Platelet Glycoprotein IIb/IIIa Receptor Antagonists in Cardiovascular Disease

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The role of 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.

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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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* |
|---------------------------------|-----------------|-----------------|-----------------|
| Molecular structure             | Abciximab        | Epifibatide      | Tirofiban       |
| Coronary intervention approved  | Yes              | Yes              | No              |
| Acute coronary syndromes approved | Yes†            | Yes              | Yes†            |
| Approved dose‡                  | Bolus 0.25 mg/kg | 135 µg/kg§       | . . .            |
|                                | Infusion 0.125 µg/kg min × 12 h (10 µg/min, maximum) | 0.5 µg/kg × 20 to 24 h | . . . |
|                                | Acute coronary syndromes Bolus 0.25 mg/kg | 180 µg/kg | 0.4 µg/kg per min × 30 min |
|                                | Infusion 10 µg/min × 18 to 24 h before intervention; continue 1 h post PCI | 2.0 µg/kg per min up to 72 h | 0.1 µg/kg per min × 48 to 108 h¶ |

*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. Target aPTT levels for patients with acute coronary syndrome receiving adjunctive unfractionated heparin with GP IIb/IIIa antagonists, according to manufacturers’ instructions, are aPTT 60 to 85 seconds for abciximab, aPTT 50 to 70 seconds for epifibatide, and aPTT approximately 2 times control for tirofiban.
§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.
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 antagonists 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).

Intravenous GP IIb/IIIa Receptor Antagonists in Percutaneous Coronary Intervention
In the Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) study,23 2099 patients undergoing high-risk angioplasty or atherectomy were randomly assigned in a double-blind fashion to either bolus plus infusion of abciximab, bolus alone, or standard therapy for 12 hours. Patients receiving bolus plus infusion had a significant 35% reduction in the composite primary end point of death, nonfatal MI, refractory ischemia, or urgent revascularization within 30 days. Bleeding episodes and transfusions were doubled among patients receiving the bolus plus infusion regimen, although this was attributed to the high doses of heparin administered.24 The benefit of abciximab treatment persisted over 6 months of follow-up, with a significant 23% reduction in ischemic events or need for elective revascularization,25 and recent data showed improved outcome up to 3 years after the procedure.26

The Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade (EPILOG) trial27 was designed to determine whether the benefits of abciximab therapy could extend to all patients undergoing coronary intervention regardless of risk of ischemic complications and to evaluate whether hemorrhagic complications could be reduced by lowering the heparin dose. In the EPILOG trial, patients received abciximab with standard-dose weight-adjusted heparin, abciximab with low-dose weight-adjusted heparin, or standard-dose weight-adjusted heparin alone. This trial was terminated prematurely with only 2792 subjects enrolled (of a planned 4800) because patients treated with abciximab had a 57% reduction in the composite 30-day end point of death, MI, or urgent revascularization, compared with patients receiving standard heparin therapy (11.7% vs 5.2%). Bleeding rates were acceptably low in all 3 arms (major bleeding in 2.0%-3.5%), confirming that the higher bleeding rates noted in the EPIC study (major bleeding in 7%-14%) were related to adjuvant heparin therapy and demonstrating that the benefit of abciximab could be maintained with lower-dose heparin.

The EPIC and EPILOG trials examined the benefits of abciximab given at the time of intervention followed by a 12-hour infusion. The Chimeric 7E3 Antiplaquelet Therapy in Unstable Angina Refractory to Standard Treatment (CAPTURE) trial28 studied prolonged preintervention treatment with abciximab in patients with refractory angina (recurrent ischemia despite heparin and nitrate therapy). Following angiography, patients were randomly assigned

