LEADING ARTICLE

Drugs 1998 Dec; 56 (6): 965-976
0012-6667/98/0012-0965/$12.00/0

Recent Antiplatelet Drug Trials in the Acute Coronary Syndromes

Clinical Interpretation of PRISM, PRISM-PLUS, PARAGON A and PURSUIT

John H. Alexander and *Robert A. Harrington*

Duke Clinical Research Institute, Durham, North Carolina, USA

Abstract

This paper reviews the results of 4 recent clinical trials, Platelet Receptor inhibition for Ischaemic Syndrome Management (PRISM), Platelet Receptor inhibition for Ischaemic Syndrome Management in Patients Limited to very Unstable Signs and symptoms (PRISM-PLUS), Platelet IIb/IIIa Antagonist for the Reduction of Acute coronary syndrome events in a Global Organisation Network (PARAGON A), and Platelet IIb/IIIa in Unstable angina Receptor Suppression Using Integrilin Therapy (PURSUIT), that have investigated the use of glycoprotein (GP) IIb/IIIa inhibitors in with non–ST-segment elevation acute coronary syndromes.

The PRISM trial randomised 3232 patients with non–ST-elevation acute coronary syndromes to either tirofiban or heparin. Patients receiving tirofiban had a 32% reduction in the likelihood of death, myocardial infarction (MI) or refractory ischaemia at 48 hours and a 36% reduction in death at 30 days (2.3 *vs* 3.6%, p = 0.02).

The PRISM-PLUS trial randomised 1915 patients with severe non–ST-elevation acute coronary syndromes to either tirofiban alone, heparin alone or the combination of tirofiban and heparin. Patients treated with the combination of tirofiban and heparin had a 27% reduction in death or nonfatal MI at 30 days (8.7 *vs* 11.9%, p = 0.027).

The PARAGON A trial randomised 2282 patients with non–ST-elevation acute coronary syndromes to either high or low dose lamifiban, with or without heparin, or heparin alone. There was no reduction in the rate of death at day 30 or nonfatal MI in patients who received lamifiban; however, at 6 months a significant treatment effect was seen in patients who received low dose lamifiban (13.7%, p = 0.02) but not high dose lamifiban (16.4%, p = 0.38) compared with those who received heparin alone (18.1%).

The PURSUIT trial randomised 10 948 patients with non–ST-elevation acute coronary syndromes to either eptifibatide or placebo. Patients receiving eptifibatide had a 9.6% relative, and 1.5% absolute, reduction in death or MI at 30 days (15.7 *vs* 14.2%, p = 0.04).

GP IIb/IIIa inhibitors are revolutionising the way we treat patients with atherosclerotic coronary artery disease. The results of these trials demonstrate that the GP IIb/IIIa inhibitors tirofiban, lamifiban, and eptifibatide are beneficial in the non–ST-elevation acute coronary syndrome population. In the future, acute

therapy with an intravenous GP IIb/IIIa inhibitor followed by long term administration of an oral GP IIb/IIIa inhibitor may be the cornerstone of the management of patients with acute coronary syndromes.

Despite significant advances in the treatment of patients with coronary artery disease, the acute coronary syndromes remain a major cause of morbidity and mortality.[1] The acute coronary syndromes share a common pathophysiological mechanism, the thrombosis of an epicardial coronary artery.[2] Arterial thrombosis involves complex interactions between the atherosclerotic vessel wall, soluble coagulation factors and circulating platelets.[3]

Current therapies for patients with acute coronary syndromes focus on the restoration of normal flow in the coronary artery. In the case of ST-segment elevation myocardial infarction, this is achieved with either thrombolytic therapy or direct angioplasty. In the case of acute coronary syndromes without ST-segment elevation, this is achieved primarily through the use of antithrombotic drugs, specifically antiplatelet and antithrombin agents.

This paper will review the role of antiplatelet agents, specifically the glycoprotein (GP) IIb/IIIa inhibitors, in the treatment of patients with acute coronary syndromes without ST-segment elevation and will discuss the results of 4 recent clinical trials of GP IIb/IIIa inhibitors in this population.

1. Pathophysiology of Acute Coronary Syndromes

The arterial thrombosis responsible for the acute coronary syndromes begins with the rupture of the atherosclerotic plaque.[2] Plaque rupture exposes platelets, present in circulating blood, to the highly thrombogenic contents of the exposed subendothelium. Exposure to subendothelial contents, in conjunction with shear forces and other factors, leads to platelet activation, platelet adhesion to the site of plaque rupture, and finally platelet aggregation within the arterial lumen (fig. 1). Platelet activation, adhesion and aggregation are the necessary first steps in the formation of thrombi responsible for the acute coronary syndromes.

