful platelet activators (Figure). Angiographic,4,5 angioscopic,6 pathologic,7 and biochemical8 evidence support the role of thrombus in the pathogenesis of acute myocardial infarction (MI), unstable angina, and percutaneous coronary intervention.9

Platelets play a crucial role in thrombus formation. Platelet function depends on the interactions of membrane glycoproteins (GPs) that are receptors for adhesive proteins. The most abundant receptor is the integrin family, which includes GP IIb/IIIa and fibronectin and vitronectin receptors. The integrins consist of heterodimeric molecules composed of α and β subunits.10 The surface of the resting platelet contains 50,000 to 80,000 copies of the GP IIb/IIIa (αIIbβ3) receptor.11,12 Agonists of platelet activation (Figure) facilitate the conformational change necessary for the receptor to become receptive to fibrinogen, von Willebrand factor, and vitronectin.13 These ligands all contain the identical peptide sequence, arginine-glycine-aspartic acid (single-letter code, RGD). Fibrinogen is by far the most important ligand for IIb/IIIa, probably because of its high plasma concentration.12 Fibrinogen simultaneously binds to GP IIb/IIIa receptors on 2 separate platelets,14 resulting in platelet cross-linking critical to platelet aggregation (Figure).

The role of the GP IIb/IIIa receptor was elucidated from studies of patients with Glanzmann thrombasthenia.15 This inherited disease is characterized by recurrent mucocutaneous bleeding but rare significant visceral bleeding.16 Laboratory studies revealed bleeding time prolongation and absent platelet aggregation. The patho-

Context Thrombus formation on disrupted atherosclerotic plaque is the major cause of acute coronary events. Platelet inhibitors are the mainstay of drug therapy to reduce cardiac events in patients with acute coronary syndromes. The platelet glycoprotein (GP) IIb/IIIa receptor is the final common pathway of platelet aggregation.

Objectives To review mechanisms of platelet activation and aggregation and the role of the GP IIb/IIIa receptor in the acute coronary syndromes and to summarize completed clinical trials of GP IIb/IIIa receptor antagonists.

Data Sources English-language journal articles, reviews from a MEDLINE search from 1993 through 1998, as well as abstracts and presentations from major national or international cardiology meetings through November 1998.

Study Selection/Data Extraction Randomized, placebo-controlled clinical trials testing intravenous GP IIb/IIIa receptor antagonists and having more than 500 subjects were included. Data quality and validity included publication or presentation venue.

Data Synthesis/Conclusions The GP IIb/IIIa receptor is the final common pathway of platelet aggregation. Intravenous monoclonal antibody and peptide and nonpeptide antagonists of the GP IIb/IIIa receptor have been tested in randomized, placebo-controlled trials of the acute coronary syndromes and percutaneous coronary interventions. For patients undergoing percutaneous revascularization, these agents have demonstrated efficacy in reducing death, myocardial infarction, or urgent reintervention. Odds ratios of death or myocardial infarction at 30 days range from 0.42 to 0.84 for the drugs in these studies. More modest benefits have been seen in trials of IIb/IIIa receptor antagonists for patients with the acute coronary syndromes, with odds ratios for death or myocardial infarction at 30 days ranging from 0.70 to 0.89. The efficacy of oral agents for chronic GP IIb/IIIa receptor antagonism has not been sufficiently studied.

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One genetic mechanism is the absence of or a significant decrease in functional GP IIb/IIIa receptors.

Platelet inhibitors are widely used in clinical practice. Aspirin is recommended for treatment of unstable angina, acute and following MI, and before and after percutaneous transluminal coronary angioplasty (PTCA). Aspirin only partially inhibits platelet aggregation by inhibiting the thromboxane A2 pathway of platelet aggregation. Ticlopidine hydrochloride and clopidogrel selectively inhibit the binding of adenosine diphosphate to its platelet receptor and block adenosine diphosphate–dependent platelet activation. These platelet inhibitors inactivate only 1 pathway of platelet activation. Despite optimal inhibition of a specific pathway, platelet activation occurs through other pathways. Regardless of the stimulus for activation, platelet-platelet interaction and thrombus formation is ultimately regulated through the GP IIb/IIIa receptor complex. These observations provide the rationale for pharmacological intervention directed against the GP IIb/IIIa receptor. We review the studies of efficiency of GP IIa/IIIb antagonists to evaluate their efficacy and indications.

