Platelet Glycoprotein IIb/IIIa Inhibitors
Recognition of a Two-Edged Sword?

Martin J. Quinn, MD, PhD; Edward F. Plow, PhD; Eric J. Topol, MD

 Glycoprotein (GP) IIb/IIIa antagonists are potent inhibitors of platelet aggregation that provide marked protection from ischemic events in patients undergoing percutaneous coronary intervention (PCI).1,2 Abciximab, the prototypic GP IIb/IIIa inhibitor, has been studied in >8000 patients undergoing elective or high-risk PCI.2,3,4 In these patients, it produces a consistent 35% to 56% reduction in ischemic end points at 30 days, with a significant 22% reduction in the risk of death, as shown in a combined analysis of long-term (3-year minimum) follow-up of the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC), Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade (EPILOG), and Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trials.5 Similar results, albeit of a smaller magnitude, have been seen with the small-molecule antagonists tirofiban and eptifibatide, with a 16% to 35% reduction in ischemic events in patients undergoing PCI.1,6 Attempts to expand the therapeutic indication of GP IIb/IIIa antagonists to other conditions associated with platelet-mediated thrombosis, however, have been less fruitful than expected. Instead of reducing major ischemic events, long-term oral GP IIb/IIIa inhibitor therapy7 has uniformly increased the fatality rate. Furthermore, the overall efficacy of a number of the intravenous antagonists in non–ST-segment elevation acute coronary syndromes (ACS), or in combination with thrombolysis in ST-segment elevation myocardial infarction (MI), has been less than anticipated.8 Of particular concern is the fact that there has been a paradoxical increase in adverse events in 2 of the trials of intravenous therapy in ACS.9,10 Platelets are known to play an important role in the pathogenesis of ACS, yet the high levels of platelet inhibition attainable with GP IIb/IIIa antagonists have failed to dramatically improve clinical outcomes outside of PCI. In this article, we discuss these issues and lend support to the perception that these agents represent a double-edged sword: potent efficacy in the right indication and at the right level of platelet inhibition, but with the capability of potentiating serious adverse events, including death, in other situations.

Trials of Oral GP IIb/IIIa Blockade in ACS
The advent of orally active GP IIb/IIIa antagonists provided the potential to extend the benefit of short-term, intravenous GP IIb/IIIa inhibition to long-term therapy in the secondary prevention of cardiovascular disease. The initial promise of phase II studies led to a number of larger phase III randomized trials in a broad spectrum of patients with vascular disease. The Evaluation of oral Xemilofiban in Controlling Thrombotic Events (EXCITE)11 (n=7232) trial focused on patients undergoing PCI, whereas the Orbofiban in Patients with Unstable coronary Syndromes–Thrombosis In Myocardial Infarction (OPUS-TIMI 16)12 (n=10 288), Sibrafiban versus aspirin to Yield Maximum Protection from Ischemic Heart events Post acute coronary syndromes (SYMPHONY)13 (n=9233), and 2nd SYMPHONY14 (n=6671) trials recruited patients with ACS. In the Blockade of the glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion (BRAVO)15 (n=9197) trial, a broad spectrum of patients with coronary, cerebral, or peripheral arterial diseases were studied. Overall, the results have been quite disappointing. Long-term oral GP IIb/IIIa inhibition has uniformly failed to provide protection from ischemic events and was associated with a paradoxical increase in adverse events. Mortality increased in each of the five trials (EXCITE, OPUS-TIMI 16, BRAVO, SYMPHONY, 2nd SYMPHONY). A combined analysis reveals a highly significant 35% relative (or 0.7% absolute) increase in the risk of death in the 45 523 patients studied16 (Figure 1), with a 2-fold increase in the risk of bleeding.

Trials of Intravenous GP IIb/IIIa Inhibition in ACS
Six large, randomized trials have examined intravenous GP IIb/IIIa blockade in ACS. The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM)17 (n=3232) trial compared 48-hour infusions of tirofiban and heparin, whereas the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable signs and Symptoms (PRISM-PLUS) study9 (n=1915) compared either tirofiban or heparin with the combination of both. The Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network A (PARAGON A)18 (n=2282) dose-finding study and the larger Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network B (PARAGON B)19 (n=5225) trials compared various doses of lamifiban to...
The Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries-IV (GUSTO IV)10 (n=7800) trial was the first to study abciximab in the medical management of patients with ACS. In the trial, patients were randomized to placebo or an abciximab bolus (0.25 mg/kg) and 24- or 48-hour infusion (0.125 g/kg per minute to a maximum of 10 g/min).

