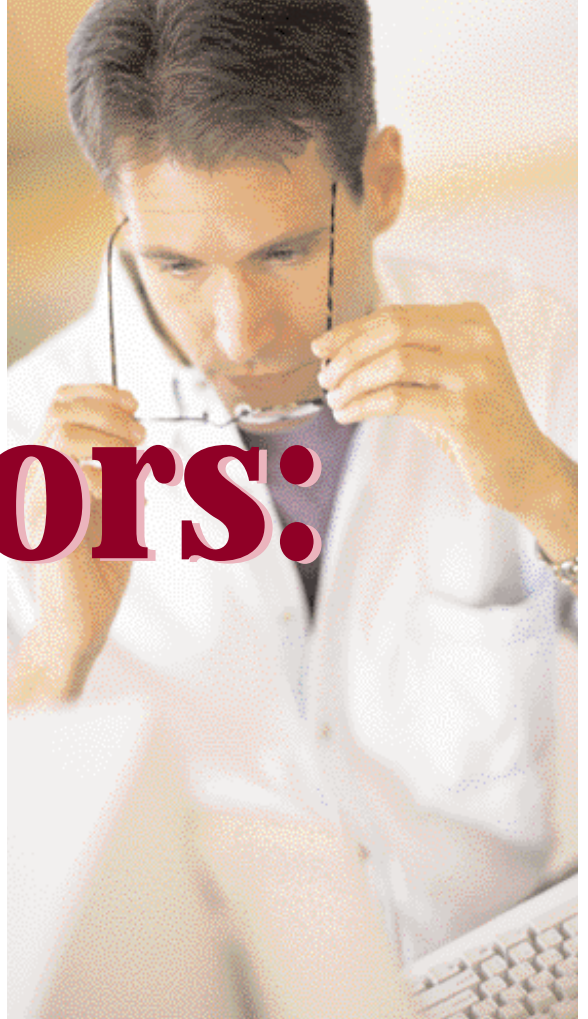


Glycoprotein IIb/IIIa Inhibitors:

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.



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Coronary artery disease (CAD) results from arterial thrombosis after atherosclerotic plaque rupture.^{1,2} Since platelets play a piv-

otal 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.

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Table 1

Glycoprotein IIb/IIIa Antagonists

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

*50% return of platelet function without platelet transfusion

Percutaneous Coronary Interventions

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).⁴ 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.⁵ 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 2

Clinical Trials in Percutaneous Coronary Interventions			
Acronym	Trial Name	# of Patients	Agent Tested
EPIC	Evaluation of 7E3 for the Prevention of Ischemic Complications	2,099	Abciximab
EPILOG	Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade Trial	2,792	Abciximab
CAPTURE	c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina	1,265	Abciximab
EPISTENT	Evaluation of Platelet IIb/IIIa Inhibitor for Stenting	2,399	Abciximab
IMPACT II	Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis — II	4,010	Eptifibatide
ESPRIT	Enhanced Suppression of the Platelet Receptor with Integrilin Therapy	2,064	Eptifibatide
TARGET	Tirofiban and Reopro Give Similar Efficacy	4,812	Tirofiban <i>versus</i> abciximab

plasty.⁶ 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 IIb/IIIa Receptor with Integrilin Therapy



(ESPRIT) trial.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.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% reduc-

tion in the relative risk of death or MI at 30 days, which was maintained throughout the six-month follow-up period.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.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

Table 3

Clinical Trials in Non-ST-Segment Elevation Acute Coronary Syndromes			
Acronym	Trial Name	# of Patients	Agent Tested
PRISM	Platelet Receptor Inhibition In Ischemic Syndrome Management	3,232	Tirofiban
PRISM-PLUS	Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms	1,915	Tirofiban
PURSUIT	Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy	10,948	Eptifibatide
GUSTO-IV-ACS	Global Use of Strategies To Open Occluded Arteries-IV-Acute Coronary Syndrome	7,800	Abciximab

3,232 patients with unstable angina or non-Q-wave MI to receive either standard heparin or a 48-hour infusion of tirofiban.¹⁵ 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.¹⁶ 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 GP 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.¹⁷ 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.¹⁸ 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

Table 4

Clinical Trials in Non-ST-Segment Elevation Myocardial Infarction

Acronym	Trial Name	# of Patients	Agent Tested
RAPPORT	ReoPro in Acute MI and Primary PTCA Organization and Randomized Trial	483	Abciximab
ISAR-2	Intracoronary Stenting and Antithrombotic Regimen-2	401	Abciximab
ADMIRAL	Abciximab Before Direct Angioplasty and Stenting in MI Regarding Acute and Long-Term Follow-up	300	Abciximab
CADILLAC	Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications	2,625	Abciximab
IMPACT-AMI	Integrilin to Minimize Platelet Aggregation and Prevent Coronary Thrombosis Acute MI	132	Eptifibatide
INTRO-AMI	Integrilin and Reduced Dose Thrombolytic in Acute MI	344	Eptifibatide
GUSTO-V	Global Use of Strategies To Open Occluded Arteries-V	16,588	Abciximab
ASSENT-III	Assessment of the Safety and Efficacy of a New Thrombolytic-III	6,095	Abciximab

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).¹⁹ 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%

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 administered a platelet GP IIb/IIIa inhibitor during the procedure. He had a successful PCI with restoration of Thrombolysis In Myocardial Ischemia — Phase III (TIMI III) flow and he had an uncomplicated recovery.

versus 5.8%) and at six months (17.8% *versus* 11.6%). A higher incidence of major bleeding was noted in the abciximab 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 undergoing stenting for acute ST-segment elevation MI were randomly assigned to abciximab or placebo. Treatment with abciximab was associated with a 52% reduction in the rate of death, reinfarction, or target vessel revascularization at 30 days.²⁰ A 5% reduction in the composite end point was sustained 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 placebo

before attempted stenting of the culprit artery.²¹ The use of abciximab was associated with a 47% reduction in death, reinfarction, 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 (CADILLAC) trial randomly allocated 2,625 patients in a factorial design to stent *versus* no stent, and abciximab *versus* placebo.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



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 ele-

vation 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 thrombolytics 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. 

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