Glycoprotein IIb/IIIa Integrin Blockade

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The importance of thrombosis in the pathogenesis of acute coronary syndromes is now unequivocally established.\(^1,^2\) These syndromes (unstable angina, non–Q-wave myocardial infarction [MI], acute [ST-elevation] MI, and abrupt closure after coronary intervention) share a common pathophysiology of atherosclerotic plaque rupture, activation of the coagulation cascade, and adhesion, activation, and aggregation of platelets. Numerous investigators have shown that the glycoprotein IIb/IIIa (GP IIb/IIIa) integrin mediates the “final common pathway” in platelet aggregation, spawning the development of GP IIb/IIIa receptor antagonists.\(^3^–^5\) This article reviews the current status of GP IIb/IIIa blockade in the management of coronary artery disease, examining the results of pivotal clinical trials and reviewing current challenges and directions for future investigation.

Platelets and GP IIb/IIIa

In atherosclerotic disease, plaque rupture exposes the subendothelium and initiates hemostasis. Platelets adhere to the subendothelium principally via class I glycoproteins, an effect greatly enhanced by von Willebrand factor under conditions of flow and high shear rates.\(^6^–^7\) Platelet activation follows adhesion and can be initiated by numerous agonists (Figure 1). With activation, the platelet degranulates, releasing serotonin, ADP, and other vasoactive substances into the local environment to further recruit and stimulate platelets. GP IIb/IIIa undergoes a conformational change that results in a ligand-recognizing state that permits fibrinogen binding. Cross-linking of fibrinogen bound to activated platelets culminates in aggregation and thrombus formation. Regardless of the stimulus for platelet activation, the final common pathway to coronary thrombosis is mediated by the GP IIb/IIIa receptor.

The GP IIb/IIIa receptor belongs to the integrin family of cell membrane glycoproteins. Integrins have been isolated from cells throughout the body and are mediators of cell-cell and cell-substrate adhesion and signaling.\(^8\) The GP IIb/IIIa integrin consists of 2 noncovalently linked α (\(α_m\)) and β (\(β_3\)) subunits (Figure 2). The importance of this integrin in platelet aggregation was first noticed in patients with Glanzmann’s thrombasthenia, an inherited disorder characterized by recurrent mucocutaneous bleeding due to either absent or dysfunctional GP IIb/IIIa.\(^10^–^11\) There are 2 binding sites on GP IIb/IIIa, one that recognizes the amino acid sequence Arg-Gly-Asp (arginine-glycine-aspartic acid, or RGD) and another that recognizes Lys-Gln-Ala-Gly-Asp-Val.\(^5\) Fibrinogen is the principal ligand for this receptor; other RGD-containing ligands include fibronectin, vitronectin, and von Willebrand factor. On each circulating platelet, there are 50 000 to 80 000 GP IIb/IIIa complexes; most are distributed on the platelet surface, with a smaller pool held in an internal reserve.\(^4\)

**GP IIb/IIIa Antagonists**

The first GP IIb/IIIa antagonist developed for clinical investigation was the murine monoclonal antibody m7E3. Coller and associates\(^12\) demonstrated that m7E3 prevented platelet aggregation by inhibiting fibrinogen binding. The pharmaceutical abciximab (ReoPro, Centocor and Eli Lilly and Co), a Fab chimera that retains the mouse-derived variable portion of m7E3 joined to the constant region of human IgG Fab, has undergone extensive clinical evaluation and is approved by regulatory agencies worldwide as an adjunct to coronary intervention.\(^13^–^15\)

Many additional compounds targeting GP IIb/IIIa have been described (Table 1). One line of development has focused on the disintegrins, a class of RGD proteins found in snake venoms. Disintegrins interfere with the binding of RGD-containing adhesive proteins to cellular integrins. In particular, the peptide barbourin, containing a KGD (Lys-Gly-Asp) sequence rather than RGD, has unique specificity for GP IIb/IIIa compared with RGD-based peptides.\(^11\) Although the naturally occurring disintegrins proved too immunogenic for human use, their structure provided a template to develop synthetic peptide antagonists.\(^6\) A prototypic example is the KGD cyclic heptapeptide epitifibatide (Integrilin, COR Therapeutics).