Although a number of receptors play a role in the overall process of platelet activation, adhesion and aggregation, platelet aggregation is mediated exclusively via the GP IIb/IIIa receptor.[3] The GP IIb/IIIa receptor, a cell surface adhesion molecule of the integrin superfamily, is found only on platelets and megakaryocytes. In resting platelets, these receptors are stored internally in the platelet's α-granules, but upon platelet stimulation, they undergo a conformational change and are moved to the platelet surface. Activated platelets express as many as 50 000 to 70 000 copies of the GP IIb/IIIa receptor on their surface. Fibrinogen, the GP IIb/IIIa receptor primary ligand, binds to GP IIb/IIIa receptors on adjacent platelets leading to further platelet activation and aggregation. The platelet aggregate provides the phospholipid surface on which the coagulation process continues with the generation of thrombin and the conversion of fibrinogen to fibrin. The local generation of thrombin and fibrin further stimulate both platelet activation and aggregation, ultimately leading to the formation of a thrombus in the coronary arterial lumen.

2. Antiplatelet Drugs in Patients with Acute Coronary Syndromes

Aspirin (acetylsalicylic acid), a relatively weak antiplatelet drug, is the most common antiplatelet agent used today. Aspirin irreversibly inhibits platelet cyclooxygenase, the enzyme necessary for the production of thromboxane A_2, one of several mediators of platelet activation.[4] Although the primary mechanism of action of aspirin is thought to be through platelet inhibition, it may have other important effects that are beginning to be explored.[5]

Aspirin is a recommended therapy for all patients with non–ST-elevation acute coronary syndromes.[1,6] Although it has not been investigated in a large definitive trial in this population, its

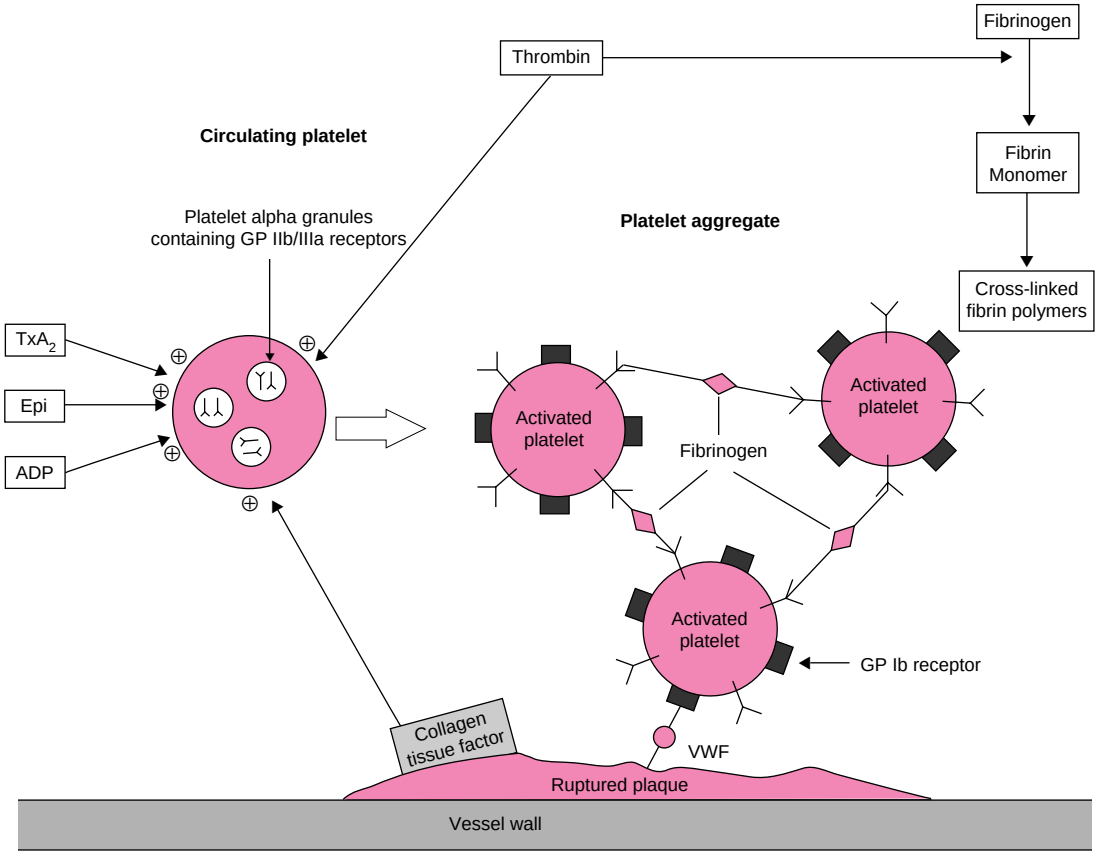

Fig. 1. Process of platelet activation and aggregation in acute coronary syndromes. **ADP** = adenosine diphosphate; **Epi** = adrenaline (epinephrine); **GP** = glycoprotein; **TxA_2** = thromboxane-A_2; **VWF** = von Willebrand factor.

