Glycoprotein IIb/IIIa receptor antagonists: a review of the pivotal trials

CHERYLE GURK-TURNER, RPH

Major advancements in the past decade have improved our understanding of the events that occur during acute coronary syndromes. We know that atherosclerotic plaque disruption and, ultimately, platelet adhesion, activation, and aggregation are critical in the pathogenesis of this process. We have also learned that various substrates in the biochemical pathways that lead to the final common receptor involve the glycoprotein IIb/IIIa receptor. Several trials in the 1990s focused on the development of new pharmacologic agents designed to block the activities occurring at this receptor.

Abciximab (ReoPro, Centocor, Malvern, Pa) was the first agent to be used in conjunction with coronary angioplasty, but 2 additional agents were approved by the Food and Drug Administration, eptifibatide (Integrilin, COR Therapeutics, South San Francisco, Calif) and tirofiban (Aggrastat, Merck, West Point, NJ). Because no comparative trials of the 3 agents have been conducted, we are forced to compare results of trials that have taken place over a large span of time. The picture is further clouded because trial designs are not consistent, endpoints are not defined in the same manner, and catheterization techniques and standards of practice have improved since the first trial with abciximab was reported in 1994. In an attempt to make this comparison easier, I have provided a review of the major trials conducted for each agent (*Table*). All studies were double blind, randomized, and placebo controlled.

ABCIXIMAB TRIALS

Four landmark trials involved the agent abciximab, a monoclonal antibody that acts by receptor blockade, thereby inhibiting platelet aggregation. They are Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC), Evaluation in PTCA (percutaneous transluminal coronary angioplasty) to Improve Long-term Outcome with Abciximab Glycoprotein IIb/IIIa Blockage (EPILOG), c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE), and Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT).

The EPIC trial was conducted from November 1991 to November 1992 and enrolled 2099 high-risk patients with unstable angina (UA) or an evolving myocardial infarction (MI) who were scheduled for coronary angioplasty. The primary endpoint was met if any of the following were seen within the first 30 days: death from any cause, nonfatal MI, coronary artery bypass grafting (CABG), repeat percutaneous intervention for acute ischemia, or insertion of a coronary stent or balloon pump.

A statistically significant reduction in the composite endpoint was seen for patients who received the abciximab bolus plus infusion vs those who received a placebo ($P = 0.008$). This benefit was maintained at 6 months and at 3 years. Also noteworthy in this trial was the increased number of bleeding complications experienced by patients who received the abciximab bolus plus infusion regimen. Heparin dosing was quite liberal in this study, and infusions continued for at least 12 hours (1).

The 2792 patients included in the EPILOG study were undergoing elective or urgent revascularization procedures. Patients could be at all risk levels, but those with UA or acute MI were excluded. Heparin dosing was adjusted for weight, which was not done in the EPIC trial. The primary endpoints for this study were death from any cause, MI or reinfarction, or severe MI requiring urgent CABG or repeat revascularization within 30 days.

After the first interim analysis, statistical significance was reached between the responses of the abciximab plus low-dose heparin group vs the placebo group, and patient enrollment was therefore terminated. Patients in the placebo group had a higher rate of endpoint events ($P < 0.001$). The incidence of bleeding was not higher for patients receiving abciximab plus heparin therapy (2).

The CAPTURE study was designed to evaluate patients with refractory UA. The primary endpoints were defined as death, MI, or the need for an urgent procedure to treat a recurrent ischemic episode. In contrast to the previously described abciximab studies, infusions were started 18 to 24 hours before the start of the scheduled angioplasty procedure and were continued for 1 hour afterwards.

The study was discontinued prematurely, after 1265 patients were enrolled. At the third interim analysis, a statistically significant higher percentage of patients in the placebo group had reached the primary endpoint compared with those in the abciximab group ($P = 0.0064$) (3).

The final abciximab study is the EPISTENT trial. Previous work had established that stenting was superior to balloon angioplasty because stenting reduced the need for repeat revascularization. Despite this technological advancement, the rates of death and MI had not decreased proportionately. The other

From the Department of Pharmacy Services, Baylor University Medical Center, Dallas, Texas.

Corresponding author: Cheryle Gurk-Turner, RPh, Department of Pharmacy Services, Baylor University Medical Center, 3500 Gaston Avenue, Dallas, Texas 75246.