Overall, the outcomes of these trials have been modestly positive. However, the magnitude of benefit has varied and, for the most part, fallen short of expectations (Table). A combined analysis reveals an 8.5% relative reduction in 30-day death/MI from 11.5% to 10.7% (P=0.005).21 This seems modest when compared with the 38% relative reduction (absolute 4% to 6% reduction) in ischemic events seen after PCI. The disparity between the efficacy of these agents at the times of PCI and ACS was particularly evident with abciximab. Multiple trials have confirmed the efficacy of abciximab at the time of PCI; indeed, one comparative trial indicated its superiority compared with a small-molecule agent in this setting.22 In contrast, in GUSTO IV, abciximab failed to reduce the primary end point of 30-day death or MI. There was a stepwise increase in events from 8.0% in the placebo to 8.2% in the 24-hour- and 9.1% in the 48-hour–treated groups (P=0.19).10 This represents a 14% increase in the death or MI primary end point for the long-infusion abciximab strategy. Although not statistically significant, it is of great concern, given an expected a priori 8% to 10% reduction in events on the basis of the results of the antecedent 5 trials. Furthermore, mortality in the first 48 hours was increased from 0.3% in the placebo to 0.7% in the 24-hour and 0.9% in the 48-hour abciximab infusion groups (OR 2.9; 95% CI 1.28 to 6.44; P=0.007 for the comparison of the 48-hour infusion and placebo; Figure 2). It is worth noting that the infusion of the study drug was given for 48 hours in a blinded fashion, such that this excess in death occurred while the patients were on abciximab. A similar increase in mortality had been found in the tirofiban-only arm of PRISM-PLUS9; however, this was based on a small population of patients (n=345) not receiving heparin and was not repeated in the larger PRISM study. In GUSTO IV, the adverse trend was observed in a considerably larger population (n=2590 for the 24-hour and n=2612 for the 48-hour infusion group) of patients receiving heparin during the abciximab infusion and cannot be dismissed as purely the play of chance.

### Thirty-Day Outcomes

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Control %</th>
<th>Placbo %</th>
<th>P</th>
<th>Control %</th>
<th>Placbo %</th>
<th>P</th>
<th>Control %</th>
<th>Placbo %</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>EXCITE</td>
<td>7,232</td>
<td>1.9%</td>
<td>1.5%</td>
<td>0.064</td>
<td>3.7%</td>
<td>4.8%</td>
<td>0.011</td>
<td>1.4%</td>
<td>1.0%</td>
<td>0.24</td>
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<td>OPUS</td>
<td>10,280</td>
<td>1.9%</td>
<td>2.0%</td>
<td>0.430</td>
<td>1.9%</td>
<td>2.1%</td>
<td>0.336</td>
<td>2.0%</td>
<td>2.7%</td>
<td>0.028</td>
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<tr>
<td>SYMPHONY</td>
<td>9,169</td>
<td>1.9%</td>
<td>2.0%</td>
<td>0.470</td>
<td>1.9%</td>
<td>2.1%</td>
<td>0.336</td>
<td>2.0%</td>
<td>2.7%</td>
<td>0.028</td>
</tr>
<tr>
<td>SYMPHONY II</td>
<td>6,637</td>
<td>1.9%</td>
<td>2.0%</td>
<td>0.470</td>
<td>1.9%</td>
<td>2.1%</td>
<td>0.336</td>
<td>2.0%</td>
<td>2.7%</td>
<td>0.028</td>
</tr>
<tr>
<td>BRAVO</td>
<td>9,197</td>
<td>1.9%</td>
<td>2.0%</td>
<td>0.470</td>
<td>1.9%</td>
<td>2.1%</td>
<td>0.336</td>
<td>2.0%</td>
<td>2.7%</td>
<td>0.028</td>
</tr>
<tr>
<td>Pooled</td>
<td>45,523</td>
<td>2.1%</td>
<td>2.8%</td>
<td>&lt;0.001</td>
<td>2.1%</td>
<td>2.8%</td>
<td>&lt;0.001</td>
<td>2.1%</td>
<td>2.8%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

P indicates placebo; T, treatment.

*Treatment arm includes all patients who received lamifiban and heparin.

†Treatment arm refers to patient in 48-hour abciximab group.
Mechanisms
These findings have generated considerable surprise and confusion. Platelets are known to play an important role in the pathogenesis of ACS, and the less-potent platelet inhibitors aspirin and clopidogrel are protective in this setting. Why do GP IIb/IIIa receptor antagonists, inhibitors of the so-called final common pathway of platelet aggregation, fail to provide consistent protection outside of PCI?