Another approach has been to mimic the charge and spatial conformation of the RGD sequence via engineered synthetic and semisynthetic compounds. Examples of parenteral peptidomimetic inhibitors include tirofiban (Aggrastat, Merck Research Laboratories) and lamifiban (Ro 44-9883, F Hoffmann-LaRoche, Ltd). Orally active GP IIb/IIIa peptidomimetic antagonists are also under investigation.\(^16^–^18\)

GP IIb/IIIa antagonists inhibit platelet function by occupying the fibrinogen binding site. Most are administered either orally or intravenously but not both. The “biological” half-life can vary widely. Whereas competitive parenteral agents have a half-life of 2 to 3 hours, abciximab has a half-life of 6 to 12 hours, with low levels of receptor occupancy (13%) detected even 2 weeks after treatment.\(^6,^19\) The half-lives of oral agents...
depend on both metabolism and clearance. Most inhibitors are quite specific for the RGD pocket in GP IIb/IIIa; abciximab also binds to the $\beta_3$-subunit on vitronectin receptors ($\alpha_\text{v}\beta_3$). Agents also differ in binding and dissociation constants, with the pharmacodynamics of abciximab being suggestive of noncompetitive kinetics, whereas the effects of others seem concentration dependent. Finally, oral agents typically require conversion from prodrug to active metabolite to be functional.

**Clinical Trials Overview**

More than 30,000 patients have participated in clinical trials involving GP IIb/IIIa antagonists (Table 2); these trials include considerable experience in acute coronary syndromes. Most of these trials used a 30-day combined incidence of major adverse cardiac events as the primary end point. The next sections highlight principal findings from these trials, focusing on remaining questions and issues.

**Coronary Intervention**

Several reasons dictated that percutaneous revascularization would be the first arena of investigation. The procedure induces obligatory vessel injury, and it seemed logical to evaluate the GP IIb/IIIa hypothesis in this setting. Because roughly 1 million procedures are performed worldwide annually, a large patient population was accessible. Perhaps most important, because plaque rupture induced by coronary intervention is easily timed, the opportunity existed to initiate treatment before vessel injury and potentially prevent subsequent events.

Five large, randomized, placebo-controlled trials of GP IIb/IIIa antagonists define our current knowledge regarding the adjunctive use of these agents during coronary intervention. These include EPIC (Evaluation of 7E3 for the Prevention of Ischemic Complications), EPILOG (Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade), CAPTURE (Chimeric 7E3 AntiPlatelet in Unstable angina REfractory to standard treatment), IMPACT II (Integrin to Minimize Platelet Aggregation and Coronary Thrombosis II) (eptifibatide), and RESTORE (Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis). In each trial, the study drug was initiated before coronary intervention. Table 3 presents the primary end-point results for each trial at 30 days and the results with regard to death or MI and MI alone. Expressed as relative risk reductions, the 30-day treatment effects of active study drug versus placebo were 35% in EPIC, 56% in EPILOG, 29% in CAPTURE, 22% in IMPACT II, and 24% in RESTORE.

What has been learned from the trials of coronary intervention? First, in the short term, GP IIb/IIIa inhibition reduces abrupt vessel closure and coronary thrombosis. Long term, significant reductions in morbidity and mortality are also realized. Second, all patients benefit from treatment. Whereas EPIC, CAPTURE, and RESTORE studied a high-risk population, both EPILOG and IMPACT II used minimally restrictive entry criteria. Subsequent subgroup analyses of EPIC and EPILOG have failed to identify risk groups that did not benefit from treatment.