Table. Summary of trials (compiled from references 1–10)

DRUG/STUDY	STUDY DESIGN	ASPIRIN/HEPARIN DOSING	RESULTS*	ADVERSE REACTIONS
Abciximab				
EPIC (1/91–11/92)	0.25 mg/kg bolus, then 10 µg/kg/min infusion up to 12 hours after event vs heparin placebo	325 mg aspirin plus 10,000–12,000 units heparin prior to angioplasty, continued until the end	Frequency of composite clinical endpoint at 30 days of 12.8% with placebo vs 11.4% for bolus vs 8.3% for bolus plus infusion ($P = 0.008$ placebo vs bolus plus infusion).	Increased bleeding risk
EPILOG (2/95–12/95)	0.25 mg/kg bolus, then 0.125 µg/kg/min (maximum, 10 µg/min) infusion for 12 hours vs heparin placebo	325 mg aspirin (2 hours prior) plus 100 units/kg bolus, then weight-adjusted heparin for low-dose and traditional arms (ACT 200–300 seconds)	Interim analysis at 30 days revealed 5.2% incidence in composite endpoints in low-dose heparin group and 5.4% with standard-dose heparin vs 11.7% with placebo ($P < 0.001$).	Decreased bleeding rate with adjusted-dose heparin arm
CAPTURE (5/93–12/95)	0.25 mg/kg bolus, then 10 µg/kg/min infusion 18–24 hours before angioplasty and 1 hour after completion vs heparin placebo	50 mg aspirin (minimum) plus 100 units/kg heparin (10,000 units maximum), then heparin infusion (ACT 300 seconds) before randomization until 1 hour after angioplasty	Study stopped after interim analysis of data showing 10.8% had primary endpoint in treatment group vs 16.4% with placebo ($P = 0.0064$); at 30 days it was 11.3% vs 15.9% for placebo ($P = 0.012$).	Major bleeding complications in 3.8% of patients
EPISTENT (7/96–9/97)	0.25 mg/kg bolus, then 0.125 µg/kg/min (maximum, 10 µg/min) infusion for 12 hours vs heparin placebo	325 mg aspirin (2 hours prior) plus weight-adjusted heparin with or without ticlopidine	10.8% incidence in composite endpoints for stent plus placebo vs 5.3% for stent plus abciximab ($P < 0.001$) and 6.9% for angioplasty plus abciximab ($P = 0.007$).	Bleeding rates similar among groups
Eptifibatide				
IMPACT	90 µg/kg bolus, then 1 µg/kg/min infusion every 4 hours vs 90 µg/kg bolus, then 1 µg/kg/min infusion every 12 hours	325 mg aspirin plus 10,000 units heparin bolus, then adjusted-dose heparin to ACT > 300 seconds (started after vascular access established)	4.1% incidence in primary composite endpoint at 30 days for 12-hour group vs 9.6% for 4-hour group vs 12.2% for placebo (insignificant).	Major bleeding incidence similar among all groups
IMPACT-II (1/93–11/94)	135 µg/kg bolus, then 0.5 µg/kg/min or 0.75 µg/kg/min for 20–24 hours vs heparin placebo	325 mg aspirin plus 100 units/kg heparin bolus, then infusion (ACT 300–350 seconds)	Composite endpoint reached by 11.4% in placebo group vs 9.9% in high-dose drug arm vs 9.2% in low-dose drug arm at 30 days (insignificant); rates maintained at 6 months.	Major bleeding incidence similar among all groups
PURSUIT (1/95–1/97)	180 µg/kg bolus, then 1.3 µg/kg/min infusion vs 180 µg/kg bolus, then 2.0 µg/kg/min infusion for 72–96 hours	Aspirin at discretion of investigator (could give ticlopidine) with or without heparin	Composite endpoint reached by 15.7% in placebo group (± heparin) vs 14.2% in high-dose drug group at 30 days ($P = 0.04$). Of patients requiring revascularization within 72 hours (59.9% vs 59.0%): 16.7% placebo vs 11.6% drug ($P = 0.01$).	Increased risk of bleeding and a greater need for blood transfusions
Tirofiban				
PRISM (4/94–10/96)	Loading dose, 0.6 µg/kg/min × 30 minutes, then 0.15 µg/kg/min infusion for 47.5 hours vs heparin placebo	325 mg aspirin with or without 5000 units heparin bolus, then 1000 units/hr infusion for 48 hours or infusion placebo; open-label therapy with heparin beginning at 48 hours if needed	Composite endpoint reached by 15.9% in tirofiban group vs 17.1% in heparin group at 30 days ($P = 0.34$). Statistical significance reached at 48 hours but not maintained when infusion stopped: 3.8% vs 5.6% ($P = 0.01$).	Infrequent major bleeding with no difference among groups
PRISM-PLUS (1/94–9/96)	Loading dose, 0.6 µg/kg/min × 30 minutes, then 0.15 µg/kg/min infusion for 47.5 hours or loading dose, 0.4 µg/kg/min × 30 minutes, then 0.1 µg/kg/min infusion plus adjusted-dose heparin vs adjusted-dose heparin placebo	325 mg aspirin with or without 5000 units heparin bolus, then 1000 units/hr infusion for 48 hours or infusion placebo for APTT twice control	Composite endpoint reached by 22.3% with heparin alone vs 18.5% with tirofiban plus heparin ($P = 0.03$) at 30 days.	Bleeding rate not increased with heparin use vs PRISM trial
RESTORE (1/95–12/95)	10 µg/kg bolus, then 0.15 µg/kg/min infusion for 36 hours vs heparin placebo	325 mg aspirin plus 150 units/kg heparin bolus (10,000 units maximum), then infusion (ACT 300–400 seconds) within 12 hours before procedure. Discontinued at end of procedure; sheath removed when ACT < 180 seconds	12.2% incidence in primary composite endpoint at 30 days vs 10.3% for placebo ($P = 0.16$).	Insignificant increase in thrombocytopenia or major bleeding with tirofiban

