Glycoprotein IIb/IIIa Inhibitors: A Review

Glycoprotein IIb/IIIa inhibitors are powerful agents that have been added to the armamentarium of drugs used to treat coronary artery disease. This article looks at the major trials that examine the role of GP IIb/IIIa inhibitors.

Coronary artery disease (CAD) results from arterial thrombosis after atherosclerotic plaque rupture.1,2 Since platelets play a pivotal role in the pathophysiology of this disease process, platelet inhibition is a logical therapeutic target. The recent development of a new class of drugs that allows direct inhibition of platelet glycoprotein (GP) IIb/IIIa receptors has raised the possibility that these potent agents may reduce thrombotic complications after percutaneous coronary interventions in non-ST-segment elevation acute coronary syndromes and in ST-segment elevation myocardial infarction (MI).3 Three intravenous GP IIb/IIIa antagonists have been widely investigated: abciximab, eptifibatide and tirofiban (Table 1). The objective of this article is to summarize some of the major trials that have been conducted and to review the role and clinical use of GP IIb/IIIa inhibitors in these clinical settings.
Case

Jack, a 58-year-old male, presented to the emergency room at the community hospital with retrosternal chest pain. He had no family history of hypertension or diabetes. ECG results showed a 5 mm ST-segment elevation in the anterior leads, with reciprocal changes inferiorly. He was then given tissue plasminogen activator (t-PA), as well as other adjunctive therapy (i.e., acetylsalicylic acid, beta blockers, intravenous nitroglycerin). Ninety minutes after the t-PA administration, his retrosternal chest pain persisted.

At this stage, what are suitable options for his medical therapy?

Discussion on page 45
The effectiveness of GP IIb/IIIa inhibition was studied in the setting of percutaneous coronary interventions (PCIs) in the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) trial, which included 2,099 high-risk patients for ischemic complications (Table 2). The administration of an intravenous bolus and 12-hour infusion of abciximab resulted in a 35% reduction in death, MI or recurrent ischemia in the first 30 days. This benefit was more pronounced in patients with unstable angina and in those undergoing PCI for MI. The major limitation of the EPIC trial, however, was the existence of a substantially increased risk of bleeding. This was subsequently attributed to high doses of heparin.

The Evaluation in Percutaneous Transluminal Coronary Angioplasty to Improve Long-term Outcome with Abciximab GP IIb/IIIa Blockade (EPILOG) trial extended the application of abciximab to 2,792 patients undergoing coronary PCI, using the same abciximab regimen as the EPIC trial, but with a lower heparin dose. There was a significant reduction in death, MI, or urgent revascularization at 30 days, which persisted through one year of follow-up. In addition, EPILOG showed the increased bleeding rates seen with abciximab (in EPIC) could be decreased when a lower dose of heparin was used.

The c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial examined the effect of abciximab prior to PCI, starting 18 to 24 hours before procedure and continuing for one hour after the intervention among 1,265 patients with unstable angina requiring coronary angio-

### Table 1

**Glycoprotein IIb/IIIa Antagonists**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Abciximab</th>
<th>Eptifibatide</th>
<th>Tirofiban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>antibody fab fragment</td>
<td>cyclic heptapeptide</td>
<td>non-peptide</td>
</tr>
<tr>
<td>Platelet-bound half-life</td>
<td>hours</td>
<td>seconds</td>
<td>2.5 hours</td>
</tr>
<tr>
<td>Plasma half-life</td>
<td>10 to 30 minutes</td>
<td>250 to 2500</td>
<td>&gt; 250</td>
</tr>
<tr>
<td>Drug-to-receptor ratio</td>
<td>1.5 to 2.0</td>
<td>&lt; 2% to 5%</td>
<td>&lt; 2% to 5%</td>
</tr>
<tr>
<td>% of dose in bolus</td>
<td>≈ 75%</td>
<td>≈ 75%</td>
<td>≈ 75%</td>
</tr>
<tr>
<td>Dosage adjustment in renal insufficiency</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Reversibility*</td>
<td>12 hours</td>
<td>4 to 6 hours</td>
<td>&gt; 4 hours</td>
</tr>
<tr>
<td>Reversibility with platelets</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*50% return of platelet function without platelet transfusion
The abciximab treatment resulted in a 29% reduction in death, MI, or urgent revascularization in the first 20 days. By six months, however, the event rates in the two groups were the same. This finding was somewhat disappointing, when compared with the sustained benefit at six months that was achieved in the EPIC trial.

The Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial extended the validity of GP IIb/IIIa inhibition into the stent era.7,8 There were 2,399 patients randomized to receive either stenting with placebo, stenting with abciximab, or balloon angioplasty with abciximab.9 The primary end point at 30 days confirmed the efficacy of abciximab with a 51% decrease in the relative risk of death, MI or urgent revascularization. This benefit was maintained throughout the six-month follow-up period. Furthermore, the rate of repeat intervention on target vessels following stent implantation in diabetics was significantly reduced (by 51%) with treatment with abciximab. Moreover, after one year, the combination of stenting and abciximab resulted in a significant reduction (60%) in mortality, compared with either therapy administered alone. Therefore, even with intracoronary stenting and improving interventional techniques, the use of GP IIb/IIIa inhibitors appears to be beneficial.10

Eptifibatide was evaluated in PCI, both in the Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis — II (IMPACT II) trial and the Enhanced Suppression of the Platelet Receptor with Integrilin Therapy (ESPRIT) trial. In the IMPACT II trial, 4,010 patients were randomized to receive either eptifibatide or placebo. The primary end point at 30 days confirmed the efficacy of eptifibatide with a 51% decrease in the relative risk of death, MI or urgent revascularization. This benefit was maintained throughout the six-month follow-up period. Furthermore, the rate of repeat intervention on target vessels following stent implantation in diabetics was significantly reduced (by 51%) with treatment with eptifibatide. Moreover, after one year, the combination of stenting and eptifibatide resulted in a significant reduction (60%) in mortality, compared with either therapy administered alone. Therefore, even with intracoronary stenting and improving interventional techniques, the use of GP IIb/IIIa inhibitors appears to be beneficial.10

Table 2

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Trial Name</th>
<th># of Patients</th>
<th>Agent Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPIC</td>
<td>Evaluation of 7E3 for the Prevention of Ischemic Complications</td>
<td>2,099</td>
<td>Abciximab</td>
</tr>
<tr>
<td>EPILOG</td>
<td>Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade Trial</td>
<td>2,792</td>
<td>Abciximab</td>
</tr>
<tr>
<td>CAPTURE</td>
<td>c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina</td>
<td>1,265</td>
<td>Abciximab</td>
</tr>
<tr>
<td>EPISTENT</td>
<td>Evaluation of Platelet IIb/IIIa Inhibitor for Stenting</td>
<td>2,399</td>
<td>Abciximab</td>
</tr>
<tr>
<td>IMPACT II</td>
<td>Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis — II</td>
<td>4,010</td>
<td>Eptifibatide</td>
</tr>
<tr>
<td>ESPRIT</td>
<td>Enhanced Suppression of the Platelet Receptor with Integrilin Therapy</td>
<td>2,064</td>
<td>Eptifibatide</td>
</tr>
<tr>
<td>TARGET</td>
<td>Tirofiban and Reopro Give Similar Efficacy</td>
<td>4,812</td>
<td>Tirofiban versus abciximab</td>
</tr>
</tbody>
</table>
(ESPRIT) trial.\textsuperscript{11-13} In the IMPACT II trial, 4,010 patients were randomized to receive either a bolus and 24-hour low-dose infusion (0.5 g/kg/min) of eptifibatide, or a bolus and high-dose infusion (0.75 g/kg/min) of eptifibatide, or placebo. Although no significant reduction in death, MI, or urgent revascularization occurred after 30 days with the use of eptifibatide, there was a 10.5% reduction in ischemic events when data from the two eptifibatide groups were combined.