**TABLE 1.** GP IIb/IIIa Antagonists

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal antibodies</td>
<td>Abciximab (Reopro)</td>
</tr>
<tr>
<td>Cyclic peptides</td>
<td>Eptifibatide (Integrilin)</td>
</tr>
<tr>
<td>Parenteral nonpeptide mimetics</td>
<td>Lamifiban, tirofiban (Aggrastat)</td>
</tr>
<tr>
<td>Oral nonpeptide mimetics</td>
<td>Xemilofiban, orbofiban, roxifiban, sibrafiban, lefradafiban, SB 214857</td>
</tr>
<tr>
<td>Parenteral and oral nonpeptide mimetics</td>
<td>RPR-109891 (Klerial)</td>
</tr>
</tbody>
</table>
Third, the combination of a parenteral GP IIb/IIIa antagonist with standard doses of heparin (achieving a procedural activated clotting time >300 seconds) results in excessive bleeding. Fortunately, the EPILOG trial demonstrated that bleeding can be attenuated to levels comparable to controls by reducing procedural heparin dosing and removing vascular access sheaths within hours after the procedure. This observation emphasizes the need for judicious use of these agents.

The fourth issue remains a vexing problem: identifying the optimal dosing regimen. The relationships and correlation among dosing, receptor occupancy, inhibition of ex vivo platelet aggregation, duration of treatment, and clinical efficacy remain nebulous. This is compounded by a lack of point-of-care testing for platelet inhibition. Given the efficacy of abciximab with a 12-hour infusion, would a 24-hour infusion provide additional advantage? Given the shorter half-lives of eptifibatide and tirofiban, should these agents be infused longer? Even if optimal duration was known, what is the optimal dose, and can excessive inhibition occur? A case in point is eptifibatide. In attempting to understand its reduced efficacy in IMPACT II (relative to abciximab in EPIC and EPILOG), investigators have postulated that eptifibatide was underdosed, leading to only 30% to 50% receptor occupancy. This situation arose because the sensitivity of ex vivo platelet function assays to the concentration of free calcium in the sample aliquot was not understood. Recent pharmacodynamic studies with eptifibatide that used blood anticoagulated in D-Phe-Pro-Arg chloromethyl ketone dihydrochloride (PPACK) instead of citrate, a calcium chelator, have verified the biochemical observation. Whether higher doses of eptifibatide during coronary intervention will result in clinical efficacy remains to be seen.

The fifth issue concerns the potential for immunogenicity. Although anaphylaxis, allergic manifestations, and granulocytopenia appear to be extremely rare, thrombocytopenia has been observed frequently enough to warrant mention. In clinical trials, thrombocytopenia has been observed at a low rate (ranging from 1.1% to 5.6%) with all parenteral GP IIb/IIIa antagonists.

### Table 2: Clinical Trials of Parenteral GP IIb/IIIa Antagonists

<table>
<thead>
<tr>
<th>Trials</th>
<th>Agents</th>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPIC</td>
<td>Abciximab</td>
<td>High-risk of abrupt closure per clinical, anatomic criteria</td>
</tr>
<tr>
<td>EPLOG</td>
<td>Abciximab</td>
<td>Broad entry criteria</td>
</tr>
<tr>
<td>CAPTURE</td>
<td>Abciximab</td>
<td>Refractory unstable angina</td>
</tr>
<tr>
<td>EPISTENT</td>
<td>Abciximab</td>
<td>Stent eligible</td>
</tr>
<tr>
<td>RAPPORT</td>
<td>Abciximab</td>
<td>Direct angioplasty</td>
</tr>
<tr>
<td>IMPACT II</td>
<td>Eptifibatide</td>
<td>Broad entry criteria</td>
</tr>
<tr>
<td>RESTORE</td>
<td>Tirofiban</td>
<td>High-risk of abrupt closure per clinical, anatomic criteria</td>
</tr>
<tr>
<td>Unstable angina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRISM</td>
<td>Tirofiban</td>
<td>CP &lt;24 h</td>
</tr>
<tr>
<td>PRISM-PLUS</td>
<td>Tirofiban</td>
<td>CP &lt;12 h, cardiac catheterization encouraged</td>
</tr>
<tr>
<td>PARAGON</td>
<td>Lamifiban</td>
<td>CP &lt;12 h, ischemic ECG changes</td>
</tr>
<tr>
<td>PURSUIT</td>
<td>Eptifibatide</td>
<td>CP &lt;24 h, ischemic ECG changes</td>
</tr>
</tbody>
</table>

*CP indicates chest pain.