METHODS

All original English-language journal articles, reviews from a MEDLINE literature search from 1993 through 1998 (using the Medical Subject Headings of platelet glycoprotein IIb/IIIa, unstable angina, myocardial infarction, and percutaneous transluminal coronary angioplasty), articles cited in reference lists of included articles, and abstracts and presentations from major national or international cardiology meetings through November 1998 were reviewed. All randomized controlled clinical trials of GP IIb/IIIa receptor antagonists with more than 500 subjects were included.

### Table 1. Available Intravenous Platelet Glycoprotein IIb/IIIa Receptor Antagonists

<table>
<thead>
<tr>
<th>Molecular structure</th>
<th>Abciximab</th>
<th>Eptifibatide</th>
<th>Tirofiban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved indication</td>
<td>Coronary intervention</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Acute coronary syndromes</td>
<td>Yes†</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Approved dose‡</td>
<td>Coronary intervention</td>
<td>Bolus 0.25 mg/kg</td>
<td>135 µg/kg§</td>
</tr>
<tr>
<td></td>
<td>Infusion</td>
<td>0.125 µg/kg min × 12 h (10 µg/min, maximum)</td>
<td>0.5 µg/kg/min × 20 to 24 h</td>
</tr>
<tr>
<td>Acute coronary syndromes</td>
<td>Bolus 0.25 mg/kg</td>
<td>180 µg/kg</td>
<td>0.4 µg/kg per min × 30 min</td>
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<tr>
<td></td>
<td>Infusion</td>
<td>10 µg/min × 18 to 24 h before intervention; continue 1 h post PCI</td>
<td>2.0 µg/kg per min up to 72 h</td>
</tr>
</tbody>
</table>

*Ellipses indicate not approved.
†Approved for refractory unstable angina when percutaneous coronary intervention (PCI) is scheduled within the next 24 hours.
‡For abciximab, platelet counts should be obtained within 2 to 4 hours after the bolus and 24 hours after the bolus. More frequent platelet counts should be obtained as indicated clinically if reductions in platelet counts are noted. A daily hemoglobin/hematocrit value should be obtained. Activated partial thromboplastin time (aPTT) should be monitored in accordance with usual practice patterns for administration of heparin.
§See “Methods” section for discussion of preferred epifibatide dosing regimen intervention.
¶See “Methods” section for discussion of preferred duration of infusion following intervention.
††Patients with severe renal insufficiency (creatinine clearance of <30 mL/min) should receive half the usual rate of infusion.

Figure. Pathways of Platelet Activation

PAF indicates platelet activating factor; ADP, adenosine diphosphate; TXA2, thromboxane A2; GP IIb/IIIa, glycoprotein IIb/IIIa; and Epi, epinephrine. Thickness of line indicates strength of activator.
Clinical Evidence
Glycoprotein IIb/IIIa receptor antagonists include the following: (1) the monoclonal antibody abciximab; (2) the peptide receptor antagonist eptifibatide; and (3) the nonpeptide receptor antagonists tirofiban and lamifiban (Table 1). Numerous oral nonpeptide mimetics of the IIb/IIIa receptor antagonist are in clinical development. More than 30,000 patients undergoing percutaneous intervention or who have unstable angina or non-Q-wave MI have been enrolled in randomized trials. Treatment with GP IIb/IIIa receptor antagonists consistently reduces the risk of ischemic end points (Table 2).

Table 2. Thirty-Day Death or Nonfatal Myocardial Infarction (MI) in All Randomized Controlled Trials of Glycoprotein IIb/IIIa Receptor Antagonists Involving at Least 1000 Patients*  

<table>
<thead>
<tr>
<th>Source, y</th>
<th>No. of Study Patients</th>
<th>IIb/IIIa Comparison</th>
<th>30-Day Death or MI, %†</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P</strong></td>
<td><strong>PR,</strong> 0.001.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPIC, 1994</td>
<td>2099</td>
<td>Abciximab Standard therapy</td>
<td>7.0‡</td>
<td>10.1</td>
</tr>
<tr>
<td>EPILOG, 1997</td>
<td>2792</td>
<td>Abciximab Heparin</td>
<td>4.0§</td>
<td>9.1</td>
</tr>
<tr>
<td>CAPTURE, 1997</td>
<td>1265</td>
<td>Abciximab Standard therapy</td>
<td>4.8</td>
<td>9.0</td>
</tr>
<tr>
<td>EPISTENT, 1998</td>
<td>2399</td>
<td>Abciximab Standard therapy</td>
<td>5.2</td>
<td>10.2</td>
</tr>
<tr>
<td>IMPACT-II, 1997</td>
<td>4010</td>
<td>Eptifibatide Standard therapy</td>
<td>7.1‖</td>
<td>8.4</td>
</tr>
<tr>
<td>RESTORE, 1997</td>
<td>2139</td>
<td>Tirofiban Standard therapy</td>
<td>5.1</td>
<td>6.3</td>
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</tbody>
</table>