In contrast, the ESPRIT trial enrolled 2,064 patients undergoing routine stent implantation.\textsuperscript{12} The patients were randomized to receive either eptifibatide in two 180 microg/kg boluses 10 minutes apart with a continuous infusion of 2.0 microg/g/min for 18 to 24 hours, or placebo. The results showed a significant reduction in ischemic events when data from the two eptifibatide groups were combined.

In contrast, the ESPRIT trial enrolled 2,064 patients undergoing routine stent implantation.\textsuperscript{12} The patients were randomized to receive either eptifibatide in two 180 microg/kg boluses 10 minutes apart with a continuous infusion of 2.0 microg/g/min for 18 to 24 hours, or placebo. The results showed a significant reduction in the primary end points from 10.5% to 6.6%. There was a 38% reduction in the relative risk of death or MI at 30 days, which was maintained throughout the six-month follow-up period.\textsuperscript{13} The higher dose of eptifibatide used in the ESPRIT trial resulted in a better outcome than in the IMPACT II trial, which used a lower dose of eptifibatide.

More recently, the Do Tirofiban and Reopro Give Similar Efficacy Trial (TARGET) randomized 4,812 patients undergoing stenting for CAD, with or without an acute coronary syndrome, to receive either abciximab or tirofiban.\textsuperscript{14} The combined primary end point of death, MI, or urgent revascularization occurred in 7.6% of the tirofiban group and 6.0% of the abciximab group. Abciximab was found to be more effective, particularly in patients with acute coronary syndromes (ACSs).

The use of GP IIb/IIIa inhibitors as an adjunct to PCIs, therefore, results in a significant reduction of early ischemic events that is sustained throughout the one-year follow-up period. Furthermore, this benefit has been reported across all the aforementioned interventional trials. The lack of trials directly comparing different agents hampers the decision as to which GP IIb/IIIa inhibitor to use. Clinical trials using PCI have shown abciximab has the most extensive track record in this patient group, although the results with eptifibatide appear to be similar.

**Non ST-Segment Elevation ACSs**

The role of intravenous GP IIb/IIIa antagonists in the treatment of acute coronary syndromes was investigated in the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) trial (Table 3). This study randomized
GP IIb/IIIa Inhibitors

3,232 patients with unstable angina or non-Q-wave MI to receive either standard heparin or a 48-hour infusion of tirofiban. Although treatment with tirofiban was associated with a statistically significant 32% reduction in death, MI, or refractory ischemia at 48 hours, this difference was no longer significant at 30 days.

The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial differed from the PRISM trial in that it sought the combined effect of tirofiban and heparin by randomizing 1,915 patients to heparin, tirofiban, or both tirofiban and heparin. All patients received acetylsalicylic acid (ASA). The tirofiban-only arm was prematurely stopped because of an excess of early deaths, although follow-up data revealed no difference in mortality at six months between the tirofiban-only and the heparin-only groups. Treatment with tirofiban plus heparin resulted in a 27% reduction in death or MI at 30 days. The observed benefit was sustained at six months.

In the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial, 10,948 patients with unstable angina or non-Q-wave MI were randomly assigned to receive either eptifibatide or placebo for 72 hours. The eptifibatide infusion treatment reduced the combined incidence of death or MI by 10% after 30 days. The beneficial effect of this therapy was maintained at six months.

Disappointing results were recently reported in the Global Use of Strategies To Open Occluded Arteries-IV-Acute Coronary Syndrome (GUSTO-IV-ACS) trial. A total of 7,800 patients with non-ST-segment elevation ACS, for whom PCIs were not planned, were randomized to receive either 24 hours of abciximab, 48 hours of abciximab, or placebo. Abciximab use in this trial was not associated with a

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<tbody>
<tr>
<td>PRISM</td>
<td>Platelet Receptor Inhibition In Ischemic Syndrome Management</td>
<td>3,232</td>
<td>Tirofiban</td>
</tr>
<tr>
<td>PRISM-PLUS</td>
<td>Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms</td>
<td>1,915</td>
<td>Tirofiban</td>
</tr>
<tr>
<td>PURSUIT</td>
<td>Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy</td>
<td>10,948</td>
<td>Eptifibatide</td>
</tr>
<tr>
<td>GUSTO-IV-ACS</td>
<td>Global Use of Strategies To Open Occluded Arteries-IV-Acute Coronary Syndrome</td>
<td>7,800</td>
<td>Abciximab</td>
</tr>
</tbody>
</table>
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reduced risk of death or MI after 30 days (8% for placebo, 8.2% for 24-hour abciximab and 9.2% for 48-hour abciximab).