First, to consider these issues, it is important to review the underlying hypothesis on which the benefit of GP IIb/IIIa inhibition is based. GP IIb/IIIa antagonists are potent platelet inhibitors, and thus their efficacy is greatest in conditions associated with acute platelet-mediated thrombosis. Consequently, major benefits are seen at the time of the iatrogenic arterial injury related to PCI. Conversely, in ACS, the role of platelet-mediated thrombosis probably varies according to the acuity and pathogenesis of the syndrome. For example, in patients with diabetes, there has been a consistent and important reduction of mortality rate across the 6 trials of GP IIb/IIIa–blockers in ACS. Similarly, the high-risk group of patients positive for troponin derived particular benefit in 2 small-molecule inhibitor trials. These 2 patient subgroups are at heightened risk and likely have a greater extent of platelet activation, which has been substantiated in patients with diabetes and in the pathophysiological state of microvascular obstruction reflected by elevated troponin. The peculiar and unique results of the patients with abnormal troponin in GUSTO IV, in whom there was a paradoxical trend of worsened death or nonfatal MI with GP IIb/IIIa blockade, lends further support to potential toxicity. It is most unlikely that these findings can be attributed to the different populations enrolled in the trials. Although first signaled with the premature cessation of one arm of the PRISM-PLUS trial due to excess mortality, the oral IIb/IIIa inhibitor programs and the GUSTO IV abciximab findings, in aggregate, demonstrate the untoward potential of these agents. Recent data now provide biological explanations for the unanticipated clinical findings, and 3 related factors, discussed below, may be central to their understanding: antagonist-induced platelet activation, the level of platelet inhibition, and inflammation. In the appropriate clinical setting, particularly with prolonged exposure or in the absence of revascularization, any of these 3 factors, or a combination of them, has the potential to cause a paradoxical increase in ischemic events when combined with GP IIb/IIIa receptor antagonist therapy.

Level of Platelet Inhibition: Platelet “Escape”
The clinical efficacy of GP IIb/IIIa antagonists is closely related to the level of platelet inhibition. At the time of PCI, >80% inhibition is required for maximum efficacy. Failure to achieve these high levels of inhibition is associated with lack of protection from acute events, mainly periprocedural MI. In fact, it is likely that the level of platelet inhibition, rather than pharmacological differences between the compounds, is the major factor in the observed differences in efficacy between the agents at the time of PCI. This was clearly seen in TARGET (do Tirofiban And ReoPro Give similar Efficacy Trial?), in which abciximab was superior to tirofiban in the prevention of early ischemic events after coronary stenting.

Recent data suggest that the tirofiban dose used in this trial fails to achieve >80% platelet inhibition in the early stages of the infusion. Similar conclusions can be drawn from the AU-Assessing Ultegra (GOLD) study, which related the degree of inhibition after an abciximab bolus and 12-hour infusion to ischemic outcome in patients undergoing PCI. Platelet inhibition below 95% at 10 minutes, 80% at 1 hour, or 70% at 8 hours was associated with a marked increase in ischemic event rates; as many as 1 in 4 patients suffered an event with the lowest levels of inhibition. The relationship of platelet inhibition to protection from long-term events after PCI is less clear. In the combined analysis of the abciximab/PCI trials, EPIC/EPILOG, and EPISTENT, the long-term mortality benefit of abciximab seemed largely independent of its protection from early postprocedural events and was even suggested in the abciximab bolus–only arm of the EPIC trial. Similarly, the superior efficacy of abciximab in the prevention of periprocedural events in TARGET did not translate into a longer-term benefit at the 6-month or 1-year follow-up. The explanation for this dissociation between early and late benefits after PCI is unknown. However, an overall relationship between lower periprocedural MI and lower overall mortality rate during extended follow-up, as well as the converse of higher periprocedural MI with increased mortality, has been demonstrated in multiple trials.