<p>| 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* |
|---------------------------------|--------------|--------------|-------------|--------------|-------------|------------------|</p>
<table>
<thead>
<tr>
<th><strong>Source, y</strong></th>
<th><strong>No. of Study Patients</strong></th>
<th><strong>IIb/IIIa</strong></th>
<th><strong>Comparison</strong></th>
<th><strong>IIb/IIIa Standard Therapy</strong></th>
<th><strong>10.1</strong></th>
<th><strong>Odds Ratio (95% Confidence Interval)</strong></th>
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<tr>
<td><strong>Percutaneous Coronary Intervention</strong></td>
<td></td>
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<tr>
<td>EPIC,23 1994</td>
<td>2099</td>
<td>Abciximab</td>
<td>Standard therapy</td>
<td>7.0‡</td>
<td>10.1</td>
<td>0.67 (0.49-0.93)</td>
</tr>
<tr>
<td>EPILOG,27 1997</td>
<td>2792</td>
<td>Abciximab</td>
<td>Heparin</td>
<td>4.0§</td>
<td>9.1</td>
<td>0.42 (0.30-0.58)</td>
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<td>CAPTURE,26 1997</td>
<td>1265</td>
<td>Abciximab</td>
<td>Standard therapy</td>
<td>4.8</td>
<td>9.0</td>
<td>0.50 (0.30-0.83)</td>
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<tr>
<td>EPISTENT,29 1998</td>
<td>2399</td>
<td>Abciximab</td>
<td>Standard therapy</td>
<td>5.2</td>
<td>10.2</td>
<td>0.49 (0.36-0.67)</td>
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<tr>
<td>IMPACT-II,30 1997</td>
<td>4010</td>
<td>Eptifibatide</td>
<td>Standard therapy</td>
<td>7.1</td>
<td></td>
<td></td>
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<tr>
<td>RESTORE,31 1997</td>
<td>2139</td>
<td>Tirofiban</td>
<td>Standard therapy</td>
<td>5.1</td>
<td>6.3</td>
<td>0.81 (0.56-1.17)</td>
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<td><strong>Acute Coronary Syndromes</strong></td>
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<tr>
<td>PRISM,22 1998</td>
<td>3231</td>
<td>Tirofiban</td>
<td>Heparin and aspirin</td>
<td>5.7</td>
<td>7.0</td>
<td>0.80 (0.61-1.07)</td>
</tr>
<tr>
<td>PRISM-Plus,24 1998</td>
<td>1570†</td>
<td>Tirofiban</td>
<td>Heparin and aspirin</td>
<td>8.7</td>
<td>11.9</td>
<td>0.70 (0.50-0.98)</td>
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<tr>
<td>PARAGON,25 1998</td>
<td>2282</td>
<td>Lamifiban</td>
<td>Heparin and aspirin</td>
<td>11.3#</td>
<td>11.7</td>
<td>0.87 (0.58-1.29)</td>
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<tr>
<td>PURSUIT,26 1998</td>
<td>10,948</td>
<td>Eptifibatide</td>
<td>Heparin and aspirin</td>
<td>14.2</td>
<td>15.7</td>
<td>0.89 (0.79-0.99)</td>
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<tr>
<td><strong>Overall</strong></td>
<td>32,736</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.79 (0.73-0.85)**</td>
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*Adapted with permission from Topol.51
†Outcome measures were determined by TopolP1 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.
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) 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) study 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 Integritin to Manage Platelet Activation to Prevent Coronary Thrombosis (IMPACT-II) study, 4010 patients of all risk strata undergoing angioplasty were randomized to placebo or 1 of 2 doses of the synthetic cyclic heptapeptide eptifibatide (Integritin). 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, 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 study, 24% 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 following by a 12-hour infusion. Compared with the abciximab studies, more modest benefits were observed in the IMPACT-II and RESTORE studies. Perhaps this is due to differences between the agents (abciximab has a longer biological half-life, with a lower dissociation constant than eptifibatide 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 study (10-60 minutes) vs the EPIC study (18-24 hours), underdosing of eptifibatide (preclinical studies of eptifibatide measured platelet aggregation in blood anticoagulated with citrate, which chelates calcium, and underestimated the in vivo platelet inhibitory effect of eptifibatide), 34 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) and Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited to Very Unstable Signs and Symptoms (PRISM-Plus) 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 eptifibatide and tirofiban in patients initially presenting with unstable angina or non–ST-segment elevation MI who then require coronary revascularization. In the PURSUIT and PRISM-Plus studies, treatment reduced 30-day death and MI by 31% to 44%. It is, therefore, unclear whether patients initially treated with eptifibatide 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 EPISODE study (70 U/kg bolus, target activated clotting time of ≥200 seconds) is associated with the most favorable
risk-benefit profile. In the absence of specific data regarding heparinization from the RESTORE study or IMPACT II trials, 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, 2,282 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) study randomized 3,232 patients to either tirofiban or heparin. At 48 hours (the primary end point), the incidence of the composite end point of death, MI, or refractory ischemia 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 readmission for unstable angina) between the 2 groups (17.1% vs 15.9%).