Acute Coronary Syndromes

<table>
<thead>
<tr>
<th>Source, y</th>
<th>No. of Study Patients</th>
<th>IIb/IIIa Comparison</th>
<th>30-Day Death or MI, %†</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
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<tbody>
<tr>
<td>PRISM, 1998</td>
<td>3231</td>
<td>Tirofiban Heparin and aspirin</td>
<td>5.7</td>
<td>7.0</td>
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<tr>
<td>PRISM-Plus, 1998</td>
<td>1570‡</td>
<td>Tirofiban Heparin and aspirin</td>
<td>8.7</td>
<td>11.9</td>
</tr>
<tr>
<td>PARAGON, 1998</td>
<td>2282</td>
<td>Lamifiban Heparin and aspirin</td>
<td>11.3#</td>
<td>11.7</td>
</tr>
<tr>
<td>PURSUIT, 1998</td>
<td>10,948</td>
<td>Eptifibatide Heparin and aspirin</td>
<td>14.2</td>
<td>15.7</td>
</tr>
<tr>
<td>Overall</td>
<td>32,736</td>
<td></td>
<td>9.0</td>
<td>11.1</td>
</tr>
</tbody>
</table>

*Adapted with permission from Topol.51  †Outcome measures were determined by Topol51 from original study results to facilitate comparisons across studies.  ‡Abciximab bolus plus infusion arm only.  §Abciximab plus high-dose and low-dose heparin arms combined.  ‖High-dose and low-dose eptifibatide arms combined.  †Tirofiban plus heparin and heparin monotherapy arms only.  #High-dose lamifiban with heparin and low-dose lamifiban with heparin arms combined.  **P<.001.

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to receive abciximab or placebo for 18 to 24 hours after angioplasty, continuing until 1 hour after the intervention. The CAPTURE trial was terminated prematurely after enrollment of 1265 patients (of a planned 1400) when abciximab-treated patients had a significant reduction in the composite end point of death, MI, or revascularization at 30 days (11.3% vs 15.9%). In the CAPTURE trial, the progression to MI before PTCA was significantly lower in patients receiving abciximab (0.6% vs 2.1%; P = .03), suggesting that GP IIb/IIIa inhibition benefits unstable angina patients not undergoing angioplasty.

The Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT)29 trial assessed abciximab in 2399 patients undergoing elective stenting. The primary end point (composite 30-day death, MI, or urgent revascularization) occurred in 10.8% of patients in stent plus placebo, 5.3% in the stent plus abciximab group (P < .001), and 6.9% in the balloon angioplasty plus abciximab group (P = .007). The principal end points prevented with stent plus abciximab treatment were death and large MI.

In the ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) study30 of 483 patients with acute MI less than 12 hours of undergoing primary PTCA, abciximab therapy reduced composite death, reinfarction, or urgent revascularization at 7 days (9.9% vs 3.3%, P = .003) and 30 days (11.2% vs 5.8%, P = .03). However, there was no difference in the primary 6-month end point of death, reinfarction, or target vessel revascularization.

In the Integrilin to Manage Platelet Activation to Prevent Coronary Thrombosis (IMPACT-II) study,31 4010 patients of all risk strata undergoing angioplasty were randomized to placebo or 1 of 2 doses of the synthetic cyclic heptapeptide epifibatide (Integrilin). By 30 days, analysis of all randomized patients revealed a strong trend toward improved outcome in the low-dose arm. Analysis of treated patients only showed a 24% reduction in the composite end point of death, MI, or revascularization (11.6% vs 9.1%, P = .04).