efficacy in the ST-elevation population, shown in the second International Study of Infarct Survival (ISIS-2),[7] its efficacy in several small studies in the unstable angina population and the impressive overall experience with aspirin in patients with atherosclerotic disease has led to its acceptance as standard therapy for patients with non-ST-elevation acute coronary syndromes (fig. 2).[1]

Despite treatment with currently available medical therapies, patients with non–ST-elevation acute coronary syndromes continue to have significant morbidity and mortality. Between 12 and 15% of patients presenting with unstable angina and non–ST-elevation myocardial infarction either die or experience nonfatal myocardial infarctions over the following 30 days.[8,9] Because of the central role of platelets in the pathogenesis of the acute coronary syndromes and the beneficial effects of the weak antiplatelet drug, aspirin, recent research has focused on the development of new, more potent antiplatelet agents. A number of antagonists to the GP IIb/IIIa receptor have recently been developed. These agents are potent inhibitors of platelet aggregation and are dramatically changing the way we treat patients with non–ST-elevation acute coronary syndromes.[10]

3. Glycoprotein IIb/IIIa Inhibitors

The first GP IIb/IIIa inhibitor developed was the murine monoclonal antibody to the GP IIb/IIIa

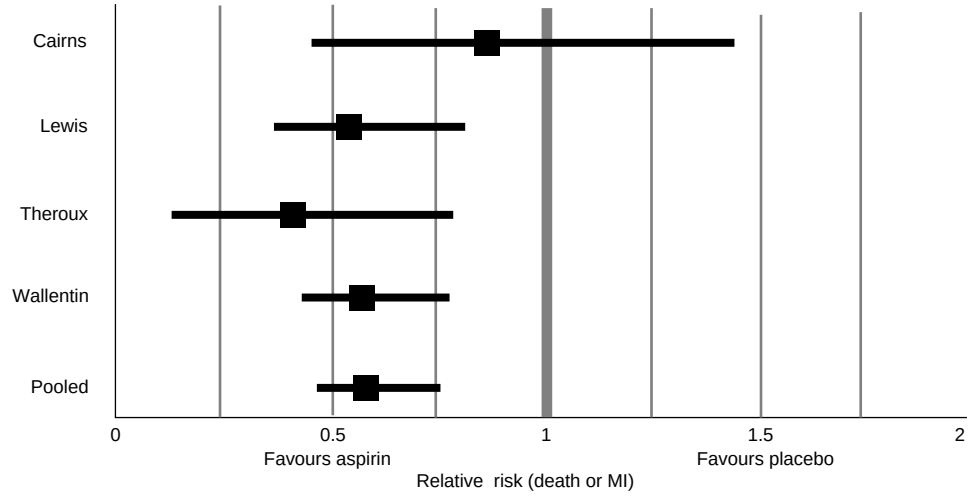

Fig. 2. Effect of aspirin (acetylsalicylic acid) on the risk of death or myocardial infarction in patients with unstable angina (reproduced from Braunwald et al.[1]). **MI** = myocardial infarction

receptor, m7E3.[11] Development of the chimeric monoclonal antibody Fab fragment (c7E3), now commercially available as abciximab, soon followed. Abciximab is a high-affinity, nonselective inhibitor of platelet aggregation that binds irreversibly to the GP IIb/IIIa receptor and inhibits platelet aggregation for prolonged periods.

In an attempt to design more specific and reversible inhibitors of the GP IIb/IIIa receptor, several small-molecule inhibitors have been developed that either contain or mimic the peptide sequence (arginine-glycine-aspartic acid, R-G-D) critical for ligand recognition by the IIb/IIIa receptor. These include a cyclic heptapeptide, eptifibatide, and nonpeptide agents, lamifiban and tirofiban. Like abciximab, these agents are given intravenously, typically as a bolus followed by infusion and have a rapid onset of action. Unlike abciximab, however, eptifibatide, lamifiban and tirofiban are all reversible antagonists of the GP IIb/IIIa receptor and have a duration of action of only a few hours after drug discontinuation (table I).