The target level of platelet inhibition with GP IIb/IIIa use outside of PCI varies according to the strategy being tested. With long-term oral therapy, lower levels of platelet inhibition were targeted because unacceptable levels of minor (up to 70%) and major bleeding (11.8%) were seen with sustained high-grade inhibition. The trials of intravenous antagonists in ACS targeted higher levels of platelet inhibition; however, in a number of the trials, the dosing regimen differed from those tested in PCI and may not have provided sustained high levels of platelet inhibition. For example, in the PRISM-PLUS trial, a 0.1-µg/kg per minute infusion was used in combination with heparin, whereas in the tirofiban-PCI trials, TARGET and RESTORE, a 0.15-µg/kg per minute infusion of tirofiban was used. The lower dose is associated with significantly less inhibition of fibrinogen binding than the higher dose. Similarly, in the GUSTO IV trial, the abciximab bolus and 12-hour infusion was extended to 24 and 48 hours. Recent data indicate that the extended abciximab infusion may fail to provide sustained high levels of platelet inhibition and that considerable subthreshold inhibition is seen at 12 and 24 hours with a 36-hour infusion schedule (Figure 3). Moreover, the level of inhibition is dependent on the stimulus used: Minimal levels of platelet inhibition are seen with potent agonists, such as thrombin, at 12 and 24 hours into a 36-hour infusion. It is important to note that the loss of threshold-level platelet inhibition (or platelet escape) with a 36-hour abciximab infusion is extensive and lasts for up to 24 hours. In contrast, with the small-molecule intravenous antagonists, any loss of platelet inhibition is short-lived and platelet inhibition is usually maximal for the majority of the infusion. This is the critical difference between the trials that have demonstrated beneficial or neutral effects and those in which there was harm. It is not only the loss of platelet inhibition but also prolonged exposure to low, subthreshold
levels of platelet inhibition, as occurred in GUSTO IV and with long-term oral therapy, that has the potential to lead to a paradoxical increase in events. Moderate levels of platelet inhibition not only lack efficacy but, when prolonged, are associated with a paradoxical increase in ischemic events due to the unmasking of antagonist-induced prothrombic and proinflammatory effects.

**GP IIb/IIIa Antagonist-Induced Activation**

Fibrinogen binding to GP IIb/IIIa not only enables platelet-platelet binding but also transmits an array of signals into the platelet (so-called outside-in signaling) that are important for normal platelet function. Evidence is accumulating that GP IIb/IIIa receptor antagonists also induce these signals, leading to fibrinogen binding, calcium transients, thromboxane A2 production, and increased expression of markers of platelet activation. The generated signals are weak and dependent on the level of platelet inhibition, often requiring the presence of a costimulant. As a result, evidence of partial agonist activity is often difficult to detect, and conflicting results have been reported. For example, the initial description of abciximab- and fradafiban-induced fibrinogen binding and platelet aggregation may have resulted from artifactual thrombin generation. However, although conclusive evidence of in vitro GP IIb/IIIa–induced platelet activation is still lacking, ex vivo evidence of paradoxical platelet activation was found in the OPUS-TIMI 16 trial. Patients treated with orbofiban showed an increase in expression of the platelet activation–dependent markers CD63 and P-selectin, supporting the role of this phenomenon in the paradoxical increase in adverse events.

Antagonist-induced cardiomyocyte apoptosis has also been demonstrated secondary to the activation of procaspase-3. However, the role of this phenomenon in the unexpected findings to date is unclear; abciximab fails to induce apoptosis in vitro because of its inability to cross the cell membrane.

**Platelets and Inflammation: Interrelationship of CD40L and Revascularization**

Platelets are not merely sticky participants in thrombus formation; activated platelets are a rich source of chemokines, cytokines, and growth factors, and they serve as a reservoir for proinflammatory activity. Many of these mediators are stored in platelet cytoplasmic granules and are released rapidly after platelet activation. Others, such as the inflammatory cytokine IL-1β, may be synthesized de novo from platelet mRNA, providing a more sustained inflammatory stimulus. In fact, recent evidence suggests that platelets are capable of synthesizing an array of proteins on stimulation, many of which influence the inflammatory process. One of the most important platelet mediators is the CD40 ligand (CD40L); most of the body’s CD40L is derived from platelets. Furthermore, the CD40 receptor has also recently been found on platelets but is principally expressed on monocytes, macrophages, and endothelial cells. When bound by CD40L, an inflammatory response is unleashed by the expression of adhesion molecules, synthesis of interleukins, and chemokines. CD40L also binds to GP IIb/IIIa, and thrombin stability is markedly reduced in CD40L-knockout mice, indicating an important link between the inflammatory and thrombotic cascades.

In addition to acting as inflammatory mediators themselves, platelets also influence the inflammatory activity of white blood cells through the formation of platelet-leukocyte aggregates. These cell-cell aggregates can induce increases in tissue factor expression and leukocyte adhesion to the vessel wall, both key events in the inflammatory response.