In the Randomised Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) trial,32 2139 patients undergoing high-risk angioplasty or atherectomy were assigned to bolus plus infusion of placebo or the nonpeptide mimetic tirofiban. While there was a significant 38% reduction in the composite end point at 48 hours, by 30 days (the primary end point), only a nonsignificant 16% reduction was observed (12.2% vs 10.3%). When the 30-day end point was reanalyzed using the same composite end point as previous trials (counting repeat angioplasty or coronary artery bypass grafting only when performed urgently), a 24% relative reduction was seen (10.5%-8.0%, P = .052).

**Indications for Therapy**

**Clinical Characteristics.** These trials indicate benefit for patients undergoing coronary intervention with risk reductions of up to 30% in some studies. Treatment benefits were observed within hours following intervention, were sustained through 6 to 12 months, and occur regardless of revascularization technique (treatment is still beneficial in the setting of stent implantation).

In the EPIC study23 and EPILOG27 trials, abciximab resulted in similar reductions of ischemic end points in patients with stable angina, unstable angina, or after MI. In the EPIC study,23 the magnitude of risk reduction was greater among patients with unstable angina compared with patients without unstable angina.33 Patients at highest risk for ischemic complications identified on the basis of clinical presentation (during, or after MI, or unstable angina) or procedural considerations (lesion morphology, multivessel intervention, or bailout stent) may derive the greatest treatment effect.

Clinical trials have shown greater magnitude of benefit with abciximab. The optimal regimen includes a bolus followed by a 12-hour infusion. Compared with the abciximab studies, more modest benefits were observed in the IMPACT-II31 and RESTORE32 studies. Perhaps this is due to differences between the agents (abciximab has a longer biological half-life, with a lower dissociation constant than epifibatide and also binds to the vitronectin receptor). It could also be due to trial design features such as shorter duration of preintervention treatment in the IMPACT-II study23 (10-60 minutes) vs the EPIC study23 (18-24 hours), underdosing of epifibatide (preclinical studies of epifibatide measured platelet aggregation in blood anticoagulated with citrate, which chelates calcium, and overestimated the in vivo platelet inhibitory effect of epifibatide),34 or failure to deliver GP IIb/IIIa antagonists until after the guidewire had crossed the lesion (RESTORE study).32 In both the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT)35 and Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited to Very Unstable Signs and Symptoms (PRISM-Plus)36 studies, the patient subgroup ultimately referred for coronary angiography and percutaneous intervention experienced a larger treatment benefit compared with the study populations as a whole. These data support the use of epifibatide and tirofiban in patients initially presenting with unstable angina or non–ST-segment elevation MI who then require coronary revascularization. In the PURSUIT35 and PRISM-Plus36 studies, treatment reduced 30-day death and MI by 31% to 44%. It is, therefore, unclear whether patients initially treated with epifibatide or tirofiban would benefit if their GP IIb/IIIa antagonist were switched to abciximab for subsequent intervention, and it is unclear whether such a practice would be safe, since the conventional abciximab bolus and infusion regimen has not been studied when administered following pretreatment with a different GP IIb/IIIa antagonist.

**Adjunctive Heparin.** Heparin is administered routinely during coronary intervention. The low-dose, weight-adjusted regimen used in the EPILOG study27 (70 U/kg bolus, target activated clotting time of ≥200 seconds) is associated with the most favorable...
Clinical Characteristics. Differences in the contribution of thrombus to the pathophysiology of various subgroups of patients with acute syndromes, particularly the broad populations studied in the larger clinical trials, result in more variable effect with thrombolytic agents. The results of TIMI 1442 (higher levels of TIMI 3 flow with abciximab plus half-dose [50-mg] accelerated tissue-type plasminogen activator) and the Strategies for Patency Enhancement in the Emergency Department (SPEED) pilot trial,45 using a half-dose of reteplase, form the basis for Global Strategies to Open Occluded Coronary Arteries (GUSTO-IV), a large-scale phase 3 trial evaluating treatment with a full dose of abciximab plus a half-dose of reteplase vs treatment with a full dose of reteplase alone.

**Indications for Therapy**

In the Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndromes (PARAGON) study, this heparin regimen should also be used for patients undergoing interventional procedures treated with tirofiban or eptifibatide.