The overall results of these four placebo-controlled trials, therefore, have demonstrated that differences in the trials’ patient selection and in the study protocol prevent definitive comparisons of the benefits achieved by different GP IIb/IIIa inhibitors. However, the addition of a GP IIb/IIIa inhibitor to standard medical therapy resulted in reductions in ischemic complications among high-risk patients (patients with ST depression or elevated troponin levels).

ST-Segment Elevation MI

The effectiveness of GP IIb/IIIa blockade in patients presenting with acute ST-segment elevation MI was seen in the ReoPro in Acute Myocardial Infarction and Primary PTCA Organization and Randomized Trial (RAPPORT) (Table 4). A total of 483 patients were randomized, within 12 hours of the onset of acute MI, to receive either an abciximab bolus followed by infusion of abciximab for 12 hours, or placebo. Abciximab significantly reduced the incidence of death, reinfarction, or urgent target vessel revascularization at 30 days (11.2%...
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versus 5.8\%) and at six months (17.8\% 

versus 11.6\%). A higher incidence of 

major bleeding was noted in the abcix-

imab group (16.6\% versus 9.5\%), similar 

to the EPIC trial in which a higher dose of 

heparin was also used.

Stenting has now become common after 

primary angioplasty for acute MI.10 In the 

Intracoronary Stenting 

and Antithrombotic 

Regimen 2 (ISAR-2) 

trial, 401 patients under-

going stenting for acute 

ST-segment elevation MI 

were randomly assigned 

to abciximab or placebo. 

Treatment with abcix-

imab was associated with 

a 52\% reduction in the 

rate of death, reinfar-

ction, or target vessel 

revascularization at 30 days.20 A 5\% reduc-

tion in the composite end point was sus-

tained during one-year follow-up.

The Abciximab before Direct Angioplasty 

and Stenting in Myocardial Infarction 

Regarding Acute and Long-term Follow-up 

(ADMIRAL) trial randomly assigned 300 

patients with acute MI to abciximab or place-

bo before attempted stenting of the culprit 

artery.21 The use of abciximab was associat-

ed with a 47\% reduction in death, reinfar-

ction, or revascularization at 30 days. Major 

bleeding was not significantly higher in the 

abciximab group (4\% versus 2.6\%).

The Controlled Abciximab and Device 

Investigation to Lower Late Angioplasty 

Complications (CADIL-

LAC) trial randomly allo-

cated 2,625 patients in a 

factorial design to stent 

versus no stent, and 

abciximab versus place-

bo.22 Patients who 

received both a stent and 

abciximab achieved the 

best results, with 96.7\% attaining Thrombolysis in 

Myocardial Infarction 

(TIMI) grade 3 flow (brisk, 

complete flow). Among all four groups, the 

mortality rate was very low and similar 

(approximately 1.4\%).

There have been angiographic trials 

evaluating TIMI grade 3 flow rates in 

patients with acute MI when GP IIb/IIIa 

inhibitors are combined with thrombolytic 

agents. The Integrilin to Minimize Platelet

Case Discussion

Jack was immediately transferred to a tertiary-care hospital for rescue percutaneous coronary intervention (PCI). Based on small studies in the setting of rescue PCI, the patient was adminis-

tered a platelet GP IIb/IIIa inhibitor during the procedure. He had a successful PCI with restora-
tion of Thrombolysis In Myocardial Ischemia — Phase III (TIMI III) flow and he had an uncom-

plicated recovery.
Aggregation and Prevent Coronary Thrombosis acute MI (IMPACT-AMI) trial was a dose-ranging trial in which 132 patients, who received accelerated alteplase (recombinant tissue plasminogen activator [rtPA]), were randomized to eptifibatide or placebo.23 Patients treated with the highest eptifibatide dose achieved 90-minute TIMI 3 flow in 66% of patients, compared with 39% of patients receiving placebo. Composite clinical end points were similar in both groups (43% versus 42%). The incidence of excessive bleeding was not increased in the active treatment group, compared with the placebo group (4% versus 5%).