* Composite endpoints for studies were generally identified as death from any cause, myocardial infarction, or refractory ischemia requiring intervention. Please refer to the specific study for actual study design. ACT indicates activated coagulation time; APTT, activated partial thromboplastin time.

abciximab trials involved balloon angioplasty techniques. EPISTENT enrolled 2399 patients who were scheduled to receive elective or urgent revascularization. This trial compared the use of stents with a heparin placebo, stents with abciximab, and balloon angioplasty with abciximab. The primary endpoint criteria were met if patients experienced death, had an MI or reinfarction, or were required to undergo urgent revascularization or CABG surgery within 30 days.

Patients assigned to the stent plus placebo group reached the primary endpoint at a higher rate compared with those in either treatment group (stent plus abciximab, $P < 0.001$; angioplasty plus abciximab, $P = 0.007$) (4).

EPTIFIBATIDE TRIALS

Three trials were conducted involving the agent eptifibatide, a synthetic cyclic heptapeptide that competitively binds to the arginine-glycine-aspartate recognition site. They were Integrilin to Minimize Platelet Aggregation and Prevent Coronary Thrombosis (IMPACT), Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis-II (IMPACT-II), and Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT).

IMPACT was a phase II clinical trial enrolling 150 patients who were scheduled for elective balloon angioplasty or directional coronary atherectomy. Patients received either placebo or a bolus of eptifibatide followed by a 4- or 12-hour infusion of the study drug. The primary efficacy endpoint was the occurrence of death, MI, or urgent coronary intervention. Results of the study were not statistically significant, probably due to study design and a small sample size (5).

IMPACT-II was a phase III clinical trial that enrolled 4010 patients. Patients met criteria for enrollment if they had scheduled an elective, urgent, or emergency coronary intervention. Patients were randomized to receive either a placebo regimen or a bolus of eptifibatide with 1 of 2 treatment dose infusions. Infusions continued for 20 to 24 hours after the procedure was completed. Primary endpoints were defined as death, MI, or unanticipated revascularization, including stent placement, for management of abrupt closure or recurrent ischemia within the first 30 days.

The composite primary endpoint occurred at a similar rate for all of the treatment groups. The higher-dose regimen did not improve clinical efficacy compared with the lower-dose arm (6).