### Table 3: Clinical Trials of GP IIb/IIIa Antagonists in Coronary Intervention: 30-Day Outcomes

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>% All Events*</th>
<th>% Death+MI</th>
<th>% MI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>Drug</td>
<td>Placebo</td>
</tr>
<tr>
<td>EPIC</td>
<td>2099</td>
<td>12.8</td>
<td>8.3</td>
<td>10.3</td>
</tr>
<tr>
<td>CAPTURE</td>
<td>1265</td>
<td>15.9</td>
<td>11.3</td>
<td>9.0</td>
</tr>
<tr>
<td>EPLOG</td>
<td>2792</td>
<td>11.7</td>
<td>5.2</td>
<td>9.1</td>
</tr>
<tr>
<td>IMPACT II</td>
<td>4010</td>
<td>11.6</td>
<td>9.1</td>
<td>8.6</td>
</tr>
<tr>
<td>RESTORE</td>
<td>2141</td>
<td>10.5</td>
<td>8.0</td>
<td>6.4</td>
</tr>
<tr>
<td>Pooled</td>
<td>12,307</td>
<td>12.1</td>
<td>8.1</td>
<td>8.7</td>
</tr>
</tbody>
</table>

*In each trial, P<0.05 (vs placebo).

EPIC, CAPTURE, and EPLOG data (abciximab) reflect intention-to-treat analyses and represent the primary study end point (all events = death, MI, or urgent/emergency repeat intervention or coronary bypass surgery). Data from IMPACT II (eptifibatide) and RESTORE (tirofiban) are derived data, calculated on a treated-patient basis and adjusted to reflect the primary end point used for abciximab trials. Both EPLOG and IMPACT II evaluated 2 treatment strategies against placebo; data for the best treatment comparison are shown. Pooled data are average results for each group weighted for number of patients in each trial.
**TABLE 4. Clinical Trials of GP IIb/IIIa Antagonists in Unstable Angina/NQWMI**

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>% All Events</th>
<th>% Death+MI (30 days)</th>
<th>% Relative Risk Reduction (30 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRISM²¹†</td>
<td>3231</td>
<td>5.9</td>
<td>3.8*</td>
<td>7.1</td>
</tr>
<tr>
<td>PRISM-PLUS²²‡</td>
<td>1815</td>
<td>17.9</td>
<td>12.9*</td>
<td>11.9</td>
</tr>
<tr>
<td>PARAGON²³§</td>
<td>2282</td>
<td>11.7</td>
<td>10.6</td>
<td>11.7</td>
</tr>
<tr>
<td>PURSUIT²⁴∥</td>
<td>10 498</td>
<td>15.7</td>
<td>14.2*</td>
<td>15.7</td>
</tr>
<tr>
<td>Pooled</td>
<td>18 276</td>
<td>13.3</td>
<td>11.4</td>
<td>13.3</td>
</tr>
</tbody>
</table>

“All Events” represents primary end-point comparison in each trial (see text).

*P<0.05 (vs placebo).
†Tirofiban monotherapy: 0.6 μg · kg⁻¹ · min⁻¹ for 30 minutes plus 47.5-hour infusion at 0.15 μg · kg⁻¹ · min⁻¹.
‡Tirofiban (and IV heparin): 0.4 μg · kg⁻¹ · min⁻¹ for 30 minutes plus 47.5-hour infusion at 0.1 μg · kg⁻¹ · min⁻¹.
§Lamifiban: 300-μg bolus plus 72-hour infusion at 1.0 μg/min.
∥Epifibatide: 180-μg/kg bolus plus 72-hour infusion at 2.0 μg · kg⁻¹ · min⁻¹.

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IIb/IIIa antagonists; unfortunately, differentiation from heparin-induced thrombocytopenia has proven difficult, albeit understudied. Furthermore, a distinct group of patients with abciximab-related acute profound thrombocytopenia has been described. The clinical syndrome is a precipitous drop in platelet count to ≤10 9/L within 24 hours of receiving the drug. In EPIC and CAPTURE, acute profound thrombocytopenia developed in 2 (0.3%) of 708 and 2 (0.3%) of 622 patients; in a consecutive series from Duke University, the incidence was 10 (0.79%) of 1446 patients.