**Intravenous GP IIb/IIIa Receptor Antagonists in Acute Coronary Syndromes**

**Unstable Angina/Non–ST-Segment Elevation MI.** In the Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndromes Events in a Global Organization Network (PARAGON) study,37 2282 patients were randomized to 72 hours of high- or low-dose lamifiban, with or without heparin, or heparin alone in a 2 × 2 factorial design. No difference in the primary end point of 30-day death myocardial infarction or reinfarction was seen among any of the groups (10.3%-12.3%). However, reexamination at the 6-month follow-up revealed a significant reduction in the low-dose lamifiban arm and especially in the group receiving low-dose lamifiban plus heparin (17.9% in the placebo/heparin arm vs 12.6% in the lamifiban arm, a 30% reduction).37

The Platelet Receptor Inhibition for Ischemic Syndrome Management (PRISM) study38 randomized 3232 patients to either tirofiban or heparin. At 48 hours (the primary end point), the incidence of the composite end point of death, MI, or reinfarction was reduced by 33% from 5.9% in the heparin group to 3.8% in the tirofiban group (P = .01). However, at 30 days, there was no significant difference in the composite end point (including admission for unstable angina) between the 2 groups (17.1% vs 15.9%).

The PRISM-Plus study39 enrolled 1915 patients with prolonged or repetitive chest pain (<24 hours) with either significant electrocardiographic changes or enzymatic confirmation of myocardial necrosis. Thus, patients in the PRISM-Plus study39 were at higher risk than those enrolled in the PRISM study.38 The PRISM-Plus study39 was initially designed to compare 3 study arms testing heparin, tirofiban, and tirofiban plus heparin for an average of 72 hours. However, after interim analysis by the data and safety monitoring committee revealed a 32% reduction in the tirofiban monotherapy arm (+6.6% vs 1.5% in tirofiban plus heparin arm and 1.1% in the heparin monotherapy arm, P = .01), the tirofiban monotherapy arm was terminated. Compared with heparin monotherapy, treatment with tirofiban and heparin was associated with a 32% reduction in the primary end point (composite of death, MI or refractory ischemia) at 7 days (17.9% vs 12.9%, P = .004). The benefit for death, or MI was maintained to 30 days (11.9% vs 8.7%, P = .03), although this finding did not achieve statistical significance at the prespecified level (P = .025) for this trial, which initially commenced with a comparison of 3 treatment arms.

The PURSUIT trial35 enrolled 10 948 patients within 24 hours of the last episode of chest pain and electrocardiographic changes to placebo and 2 eptifibatide arms. The study was designed to have an interim safety analysis after enrollment of 2100 patients, with the elimination of the low-dose eptifibatide arm, and continuation of the study with patients enrolled in a 1-to-1 manner in the placebo or high-dose eptifibatide arms (all patients received aspirin at the discretion of the treating physician and heparin was recommended). The eptifibatide group had a 1.5% absolute reduction in the incidence of the primary end point of death or MI at 30 days (15.7% placebo vs 14.2% eptifibatide, P = .04). This benefit was apparent by 96 hours and persisted through 30 days, up to 6 months.35,39 Treatment effect varied among the 4 geographic enrollment regions. The greatest benefit was observed among North American patients (16.2% in the placebo group vs 12.4% in the eptifibatide group, P = .006). Differences in baseline patient characteristics or management strategies may explain the observed geographic variability.

**Acute MI.** Glycoprotein IIb/IIIa antagonists could be effective in acute MI given the role of platelets in thrombus development and data that thrombolysis stimulates platelet aggregation.30 Early observations from small trials showed that coronary flow increased by at least 1 TIMI (Thrombolysis in Myocardial Infarction) flow grade in 11 of 13 patients with acute MI who were treated with aspirin, heparin, and abciximab without adjunctive thrombolytic therapy.41 However, data from the TIMI 14 trial32 showed reperfusion rates of only 20% to 40% with abciximab monotherapy.

The IMPACT-AMI43 and Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion (PARADIGM)44 trials studied GP IIb/IIIa receptor antagonists in conjunction with thrombolysis. These small pilot trials showed acceptable safety profiles and modest benefits in angiographic or electrocardiographic markers of reperfusion but no differences in major clinical end points. Recent trials studied the role of abciximab combined with lower-dose thrombolytic agents. The results of TIMI 1442 (higher levels of TIMI 3 flow with abciximab plus half-dose [50-mg] accelerated tissue-type plasminogen activator) and the Strategies for Patency Enhancement in the Emergency Department (SPEED) pilot trial,45 using a half-dose of reteplase, form the basis for Global Strategies to Open Occluded Coronary Arteries (GUSTO-IV), a large-scale phase 3 trial evaluating treatment with a full dose of abciximab plus a half-dose of reteplase vs treatment with a full dose of reteplase alone.
IIIa antagonist reduces the 30-day incidence of death and myocardial infarction by 10% to 30% (Table 1). This benefit is sustained at 6 months. In the PURSUIT\textsuperscript{35} and PRISM-Plus\textsuperscript{36} trials, a significant proportion of patients ultimately underwent percutaneous revascularization, and these patients may derive the greatest treatment benefit. Importantly, in the PURSUIT,\textsuperscript{35} PRISM-Plus,\textsuperscript{36} and CAPTURE\textsuperscript{27} trials, treatment benefit was most pronounced prior to the performance of the coronary intervention. For patients treated with a conservative, medical approach, the addition of a GP IIb/IIIa receptor antagonist also adds an incremental benefit beyond aspirin and heparin, although the treatment benefit is more modest than for those patients treated with an interventional approach.