The effect of GP IIb/IIIa antagonists on the inflammatory activity of platelets is mainly inhibitory: They reduce IL-1β formation, suppress leukocyte-platelet aggregates, and inhibit thrombin formation. However, their effect on platelet-leukocyte aggregates and sCD40L release is dependent on the level of platelet inhibition. At high levels of GP IIb/IIIa receptor occupancy, their action is inhibitory. In contrast, at low levels of receptor inhibition, the antagonists can enhance inflammation through the induction of platelet P-selectin expression, which is a mediator of platelet-leukocyte aggregates and increases in serum levels of CD40L. Thus, platelet shedding of CD40L at subthreshold IIb/IIIa blockade is a critical link to exacerbation of inflammation. Subthreshold levels of GP IIb/IIIa antagonists are not only nonprotective and prothrombotic, but they also promote inflammation. Inflammation is known to play an important role in the pathogenesis and progression of ACS, and markers of inflammation are predictive of outcome. Indeed, the adverse trend in GUSTO IV was particularly evident in patients with elevation of the inflammatory marker C-reactive protein (CRP). The 21.9% of patients with elevated baseline CRP (>10 mg/L) enrolled in GUSTO IV, there was a significant (35%) increase in mortality at 1-year follow-up, from 12.1% to 16.3% (P=0.04). The exclusion of early revascularization in GUSTO IV may have further compounded these effects. The interaction of coronary revascularization and inflammation in acute heart disease has recently been characterized. A principal effect of revascularization is restoration of coronary blood flow, which, by reducing shear stress, is an important path to lessened platelet activation. Additionally, the direct injury to the inflamed arterial segment may promote fibrosis or a “plaque-sealing” effect. In 2 studies, patients with heightened inflammatory markers and ACS derived particular benefit from coronary revascularization. This interaction and salutary revascularization effect likely explain the final paradox of the benefit of a 24-hour abciximab infusion in the CAPTURE trial. All patients in this
trial underwent PCI; this factor probably counter-balanced any potentially adverse proinflammatory effects from the extended abciximab infusion. Thus, clinical expression of paradoxical GP IIb/IIIa antagonist adverse effects requires either long-term exposure to low levels of platelet inhibition, as evidenced by the trials of oral blockade, or shorter-term (but >12 hours) exposure in the absence of revascularization, as seen in GUSTO IV (Figure 4).

**Therapeutic Implications**

In light of these findings, how should intravenous GP IIb/IIIa antagonists be used in ACS? The recently updated joint American Heart Association (AHA)/American College of Cardiology (ACC) guidelines for non–ST segment elevation ACS recommend the use of an intravenous GP IIb/IIIa antagonist as a class IA indication in patients treated with heparin and aspirin, in whom catheterization and PCI is planned. In the absence of PCI, tirofiban or eptifibatide are recommended as class IIA therapies in patients with continuing ischemia, positive troponin, or high-risk features. Clearly, the efficacy of intravenous GP IIb/IIIa inhibitors is greatest in these patients with ACS undergoing PCI, particularly in patients with diabetes or an abnormal troponin. The Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive Conservative Strategy (TACTICS) trial has confirmed the superiority of an early invasive strategy in patients treated with tirofiban, particularly those with elevated troponin I or T. Unless (or until) new data become available, abciximab may be considered the preferred agent for PCI with compelling results in trials, including a direct comparison with tirofiban. However, virtually all of the clinically relevant data are derived from trials in which abciximab was initiated in the catheterization laboratory. Tirofiban or eptifibatide should be considered as the agents of choice in the medical stabilization of patients with ACS, particularly those with elevated troponin or diabetes mellitus.

**Conclusion**

Inhibition of platelet aggregation has resulted in one of the most important therapeutic advances in the history of cardiovascular medicine. Aspirin and thienopyridines have a consistent effect across various doses and several clinical indications, without evidence of a prothrombotic or proinflammatory tendency. In contrast, the IIb/IIIa blockers and long infusions of abciximab have increased mortality in patients with ACS. This unexpected, untoward effect is likely related to the proinflammatory trigger of subthreshold IIb/IIIa receptor blockade, particularly in the setting of high arterial shear stress (ie, in the absence of PCI). This two-edged sword seems to be a function of the extent of IIb/IIIa receptor blockade and the clinical application.

Although not anticipated at the outset of clinical development of the IIb/IIIa class of agents, the extensive trial work has been highly instructive. In the right clinical indications with optimal dosing, intravenous IIb/IIIa inhibitors will continue to play an important role in patients with ischemic heart disease.

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**Key Words:** thrombosis ■ platelets ■ glycoproteins