In the recent follow-up Integrilin and Reduced Dose Thrombolytic in Acute Myocardial Infarction (INTRO-AMI) study, higher doses of eptifibatide were used in conjunction with reduced-dose alteplase among 344 patients enrolled.24 The results from the dose-ranging study revealed TIMI grade 3 flow rates of up to 65% at 60 minutes and 78% at 90 minutes for patients treated with 180/90/1.33 microg/kg per minute eptifibatide with 50 mg tissue plasminogen activator (t-PA). The follow-up dose-confirmation study showed a 56% incidence of TIMI flow grade 3 at 60 minutes among patients treated with the double-bolus eptifibatide (10 minutes apart) with a 48-hour infusion of 2.0 g/kg per minute with 50 mg t-PA. Eptifibatide and reduced-dose t-PA, therefore, have been shown to enhance infarct artery patency at 60 minutes in patients with acute MI.

The above results led to two recent clinical trials that tested the results obtained in these smaller angiographic trials. In the Global Use of Strategies To Open Occluded Arteries V (GUSTO-V) trial, a total of 16,588 patients who suffered an acute MI with ST-segment elevation were randomized to receive two bolus doses of reteplase (10 U) or two half-boluses of reteplase (5 U) with a full dose of abciximab (0.25 mg/kg bolus, 0.125 microg/ kg/min [10 microg/kg/min maximum] for 12 hours).25 The combination of half-dose reteplase and abciximab failed to show a significant reduction in mortality at 30 days, compared with full-dose reteplase alone. There were, however, fewer deaths or reinfarctions with the combination and less need for urgent revascularization, but more non-cranial bleeds.

The potential role of GP IIb/IIIa inhibitors, combined with reduced doses of thrombolytic therapy, was currently investigated in the Assessment of the Safety and Efficacy of a New Thrombolytic III (ASSENT-III) trial.26 In this study, 6,095 patients with acute MI were randomly assigned to one of the three following regimens:

- Full-dose tenecteplase and enoxaparin;
- Half-dose tenecteplase with low-dose heparin and a 12-hour infusion of abciximab; or
- Full-dose tenecteplase with heparin for 48 hours.

The tenecteplase plus enoxaparin or abciximab regimens studied here both reduced the frequency of ischemic complications of an acute MI. The combination of TNKase with abciximab, however, was not as encouraging as anticipated.

In summary, a reduction in death, MI, and revascularization, when abciximab is combined with either angioplasty or stenting, has been demonstrated from several trials. Significant increases in bleeding complications, however, were encountered. Recent, larger trials, with reduced doses of thrombolitics or weight-adjusted regimens, have
been carried out. Unfortunately, the anticipated results of increased benefit with reduced bleeding were not sustained.

Conclusion

The GP IIb/IIIa receptor inhibitors are powerful agents that have been added to the armamentarium of drugs used to treat CAD. In patients undergoing PCI, abciximab is the most widely investigated agent and has shown positive results, albeit with an increased risk of bleeding. In current clinical practice, however, GP IIb/IIIa inhibitors are routinely being administered as adjunct therapy to reduce the risk of acute and subacute thrombosis.

In patients with non-ST-segment elevation ACS, these agents have also proven to be beneficial, at the expense of increased bleeding, when administered in conjunction with standard medical therapy (including heparin). Because of the inherent risks associated with these agents in clinical practice, they are usually reserved for patients with high-risk ACS (i.e., those with dynamic ECG changes, diabetes and elevated troponins).

Finally, for patients with acute ST-segment elevation MI, small angiographic trials have demonstrated encouraging results. However, recent evidence using large numbers of patients have not substantiated these results. Therefore, many questions still remain to be answered, in particular which regimens, with which agents, and in which combination, would provide the best treatment in the future.

References