The PRISM-Plus study enrolled 1,915 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 study were at higher risk than those enrolled in the PRISM study. 38 The PRISM-Plus study 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 an apparent high mortality rate in the tirofiban monotherapy arm (4.6% 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 trial 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 2,100 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. 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 thrombolytic therapy stimulates platelet aggregation. 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. However, data from the TIMI 14 trial showed reperfusion rates of only 20% to 40% with abciximab monotherapy.

The IMPACT-AMI trials and Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion (PARADIGM) 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 14 showed that TIMI 3 flow with abciximab plus half-dose [50-mg] accelerated tissue-type plasminogen activator and the Strategies for Penetration Enhancement in the Emergency Department (SPEED) pilot trial, 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

**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 GP IIb/IIIa receptor antagonists for the acute coronary syndromes compared with the percutaneous intervention population. Compared with aspirin and intravenous heparin, the addition of a 48- to 96-hour infusion of a GP IIb/
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{37} 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 Ib/IIa 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 electocardiographic abnormalities or with elevations in serum troponin levels\textsuperscript{46} vs normal troponin levels appeared to derive greater benefit from GP Ib/IIa 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.

**Adjunctive Heparin.** The role of adjunctive heparin for patients with acute coronary syndromes treated with GP Ib/IIa antagonists has not been thoroughly studied: minimal prospective data exists directly comparing GP Ib/IIa 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 Ib/IIa 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 Ib/IIa receptor antagonists, although the optimal level of anticoagulation remains unknown.

**SAFETY**

**Hemorrhagic Complications**

No increase in intracerebral hemorrhage has been observed with the GP Ib/IIa 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 adjunctive 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 EPISODE 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{3}·L\textsuperscript{-1}) occurs infrequently with abciximab and tirofiban; no increase in the incidence of thrombocytopenia was observed in eptifibatide-treated patients compared with those who had received placebo in the PURSUIT and IMPACT-II studies.\textsuperscript{31,35} Treatment with eptifibatide or tirofiban is associated with an absolute increase of approximately 0.2% in the risk of severe (platelet count <50×10\textsuperscript{3}·L\textsuperscript{-1}) 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{26,49} 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{26} 0.43% to 0.65% (EPISODE study),\textsuperscript{27} and 0.0% to 1.0% (EPISTENT study).\textsuperscript{29} Acute profound thrombocytopenia (platelet count <20 × 10\textsuperscript{3}·L\textsuperscript{-1}) has been reported in approximately 0.69% of patients receiving abciximab,\textsuperscript{49} and platelet transfusions maybe 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).31 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 (α,β₃) 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,20 inhibition of thrombin generation,53 or other effects are unknown.33 Whether the antibody abciximab can be readministered without significant rise of immunological reactions is unclear.53,55 Preliminary results of a prospective 4500 patient registry undergoing percutaneous coronary intervention, including approximately 500 patients receiving abciximab administration, showed similar efficacy and incidence of hypersensitivity or anaphylaxis as first-time abciximab recipients and no significant increase in the incidence of severe thrombocytopenia.37 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.54 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 Orbofliban in Patients with Unstable Coronary Syndrome (OPUS) trial53 showed minimum benefit of the oral IIb/IIIa antagonists orbofliban (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 orbofliban arms, which resulted in the premature termination of the OPUS trial. The optimal duration of oral GP IIb/IIIa receptor blockade53 and the need for adjunctive aspirin or dose monitoring64 remain unknown.

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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)