4. Glycoprotein IIb/IIIa Inhibitors in Patients with Acute Coronary Syndromes

A number of clinical trials have investigated GP IIb/IIIa inhibitors in patients with atherosclerotic coronary artery disease (table II). The results of the Evaluation of 7E3 for the Prevention of Ischaemic Complications (EPIC) [abciximab], Evaluation in PTCA to Improve Long Term Outcome with Abciximab GP II/III (EPILOG) [abciximab], Chimeric 7E3 Anti-Platelet Therapy in Unstable angina REfractory to standard treatment (CAPTURE) [abciximab], Randomised Efficacy Study of Tirofiban for Outcomes and REstenosis (RESTORE) [tirofiban] and Integrelin to Manage Platelet Aggregation to Prevent Coronary Thrombosis-II (IMPACT-II) [eptifibatide] trials have clearly shown the beneficial effects of GP IIb/IIIa inhibition in patients undergoing percutaneous coronary intervention (fig. 3).[13-17,21]

The first evidence that GP IIb/IIIa inhibitors might benefit patients with non–ST-elevation acute coronary syndromes not undergoing coronary inter-

vention came from the EPIC trial. In EPIC, the subset of 489 patients with unstable angina who underwent subsequent coronary intervention derived a larger benefit from treatment with abciximab than other patients undergoing coronary intervention.[27] Patients with unstable angina who received an abciximab bolus plus infusion had a 62% reduction in the composite end-point of death, nonfatal myocardial infarction or urgent revascularisation at 30 days compared with those who received placebo (12.5 *vs* 4.8%, p = 0.012).[27] Patients without unstable angina who received abciximab bolus-plus-infusion had a 27% reduction in the same composite end-point (12.8 *vs* 9.4% for placebo, not significant,). The beneficial effects of abciximab were even greater at 6 months, with an 88% reduction in death or nonfatal myocardial infarction (16.6 *vs* 2.0%) seen in unstable angina patients who received a bolus plus infusion of abciximab compared with placebo.

Using regression modelling, an interaction was found between the use of abciximab and presence of unstable angina in reducing death and nonfatal myocardial infarction at 30 days and 6 months.[27] Although this was a subgroup analysis, these results suggest that patients with unstable angina who undergo percutaneous intervention derive particular benefit from GP IIb/IIIa inhibition with abciximab.

Table I. Characteristics of abciximab versus the small-molecule[a] GP IIb/IIIa inhibitors

	Abciximab	Small-molecule inhibitors
Type	Monoclonal antibody Fab fragment	Peptides and nonpeptides
Onset	Immediate	Immediate
Duration	Days	Hours
Route	Intravenous	Intravenous
Other effects	Also binds other receptors (e.g. vitronectin)	None
Antigenicity	Low incidence, unknown significance	None

a The small molecule GP IIb/IIIa inhibitors include a cyclic heptapeptide, eptifibatide, and nonpeptide agents, lamifiban and tirofiban.

GP = glycoprotein.

Additional evidence that GP IIb/IIIa inhibition might be of benefit in patients with unstable angina (not undergoing percutaneous intervention) came from the CAPTURE trial. In CAPTURE, 1265 patients with refractory unstable angina were randomised to receive either abciximab or placebo for 18 to 24 hours before, and 1 hour after, percutaneous coronary intervention. Patients receiving abciximab had a 29% reduction in the composite end-

Table II. Intravenous glycoprotein IIb/IIIa inhibitors in clinical trials

Agent	Type	Trials (population)	Manufacturer
m7E3	Murine monoclonal antibody	TAMI-8[12] (MI)	NA
Abciximab (c7E3)	Chimeric monoclonal antibody Fab fragment	EPIC[13] (PTCA), EPILOG[14] (PTCA), CAPTURE[15] (PTCA)	Centocor, Malvern, USA and Eli Lilly & Co., Indianapolis, USA
Eptifibatide	Cyclic lysine-glycine-aspartic acid (K-G-D) heptapeptide	IMPACT-I[16] (PTCA), IMPACT-II[17] (PTCA), IMPACT-Hi/Low[18] (PTCA), IMPACT-AMI[19] (MI), IMPACT-USA[20] (UA), PURSUIT[9] (UA)	COR Therapeutics, San Francisco, USA
Tirofiban	Nonpeptide	RESTORE[21] (PTCA), PRISM[22] (UA), PRISM-PLUS[23] (UA)	Merck & Co., West Point, USA
Lamifiban	Nonpeptide	CN Lamifiban Trial[24] (UA), PARAGON-A[25] (UA), PARADIGM[26] (MI)	Hoffman-La Roche, Basel, Switzerland