Thrombocytopenia responded to platelet transfusion and discontinuation of all antiplatelet and anticoagulant therapy. Complete resolution occurred within 5 to 7 days, and no major clinical sequelae were reported. To monitor for thrombocytopenia, a platelet count should be performed 2 to 4 hours after initiation of abciximab therapy and at 24 hours.

The mechanism for GP IIb/IIIa antagonist–related thrombocytopenia is unclear. Possible explanations include preformed antibodies that bind either GP IIb/IIIa receptor epitopes or ligand-induced binding sites or the induction of antibodies directed against the antagonist or the antagonist-receptor complex. After administration of abciximab, ~6% of patients develop human anti-chimeric antibodies (HACA); their role in the development of thrombocytopenia and implications for abciximab readministration are under study.

Although the effects of GP IIb/IIIa antagonists in reducing the composite incidence of death, MI, and urgent revascularization are known, another debate surrounds the potential for influencing restenosis. In EPIC, abciximab therapy was associated with a 26% reduction in 6-month target-vessel revascularization. It was speculated that this effect was mediated via vitronectin receptor blockade (α,β₃) on endothelial and smooth muscle cells, thus reducing intimal hyperplasia at the site of injury. However, these results have not been duplicated with other trials of abciximab or with competitive agents. In particular, Ellis and coworkers performed baseline and 6-month intracoronary ultrasound studies in 225 patients randomized to treatment with either placebo or a 12- or 24-hour infusion of abciximab after stenting. No differences in 6-month luminal dimensions were observed among the 3 groups.

Finally, regarding the concurrent use of GP IIb/IIIa inhibition and stenting, the EPISTENT trial has provided insight. In this prospective study, 2384 patients were randomized to balloon angioplasty with abciximab, stent implantation alone, or stent implantation with abciximab. Stent patients additionally received ticlopidine therapy. At 30 days, patients who received both stenting and abciximab experienced the greatest reduction in the primary composite end point of death, MI, or urgent revascularization (5.3% in the stent-plus-abciximab group versus 10.8% in the stent-only group [P<0.001] versus 6.9% in the balloon-plus-abciximab group). Although adjunctive use of abciximab during coronary stenting was clinically efficacious, the economic implications of this strategy deserve further attention.

**Acute Coronary Syndromes: Unstable Angina/Non–Q-Wave MI**

A second line of investigation has been the adjunctive use of GP IIb/IIIa blockade in patients who present with unstable angina/non–Q-wave MI (NQWMI). In this setting, GP IIb/IIIa blockade may promote stabilization of the ruptured plaque and passivation of the endothelium into an inert surface incapable of supporting further platelet activity. This might prevent subsequent cardiovascular events, particularly during the treatment period.

Four large, randomized, placebo-controlled trials (PRISM, PRISM-PLUS, PARAGON, and PURSUIT) evaluated parenteral GP IIb/IIIa antagonism in this syndrome. Table 4 summarizes the data for the primary end point and the composite end point of death or MI at 30 days for each trial.
The PRISM study of tirofiban examined the effect of short-term medical stabilization, randomizing 3231 patients to a 48-hour infusion of heparin or tirofiban. At 48 hours, the primary composite end point of death, MI, or refractory ischemia was reduced by tirofiban (3.8% versus 5.9%; \( P=0.014 \)). At 30 days, however, the benefit was lost (12.8% versus 13.9%; \( P=\text{NS} \)). The PRISM-PLUS trial evaluated adjunctive tirofiban as part of an "early invasive" strategy. Originally, the study was designed with 3 arms: tirofiban, heparin, or tirofiban with heparin. The tirofiban monotherapy arm was terminated prematurely owing to excess mortality at 7 days (4.6% versus 1.1% with heparin; \( P=0.012 \)). The 7-day primary composite end point of death, MI, or refractory ischemia favored treatment with the remaining tirofiban approach (12.9% for tirofiban plus heparin versus 17.9% for heparin alone; \( P=0.004 \)).