Clinical markers of patients with the acute coronary syndromes at high risk for ischemic complications may guide patient selection. In post hoc analyses, patients with ST-segment depression\textsuperscript{36} vs other electrocardiographic abnormalities or with elevations in serum troponin levels\textsuperscript{46} vs normal troponin levels appeared to derive greatest benefit from GP IIb/IIIa receptor antagonist treatment.

In the PURSUIT study, eptifibatide treatment was effectively combined with either an aggressive (percutaneous revascularization within 72 hours) or conservative (no revascularization) practice approach. Tirofiban was effective within the confines of more narrowly defined aggressive strategy encouraged in the PRISM-Plus study (coronary angiography with angioplasty if indicated). Thus far, abciximab has been evaluated only in patients with unstable angina in whom coronary anatomy is already known and intervention is planned within the next 24 hours. No direct comparisons of these 3 agents have been made, and indirect comparisons of end-point efficacy from the currently available trials may be hampered by significant differences in trial design and end-point evaluation.

### Adjuvative Heparin

The role of adjuvative heparin for patients with acute coronary syndromes treated with GP IIb/IIIa antagonists has not been thoroughly studied: minimal prospective data exists directly comparing GP IIb/IIIa receptor antagonist use with and without unfractionated heparin. The only study to examine prospectively this question was PRISM-Plus,\textsuperscript{36} in which an excess hazard for early mortality in the tirofiban monotherapy arm was observed. Some uncertainty exists about the significance of these findings, since the excess mortality observed was based on an interim analysis of only 345 patients in the tirofiban monotherapy arm, and the total number of events was small (n = 16). Thus, the findings from PRISM-Plus\textsuperscript{36} might be due to chance. Although a recent retrospective analysis from the PURSUIT study suggested a similar hazard of GP IIb/IIIa monotherapy, this analysis is more controversial due to the exclusion of all patients undergoing revascularization (to whom heparin was routinely administered) from the analysis.\textsuperscript{47} Conversely, in the PARAGON study,\textsuperscript{37} no benefit was seen at 30 days for lamifiban plus heparin vs lamifiban alone. Currently, intravenous heparin is indicated for all approved GP IIb/IIIa receptor antagonists, although the optimal level of anticoagulation remains unknown.

### SAFETY

#### Hemorrhagic Complications

No increase in intracerebral hemorrhage has been observed with the GP IIb/IIIa antagonists. Most bleeding occurred in patients who underwent percutaneous intervention; the majority of the reported bleeding events involved vascular access puncture sites. For example, in the CAPTURE study,\textsuperscript{28} 19 (79%) of 24 cases of major bleeding in the abciximab arm and 9 (75%) of 12 cases in the placebo arm occurred at the puncture site. Reduction in adjuvative heparin dosing to a target activated partial thromboplastin between 2.0 and 2.5 times control prior to percutaneous intervention and target activated partial thromboplastin time of 70 seconds or activated clotting time of 300 seconds during percutaneous coronary intervention reduced the incidence of vascular access site complications to levels comparable to control in the EPILOG and CAPTURE studies.\textsuperscript{27,28} Accordingly, the need for platelet transfusion to treat life-threatening bleeding is extremely rare, particularly for the short-acting agents tirofiban and eptifibatide. For patients undergoing percutaneous intervention with abciximab plus low-dose heparin, platelet transfusions were required in 2.1% of patients in the CAPTURE study.\textsuperscript{28} Platelet transfusions are more frequently required for patients treated with abciximab undergoing urgent coronary artery bypass graft surgery.\textsuperscript{48}