CAPTURE = Chimeric 7E3 Anti-Platelet Therapy in Unstable angina REfractory to standard treatment; **EPIC** = Evaluation of eptifibatide (7E3) for the Prevention of Ischaemic Complications; **CN** = Canadian; **EPILOG** = Evaluation in PTCA to Improve Long Term Outcome with Abciximab GP II/III; **IMPACT** = Integrelin to Manage Platelet Aggregation to Prevent Coronary Thrombosis; **MI** = myocardial infarction; **PARADIGM** = Platelet Aggregation Recpetor Antagonist Dose Investigation and reprefusion Gain in Myocardial Infarction ; **PARAGON-A** = Platelet IIb/IIIa Antagonist for the Reduction of Acute coronary syndrome events in a Global Organisation Network; **PRISM** = Platelet Receptor inhibition for Ischaemic Syndrome Management; **PRISM-PLUS** = Platelet Receptor inhibition for Ischaemic Syndrome Management in Patients Limited to very Unstable Signs and symptoms; **PTCA** = percutaneous translumenal coronary angioplasty; **PURSUIT** = Platelet IIb/IIIa in Unstable angina Receptor Suppression Using Integrilin Therapy; **RESTORE** = Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis; **TAMI** = Thrombolysis and Angioplasty in Myocardial Infarction; **UA** = unstable angina.

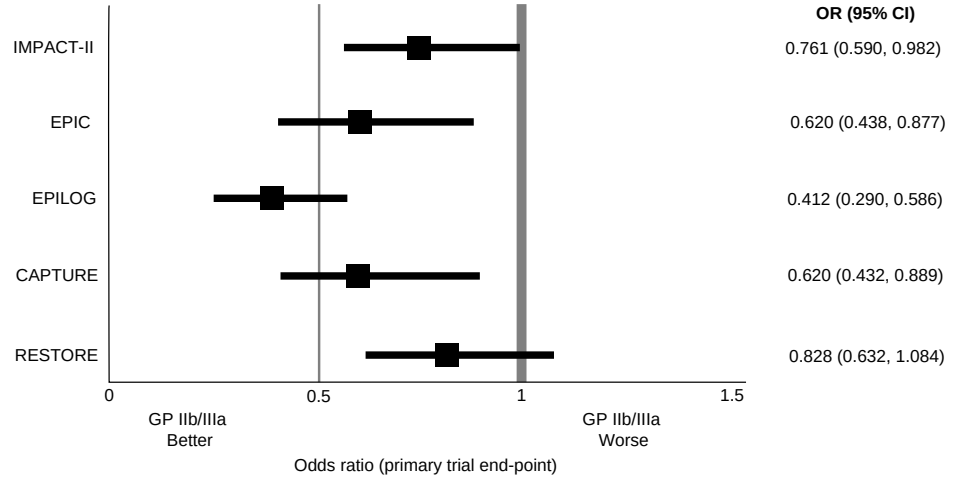

Fig. 3. Results of the Evaluation of eptifibatide (7E3) for the Prevention of Ischaemic Complications (EPIC),[12] EPILOG,[13] Chimeric 7E3 Anti-Platelet Therapy in Unstable angina REfractory to standard treatment (CAPTURE),[14] Randomised Efficacy Study of Tirofiban for Outcomes and REstenosis (RESTORE)[15] and IMPACT-II[16] trials of glycoprotein IIb/IIIa inhibitors in patients undergoing percutaneous interventions. Odds ratios and 95% confidence intervals (95% CI) are for the primary end-point of each trial. **GP** = glycoprotein; **OR** = odds ratios.

point of death, nonfatal myocardial infarction, or urgent revascularisation at 30 days compared with those who received placebo (11.3 *vs* 15.9%, p = 0.012).[21] In fact, patients treated with abciximab had a 71% reduction in the rate of myocardial infarction before they underwent coronary intervention (2.1 *vs* 0.6%, p = 0.029) (fig. 4).[15] While these data are based on a small number of events in patients who were scheduled for percutaneous intervention, they suggest that GP IIb/IIIa inhibition with abciximab may benefit patients with unstable angina who are not undergoing coronary intervention.

5. The Four Ps (PRISM, PRISM-PLUS, PARAGON A and PURSUIT)

There have been 4 recent trials, enrolling a total of more than 18 000 patients, that have investigated the use of GP IIb/IIIa inhibitors in patients with non–ST-elevation acute coronary syndromes: the Platelet Receptor inhibition for Ischaemic Syndrome Management (PRISM) and the Platelet Receptor inhibition for Ischaemic Syndrome Management in Patients Limited to very Unstable Signs and symptoms (PRISM-PLUS) trials with tirofiban, the Platelet IIb/IIIa Antagonist for the Reduction of Acute coronary syndrome events in a Global Organisation Network (PARAGON A) trial with lamifiban, and the Platelet IIb/IIIa in Unstable angina Receptor Suppression Using Integrilin Therapy (PURSUIT) trial with eptifibatide.