The PARAGON-A study was a dose-ranging precursor to a larger trial (PARAGON-B) that evaluated lamifiban in unstable angina/NQWMI. PARAGON-A compared 5 strategies by use of factorial design: 2 doses of lamifiban, each with or without heparin, and heparin alone. At 30 days, the primary end point of death or nonfatal MI was similar among treatment groups; no benefit was conferred by lamifiban. When coupled with heparin, high-dose lamifiban increased hemorrhagic events without an efficacy advantage. Interestingly, for the 6-month composite end point, benefit emerged for patients assigned to low-dose lamifiban plus heparin (12.6% versus 17.9% for placebo plus heparin; \( P=0.025 \)).

The largest study in unstable angina/NQWMI was the PURSUIT trial, in which 10,948 patients were randomized to receive eptifibatide or placebo (in addition to standard therapy) for 72 to 96 hours. Eptifibatide treatment significantly reduced the combined incidence of death or MI at 30 days compared with placebo (14.2% versus 15.7%; \( P=0.04 \)). Among 4 enrolling regions worldwide, the greatest treatment effect (and greatest use of percutaneous intervention) was observed among the 4358 North American patients (11.7% versus 15.0%; \( P=0.003 \)). As with other competitive GP IIb/IIIa antagonists, there were no significant increases in rates of major bleeding, stroke, or thrombocytopenia.

What has been learned regarding adjunctive use of GP IIb/IIIa inhibition for unstable angina/NQWMI? Perhaps most important, GP IIb/IIIa antagonism has been confirmed as the first new strategy since aspirin and heparin to improve clinical outcomes in this syndrome. At centers that favor an early invasive strategy, GP IIb/IIIa antagonists during short-term hospitalization may induce a paradigm shift in favor of early conservative management, thus reducing or obviating the need for percutaneous treatment. Overall, the unstable angina/NQWMI trials suggest a modest but tangible reduction (~15%) in death and MI at 30 days. Furthermore, benefit is conferred whether or not percutaneous revascularization is performed after initiation of treatment. Whether this modest benefit is sufficient to drive widespread adoption remains to be seen; use may be tempered by the cost of therapy.

Several other issues deserve comment. Even allowing for the vagaries of statistical chance (perhaps explaining both the increase in mortality with tirofiban in PRISM-PLUS and the decrease in long-term adverse events with lamifiban), mono-therapy of parenteral GP IIb/IIIa antagonists (without heparin) cannot be endorsed. Great uncertainty remains regarding optimal dosing and duration of treatment. Furthermore, a "dose ceiling" may exist (as observed in PARAGON-A) beyond which further dose escalation results in bleeding without improvements in efficacy. The differences in treatment effect among regions of the world (noted in PURSUIT) are counterintuitive; whether confounding factors could augment (or detract from) the overall effect will be ascertained through further analyses. Finally, it would be erroneous to conclude that important treatment differences exist among the GP IIb/IIIa antagonists given our current fund of knowledge; the clinical trials conducted thus far are dissimilar enough to invalidate direct comparisons, and head-to-head comparisons have not been undertaken.

**Acute Coronary Syndromes: Acute MI**

Until recently, overriding concern about the potential for intracranial hemorrhage induced by GP IIb/IIIa inhibition coupled with heparin, aspirin, and thrombolytic therapy has precluded the large-scale investigation of GP IIb/IIIa antagonists in acute MI. Because the accrued clinical experience with GP IIb/IIIa blockade demonstrates rates of intracranial hemorrhage comparable to those observed with thrombolytic therapy (<1%), the investigation of GP IIb/IIIa inhibition in this setting has intensified. Two potential strategies have emerged: combination therapy (with reduced-dose thrombolytics and GP IIb/IIIa blockade) and adjunctive GP IIb/IIIa blockade during direct angioplasty.