The final eptifibatide study is the PURSUIT trial. Patients who presented with symptoms of UA or a non-Q wave MI were recruited from 28 countries. They were randomized to receive 1 of 3 regimens: a placebo bolus followed by a placebo infusion or a bolus dose of eptifibatide followed by 1 of 2 eptifibatide infusions. Infusions continued for up to 72 hours, unless an intervention was performed near the end of the 72-hour period. In such a case, the infusion could continue for an additional 24 hours, or 96 hours total. Catheterization or other revascularization procedures could be performed at the treating physician's discretion. Primary endpoints were death or nonfatal MI at 30 days.

There was a statistically significant difference between the groups in the frequency of the development of the composite endpoint at 30 days. Those randomized to receive the placebo infusion had a higher incidence of death or nonfatal MI ($P =$

0.04). Noteworthy, however, was that the frequency of patients requiring revascularization within 72 hours was the same for all 3 groups. The median time for infusion of study drug was 72 hours (7).

TIROFIBAN TRIALS

There are 3 primary trials to discuss involving the agent tirofiban, a nonpeptide that mimics the geometric, stereotactic, and charge characteristics of the arginine-glycine-aspartate sequence and thus interferes with platelet aggregation. They are titled Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM), Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS), and Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE).

The PRISM study enrolled 3232 patients with ischemic symptoms of UA. Patients were randomized to receive either a placebo infusion or a loading dose of tirofiban plus a maintenance infusion for 47.5 hours. The primary endpoint was a composite of death, MI, or refractory ischemia at the end of the 48-hour infusion.

A decrease in the rate of occurrence of the composite endpoint in the tirofiban group was statistically significant at 48 hours ($P = 0.01$) but was not maintained at the 30-day mark. Angiography was performed in 62% of the cases within the first 30 days. While this study was designed for "medical management" of the patient, those treated as such were not discussed separately (8).

The PRISM-PLUS trial involved 1915 patients with UA or non-Q wave MI. Unlike the PRISM trial, where patients were enrolled within 12 hours of when their chest pain began, patients were enrolled within 24 hours of the onset of symptoms. Two different tirofiban dosing regimens, one containing heparin therapy, were chosen to be compared with placebo. Primary endpoints were defined as a composite of death, new MI, refractory ischemia within 7 days, or rehospitalization for UA.

The rate of the development of the composite endpoint was statistically lower for patients randomized to the tirofiban plus heparin dosing arm. Sixty percent of patients required revascularization procedures subsequent to drug therapy with tirofiban (9).

The RESTORE trial targeted patients who were to undergo coronary intervention within 72 hours of presenting with UA or an acute MI. A total of 2212 patients were randomized to receive either a bolus dose of tirofiban and then a constant infusion of tirofiban for 36 hours or placebo. Endpoints of the study were defined as death, MI, CABG surgery, or any revascularization procedure, including stent placement, within the first 30 days. Results of the study showed no statistically significant difference between the groups in the development of the primary endpoints (10).

SUMMARY

Many editorial reviews and supplemental analyses have been written since results of these important investigative trials were published. A thorough review of each study will provide readers with a foundation from which to critically evaluate such literature. Practitioners can put each study into the proper perspec-

tive and ultimately make decisions about the use of these agents in their own clinical practices.

1. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. The EPIC Investigation. *N Engl J Med* 1994;330:956–961.
2. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. The EPILOG Investigators. *N Engl J Med* 1997;336:1689–1696.
3. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. *Lancet* 1997;349:1429–1435.
4. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. The EPISTENT Investigators. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. *Lancet* 1998;352:87–92.
5. Tcheng JE, Harrington RA, Kottke-Marchant K, Kleiman NS, Ellis SG, Kereiakes DJ, Mick MJ, Navetta FI, Smith JE, Worley SJ, et al. Multicenter, randomized, double-blind, placebo-controlled trial of the platelet integrin glycoprotein IIb/IIIa blocker Integrilin in elective coronary intervention. IMPACT Investigators. *Circulation* 1995;91:2151–2157.
6. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II. *Lancet* 1997;349:1422–1428.
7. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. The PURSUIT Trial Investigators. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. *N Engl J Med* 1998;339:436–443.
8. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. *N Engl J Med* 1998;338:1498–1505.
9. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. *N Engl J Med* 1998;338:1488–1497.
10. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. The RESTORE Investigators. Randomized Efficacy Study of Tirofiban for Outcome and REstenosis. *Circulation* 1997;96:1445–1453.