5.1 Tirofiban (PRISM and PRISM-PLUS)

The PRISM trial was the first large trial of the GP IIb/III inhibitor tirofiban in patients with unstable angina and non–ST-elevation myocardial infarction. In PRISM, 3232 patients with chest pain and either electrocardiographic (ECG) changes or known coronary artery disease were randomised to receive 48 hours of tirofiban or heparin. Patients who received tirofiban had a 32% reduction in the composite end-point of death, myocardial infarction or refractory ischaemia at 48 hours (3.8 *vs* 5.6%, p = 0.01) compared with those receiving heparin.[22] At 30 days there was no longer a significant difference in the composite end-point (15.9

vs 17.1%, p = 0.34); however, there was a significant 36% reduction in 30-day mortality seen in patients who received tirofiban compared with those who received heparin (2.3 *vs* 3.6%, p = 0.02).[22] There was no difference in bleeding rates between the 2 treatment arms.[22]

A second trial, PRISM-PLUS, conducted concurrently with the PRISM trial, randomised 1915 patients with unstable angina or non–Q-wave myocardial infarction to tirofiban alone, heparin alone or the combination of tirofiban and heparin as part of a comprehensive management strategy for unstable angina.[23] Patients enrolled in PRISM-PLUS were more acutely ill than those in PRISM study with more recent chest pain and either significant ECG findings or positive cardiac enzymes. Patients enrolled in PRISM-PLUS also had a more aggressive use of coronary intervention encouraged as part of the comprehensive management strategy.[23] In PRISM-PLUS, patients treated with the combination of tirofiban and heparin had a significant 28% reduction in the primary composite end-point of death, nonfatal myocardial infarction or refractory ischaemia at 7 days compared with patients receiving heparin alone (12.9 *vs* 17.9%, p = 0.004).[23] They had a significant 65% reduction in death or nonfatal myocardial infarction at 48 hours (0.9 *vs* 2.6%, p = 0.012), and a 40% reduction at 7 days (4.9 *vs* 8.3%, p = 0.006), compared with the heparin alone group.[23] These beneficial effects extended to 30 days and 6 months.

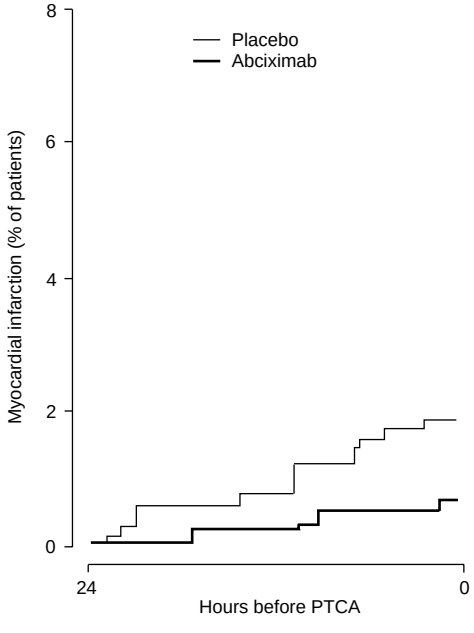

Fig. 4. Reduction in myocardial infarction with abciximab given before coronary intervention in patients with unstable angina from the Chimeric 7E3 Anti-Platelet Therapy in Unstable angina REfractory to standard treatment (CAPTURE) trial (reprinted from CAPTURE Investigators,[15] with permission). **PTCA** = percutaneous translumenal coronary angioplasty.

Patients treated with the combination of tirofiban and heparin had a 27% reduction in death or nonfatal myocardial infarction (8.7 *vs* 11.9%, p = 0.027) at 30 days and a 20% reduction in death or nonfatal myocardial infarction at 6 months (12.3 *vs* 15.3%, p = 0.06) compared with patients who received heparin alone.[23] Patients who received the combination of tirofiban and heparin did have a higher rate of major bleeding than those who received heparin alone (1.4 *vs* 0.8%, p = 0.23).[23]

In PRISM-PLUS, the tirofiban alone arm was discontinued prematurely after only 345 patients were enrolled, on the advice of the trial's Data and Safety Monitoring Board, because of an excess in 7-day mortality in these patients (4.6 *vs* 1.1% for heparin alone).[23] It is surprising that the treatment arm dropped in PRISM-PLUS was the same treatment arm that was found to be beneficial in the PRISM trial.