The goal of combination therapy is to combat the limitations of conventional thrombolytic therapy. Pioneering work by Gold and colleagues in a canine model of coronary thrombosis demonstrated 3 effects of combination therapy (tissue plasminogen activator [tPA] and m7E3): increased reperfusion, accelerated thrombolysis, and sustained vascular patency. Clinically, several small trials have yielded encouraging results. Ohman and colleagues, in a dose-ranging study of eptifibatide combined with tPA, documented significant improvement in 90-minute TIMI 3 (Thrombolysis In Myocardial Infarction grade 3) flow rates at the highest doses of eptifibatide compared with tPA alone (66% versus 39%; \( P=0.006 \)). In PARADIGM, a dose-exploration study of lamifiban in 353 patients, improved patency kinetics (ascertainable by continuous ECG monitoring) were observed with combination therapy versus thrombolytic therapy alone. Recently, the TIMI 14A investigators reported a 643-patient dose-finding study to determine whether full-dose abciximab combined with reduced-dose thrombolytic therapy improves angiographic outcomes compared with thrombolytic therapy alone. Patients with acute MI were randomized to 1 of 5 strategies: (1) full-dose accelerated tPA (100 mg), (2) full-dose streptokinase (1.5 million U), (3) abciximab with low-dose tPA, (4) abciximab with low-dose streptokinase, or (5) abciximab alone. In total, 15 dose permutations were evaluated. Ninety-minute angiography demonstrated higher coronary artery reperfusion rates with abciximab and low-dose tPA (50 mg) than with accelerated tPA alone (79% TIMI 3 flow rate versus 58% with tPA alone).
Regarding the utility of GP IIb/IIIa inhibition with direct angioplasty, the RAPPORT (ReoPro in Acute myocardial infarction and Primary PTCA Organization and Randomized Trial) investigators studied 483 patients who were randomized to receive either placebo or abciximab followed by emergency cardiac catheterization with the intent to perform angioplasty. By intention-to-treat analysis, the 30-day combined incidence of death, MI, or ischemia-driven target-vessel revascularization was not significantly different between groups (5.8% with abciximab versus 9.9% with placebo; \( P = \text{NS} \)). However, by treated-patient analysis (patients receiving both abciximab and direct angioplasty), there was a 74\% relative reduction in the composite end point (2.8\% versus 10.6\%; \( P = 0.006 \)). These results were offset by a near doubling of major bleeding (16.6\% in abciximab-treated patients versus 9.5\% in controls).

In the setting of acute MI, several preliminary conclusions are appropriate. First, combination therapy appears promising and warrants definitive investigation. Second, adjunctive therapy during direct angioplasty yields a similar treatment effect as that observed in elective angioplasty. As with elective intervention, fastidious attention to heparin dosing and sheath management is required to further improve the safety profile.

**Oral GP IIb/IIIa Antagonists**

Oral GP IIb/IIIa antagonists are being investigated for secondary prevention of cardiovascular morbidity and mortality (Table 1). Through long-term suppression of platelet aggregation, outcomes might be improved by inhibiting spontaneous vascular thrombosis and reducing thromboembolic events. Early experience with these drugs raised concerns regarding the potential for bleeding with long-term therapy. In the TIMI-12 safety study of 223 patients treated with sibrafiban or aspirin, major bleeding did not differ among treatment groups (1.5\% with sibrafiban versus 1.9\% with aspirin); however, minor bleeding occurred in 32\% of patients treated with sibrafiban. Important predictors of minor bleeding included total daily dose, twice-daily dosing schedule, and diminished renal function. Whether therapeutic goals can be realized with oral antagonists and whether side effects will prove limiting remain to be seen.

**Conclusions**

The journey leading to the clinical introduction of GP IIb/IIIa antagonists is a remarkable example of successful collaboration among basic scientists, clinical investigators, the pharmaceutical industry, and regulatory agencies. Clinical trial results have documented clear-cut efficacy with a favorable safety profile in a variety of settings. Issues precluding universal adoption include the requirement for prophylactic therapy (requiring treatment of many to benefit a few), the potential for bleeding and other adverse effects (not negligible), and costs. The greatest clinical benefits have been observed with short-term outcomes; what is required to achieve long-term gain is still unknown. Perhaps the most fundamental issue remains optimal dosing. Development of point-of-care testing for measuring platelet aggregation will allow us to address this question. Although much has already been discovered, resulting in significant improvements in patient outcomes, many questions remain to be answered on this unique path of discovery.

**References**


Key Words: glycoproteins ■ platelet aggregation inhibitors ■ coronary disease ■ trials