Platelet Glycoprotein IIb/IIIa Receptor Antagonists in Cardiovascular Disease

David A. Vorchheimer, MD
Juan Jose Badimon, PhD
Valentin Fuster, MD, PhD

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/IIa 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/IIa (αIIbβ3) receptor.11,12 Agonists of platelet activation (Figure) facilitate the conformational change necessary for the receptor to become receptive to fibrogen, 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/IIa, probably because of its high plasma concentration.12 Fibrinogen simultaneously binds to GP Iib/IIa receptors on 2 separate platelets,14 resulting in platelet cross-linking critical to platelet aggregation (Figure).

The role of the GP Iib/IIa 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/IIa 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/IIa receptor in the acute coronary syndromes and to summarize completed clinical trials of GP Iib/IIa 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/IIa 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/IIa receptor is the final common pathway of platelet aggregation. Intravenous monoclonal antibody and peptide and nonpeptide antagonists of the GP Iib/IIa 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 re-intervention. 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/IIa 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/IIa 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

<table>
<thead>
<tr>
<th>Molecular structure</th>
<th>Abciximab</th>
<th>Eptifibatide</th>
<th>Tirofiban</th>
</tr>
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<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>
</tbody>
</table>
| Approved dose‡  
Coronary intervention | Bolus 0.25 mg/kg | 135 µg/kg§ | . . . |
| Infusion | 0.125 µg/kg/min × 12 h (10 µg/min, maximum) | 0.5 µg/kg/min × 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. For eptifibatide and tirofiban, platelet counts should be obtained within 6 hours after the bolus and daily thereafter. 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 eptifibatide dosing regimen 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; TXA, thromboxane A; GP, glycoprotein; 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).

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 Antiplatelet Therapy in Unstable Angina Refractory to Standard Treatment (CAPTURE) trial28 studied prolonged pretreatment with abciximab in patients with refractory angina (recurrent ischemia despite heparin and nitrate therapy). Following angiography, patients were randomly assigned...
to receive abciximab or placebo for 18 to 24 hours before 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 (EPISTENT30) 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 eptifibatide (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 EPIC23 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,25 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 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 study31 (10-60 minutes) vs the EPIC study23 (18-24 hours), underdosing of eptifibatide (preclinical studies of eptifibatide measured platelet aggregation in blood anticoagulated with citrate, which chelates calcium, and overestimated the in vivo platelet inhibitory effect of eptifibatide),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 eptifibatide 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 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 EPILOG study27 (70 U/kg bolus, target activated clotting time of ≥200 seconds) is associated with the most favorable
necrosis. Thus, patients in the PRISM-
Significant electrocardiographic changes or
signed to compare 3 study arms testing
PRISM-Plus study 36 was initially de-

The Platelet Receptor Inhibition for
Ischemic Syndrome Management (PRISM) study 38 randomized 3232 pa-
tients 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 re-admission for unstable angina) between the 2 groups (17.1% vs 15.9%).

The PRISM-Plus study 36 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 study 36 were at higher risk than those enrolled in the PRISM study. 30 The PRISM-Plus study 36 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 37 enrolled 10 948 patients within 24 hours of the last epi-

The IMPACT-AMI 43 and Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion (PARADIGM) 44 trials studied GP IIb/ IIIa receptor antagonists in conjunc-

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Clinical Characteristics. Differences in the contribution of thrombus to the pathophysiology of various sub-
groups of patients with acute syndromes, particularly the broad popu-
lations studied in the larger clinical trials, result in more variable effect with

Acute MI. Glycoprotein IIb/IIIa antagonists could be effective in acute MI given the role of platelets in thrombus development and data that thromboly-
sis stimulates platelet aggregation. 30 Early observations from small trials showed that coronary flow increased by at least 1 TIMI (Thrombolysis in Myo-
cardial Infarction) flow grade in 11 of 13 patients with acute MI who were treated with aspirin, heparin, and ab-
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ciximab without adjunctive thrombolytic therapy. 41 However, data from the TIMI 14 trial 32 showed reperfusion rates of only 20% to 40% with abciximab monotherapy.
Illa 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, PRISM-Plus, and these patients may ultimately undergo percutaneous revascularization, and these patients may derive the greatest treatment benefit. Importantly, in the PURSUIT, PRISM-Plus, and CAPTURE 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 vs other electocardiographic abnormalities or with elevations in serum troponin levels vs normal troponin levels appeared to derive greatest benefit from GP IIb/IIIa receptor antagonist treatment.

In the PURSUIT study, epifibatide 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 heparin was routinely administered to the analysis. Conversely, in the PARAGON study, 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, 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 EPILOG and CAPTURE studies. Accordingly, the need for platelet transfusion to treat life-threatening bleeding is extremely rare, particularly for the short-acting agents tirofiban and epifibatide. For patients undergoing percutaneous intervention with abciximab plus low-dose heparin, platelet transfusions were required in 2.1% of patients in the CAPTURE study. Platelet transfusions are more frequently required for patients treated with abciximab undergoing urgent coronary artery bypass graft surgery.

Thrombocytopenia

Thrombocytopenia (platelet count <100×10⁹) 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. Treatment with epifibatide or tirofiban is associated with an absolute increase of approximately 0.2% in the risk of severe (platelet count <50×10⁹/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, the incidence increased from 0.35% to 1.0%. However, excluding the EPIC study (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), 0.43% to 0.65% (EPILOG study), and 0.0% to 1.0% (EPISTENT study). Acute profound thrombocytopenia (platelet count <20×10⁹) has been reported in approximately 0.69% of patients receiving abciximab, and platelet transfusions may be required. 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
Resolved 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 (αvβ3) 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 trials\(^ {58}\) 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) trial\(^{63}\) 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 blockade\(^ {52}\) and the need for adjunctive aspirin or dose monitoring\(^ {64}\) 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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