There are several possible hypothetical explanations that might account for this increase in 7-day mortality seen in the tirofiban alone arm of PRISM-PLUS. One hypothesis is that the more acutely ill patients enrolled in PRISM-PLUS who were treated with a strategy that included aggressive coronary intervention might have required the addition of antithrombin therapy to the potent antiplatelet effects of tirofiban. Patients in the PRISM trial, who were less acutely ill and required less coronary intervention, might have done better with antiplatelet therapy alone. A second hypothesis is that heparin rebound contributed to the increased mortality. Almost 70% of patients enrolled in

PRISM-PLUS were on heparin before enrolment.[23] Those patients randomised to tirofiban alone would have had heparin therapy discontinued, possibly resulting in an increase in ischaemic events due to increased thrombin generation during heparin therapy. A third hypothesis is that, because the excess mortality at 7 days was no longer present on 30-day or 6-month follow-up, and because this increased mortality was not seen in a similar, high-risk subset of the PRISM population, the excess mortality was a chance finding.[23] Despite these potential explanations, the possibility remains that the increased short term mortality seen in PRISM-PLUS was real and that it was not seen in the PRISM trial simply because of chance.

Taken together, the PRISM and PRISM-PLUS trials suggest a role for the GP IIb/IIIa inhibitor tirofiban in the treatment of patients with non–ST-elevation acute coronary syndromes. Further investigation regarding the tolerability and efficacy of tirofiban alone, without accompanying antithrombin therapy, is needed before this regimen can be recommended, particularly for the subset of high-risk patients undergoing aggressive coronary intervention.

5.2 Lamifiban (Canadian Lamifiban Study and PARAGON A)

The Canadian Lamifiban Study was a small, dose-ranging study with the nonpeptide IIb/IIIa inhibitor lamifiban in 365 patients with unstable angina. Patients were randomised on presentation to either 1 of 4 doses of lamifiban or placebo for 72 to 120 hours. Patients who received the 2 highest doses of lamifiban (bolus plus infusion of 600μg plus 4 μg/min or 750μg plus 5 μg/min) had a significant 69% reduction in 30-day death or nonfatal myocardial infarction compared with patients who received placebo (8.1 to 2.5%, p = 0.03).[24]

The encouraging results of the Canadian Lamifiban Study led to the larger PARAGON A trial. PARAGON A was a phase II, dose-finding trial that investigated lamifiban in patients with unstable angina and non–ST-elevation myocardial infarction. A total of 2282 patients with chest pain and either ST-depression, transient ST-elevation, or T-wave inversions were randomly assigned to receive either high (750μg bolus and 5 μg/min infusion) or low (300μg bolus and 1 μg/min infusion) dose lamifiban, with or without heparin, or heparin alone for 3 to 5 days. There was no significant reduction in the primary efficacy end-point of 30-day death or nonfatal myocardial infarction in patients who received lamifiban, at either the high (12.0%, p = 0.899) or low dose (10.6%, p = 0.48), compared with those who received heparin alone (11.7%).[25] At 6 months, however, a significant treatment effect was seen in patients who received low dose lamifiban (13.7%, p = 0.02) but not high dose lamifiban (16.4%, p = 0.38) compared with those who received heparin alone (18.1%).[25]

There was more major and intermediate bleeding in patients who received high dose lamifiban, either with heparin (2.4 and 9.7% respectively) or without heparin (1.3 and 8.1%), than in those who received low dose lamifiban with heparin (0.5 and 6.4%), or low dose lamifiban without heparin (0.8 and 4.2%), or heparin alone (0.8 and 4.8%).[25]

These data suggest that low doses of the GP IIb/IIIa inhibitor lamifiban are well tolerated and may benefit patients with non–ST-elevation acute coronary syndromes. Whether the addition of heparin is beneficial will require further investigation. Higher doses (750μg plus 5 μg/min) of the GP IIb/IIIa inhibitor lamifiban, however, appear to be toxic, resulting in worse outcomes whether used with or without concomitant heparin.

Why treatment with a reversible GP IIb/IIIa inhibitor for 3 to 5 days would result in reductions in death or myocardial infarction at 6 months but not at 30 days is unclear. Although one possibility is chance, a similar pattern was observed in the EPIC trial with continued reduction in mortality at 3-year follow-up in the subset of patients enrolled with either unstable angina or myocardial infarction.[28] Short term therapy with a potent antiplatelet agent may allow improved healing of the ruptured atherosclerotic plaque, thereby preventing future ischaemic events. A larger, phase III trial with lamifiban (PARAGON B) is being planned

and will further examine whether short term therapy with lamifiban results in long term reduction in ischaemic events in patients with non–ST-elevation acute coronary syndromes.