#### Thrombocytopenia

Thrombocytopenia (platelet count <100 × 10\textsuperscript{9}) occurs infrequently with abciximab and tirofiban; no increase in the incidence of thrombocytopenia was observed in epifibatide-treated patients compared with those who had received placebo in the PURSUIT and IMPACT-II studies.\textsuperscript{31,35} Treatment with epifibatide or tirofiban is associated with an absolute increase of approximately 0.2% in the risk of severe (platelet count <50 × 10\textsuperscript{9}/L) thrombocytopenia. The absolute excess in incidence of severe thrombocytopenia with abciximab appears to be higher (0.4%-1.4%): in a composite analysis of all abciximab trials,\textsuperscript{28,49} the incidence increased from 0.35% to 1.0%. However, excluding the EPIC study\textsuperscript{23} (for which the reported increase in severe thrombocytopenia from 0.72%-1.55% was likely attributable to high-dose heparin), analysis of the 3 other abciximab trials shows increases in the incidence of severe thrombocytopenia from 0.31% to 1.75% (CAPTURE study),\textsuperscript{28} 0.43% to 0.65% (EPILOG study),\textsuperscript{27} and 0.0% to 1.0% (EPISTENT study).\textsuperscript{28} Acute profound thrombocytopenia (platelet count <20 × 10\textsuperscript{9}) has been reported in approximately 0.69% of patients receiving abciximab,\textsuperscript{49} and platelet transfusions may be required.\textsuperscript{50} Since onset of
such profound thrombocytopenia is generally acute, platelet counts should be measured within the first 2 to 4 hours after the GP IIb/IIIa receptor antagonist has been administered, repeated, and followed through the course of therapy.50

**FUTURE CONSIDERATIONS**

**Unresolved Issues**

A combined analysis of all randomized clinical trials of at least 1000 patients receiving GP IIb/IIIa receptor antagonists in all areas of ischemic heart disease demonstrates the significant benefit of these agents (Table 2).51 However, unresolved clinical questions persist. No direct head-to-head comparisons have been performed, so the relative efficacy of the GP IIb/IIIa receptor antagonists remains to be determined. Abciximab also binds to the vitronectin (α5β3) receptor; the peptide and nonpeptide antagonists do not. Since the vitronectin receptor is present mostly on endothelial and smooth muscle cells,52 clinical implications of this cross-reactivity regarding prevention of restenosis,26 inhibition of thrombin generation,53 or other effects are unknown.54 Whether the antibody abciximab can be readministered without significant rise of immunological reactions is unclear.55,56 Preliminary results of a prospective 4500 patient registry undergoing percutaneous coronary intervention, including approximately 500 patients receiving abciximab readministration, showed similar efficacy and incidence of hypersensitivity or anaphylaxis as first-time abciximab recipients and no significant increase in the incidence of severe thrombocytopenia.57 The optimal intensity and duration of unfractionated heparin with GP IIb/IIIa receptor antagonists has not been determined. It is unknown whether low-molecular-weight heparins or other direct thrombin inhibitors would prove safer and more effective than unfractionated heparin in conjunction with GP IIb/IIIa receptor antagonists.

**Oral Administration**

In patients who have survived an episode of unstable angina or MI, increased levels of activation of the clotting system persist for months after the acute event, suggesting that oral administration of GP IIb/IIIa antagonists might be beneficial.58 Numerous oral GP IIb/IIIa antagonists are in clinical trials58 and early reports from several phase 2 studies are appearing,59-61 but important questions regarding the safety of the oral agents remain.62 Such safety concerns were magnified when the Orboflvan in Patients with Unstable Coronary Syndrome (OPUS) trial53 showed minimum benefit of the oral IIb/IIIa antagonists orbiflavan (11%, statistically nonsignificant reduction in the 30-day composite end point) but a hazard for a small increase from 1.5% to 2.3% in early mortality in 1 of the orbiflavan arms, which resulted in the premature termination of the OPUS trial. The optimal duration of oral GP IIb/IIIa receptor blockade63 and the need for adjunctive aspirin or dose monitoring64 remain unknown.

Acknowledgment: We thank Donna Bressan, Deepak Bhatt, MD, and Eric J. Topol, MD, for their assistance with the clinical trials overview summarized in Table 2.

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Science and art belong to the whole world, and the barriers of nationality vanish before them.
—Johann Wolfgang von Goethe (1749-1832)