5.3 Eptifibatide (PURSUIT)

PURSUIT investigated the use of the cyclic heptapeptide GP IIb/IIIa inhibitor, eptifibatide, in patients with non–ST-elevation acute coronary syndromes. In PURSUIT, 10 948 patients with ischaemic chest pain and either ST-segment depression, transient ST-segment elevation, T-wave inversions or positive cardiac enzymes, were randomised to up to 72 hours, or 96 hours if they underwent percutaneous intervention, to either eptifibatide or placebo. Heparin was given at the physicians' discretion. Patients receiving eptifibatide had a 16.5% reduction in death or nonfatal myocardial infarction at 96 hours (7.6 *vs* 9.1%, p = 0.011) and a 12.9% reduction at 7 days (10.1 *vs* 11.6%, p = 0.016).[9] At 30 days, a 9.6% relative, and 1.5% absolute, reduction in the primary end-point of death or nonfatal myocardial infarction remained in patients who received eptifibatide compared with those who received placebo (15.7 *vs* 14.2%, p = 0.04).[9] Similar results were seen in patients treated medically, without percutaneous intervention or coronary artery bypass surgery, (14.9 *vs* 16.4%, p = 0.58). The magnitude of benefit was greatest in North America compared with other regions that participated in the trial.[9]

Patients who received eptifibatide in PURSUIT had higher rates of mild (26.1 *vs* 12.9%), moderate (11.3 *vs* 9.0%) and severe bleeding (1.5 *vs* 0.9%) [p < 0.001 for moderate/severe *vs* mild/none], compared with those who received placebo.[9] Patients receiving eptifibatide also had higher transfusion rates (13.0 *vs* 10.5%) than those receiving placebo.[9] Most of the increase in bleeding was due to femoral access site bleeding.[9] There was no increase in the incidence of intracranial haemorrhage.[9]

PURSUIT has been the largest of the 4 trials of GP IIb/IIIa inhibition in non–ST-elevation acute coronary syndrome patients and represents almost 11 000 of the 18 000 patients studied to date. Because of the large number of patients enrolled, PURSUIT was able to show an absolute 1.5% reduction in the hard end-points of death and myocardial infarction at 30 days as its primary finding. In addition, PURSUIT included patients with the entire spectrum of non–ST-elevation acute coronary syndromes from around the world and from a wide variety of clinical practice settings, each using coronary intervention in a fashion consistent with their standard clinical practice. The positive results seen with eptifibatide in PURSUIT add significantly to the growing evidence that potent platelet inhibition with GP IIb/IIIa inhibitors is beneficial in all patients with non–ST-elevation acute coronary syndromes.

6. Overview and Future Directions

The GP IIb/IIIa inhibitors represent a new class of therapeutic compounds that are revolutionising the way we treat patients with atherosclerotic coronary artery disease. The GP IIb/IIIa inhibitors have been extensively investigated and clearly benefit patients undergoing percutaneous coronary intervention. Whether the magnitude of benefit seen in coronary intervention patients with abciximab can be achieved with other GP IIb/IIIa inhibitors will require further study.

The results of the PRISM, PRISM-PLUS, PARAGON A and PURSUIT trials demonstrate that the GP IIb/IIIa inhibitors tirofiban, lamifiban and eptifibatide are beneficial in the non–ST-elevation acute coronary syndrome population (table III; fig. 5). Each of these agents appears to result in an approximate 1.5% absolute reduction in 30-day death or non-fatal myocardial infarction when administered to patients with non–ST-elevation coronary syndromes. This 1.5% reduction is primarily driven by a reduction in non-fatal myocardial infarction; the effects on mortality are less dramatic and thus harder to demonstrate.

From a public health perspective, this 1.5% reduction translates into preventing 15 events for every 1000 patients treated with these agents. With the millions of patients worldwide that experience

TABLE 3 TO GO HERE

LANDSCAPE

acute coronary syndromes, this represents a substantial benefit. Despite the added expense of these agents, the overall savings to the healthcare system through the prevention of recurrent myocardial infarction, ischaemia and procedures, could be substantial. The apparently larger treatment effect seen in the PRISM-PLUS trial is probably attributable to the dropping of the tirofiban alone arm with its associated higher mortality (fig. 5). The fact that several GP IIb/IIIa inhibitors produce similar benefits in this population suggests that this represents a class effect of IIb/IIIa inhibitors, at least with the peptide and nonpeptide GP IIb/IIIa inhibitors, in patients with non–ST-elevation acute coronary syndromes. All patients in these trials received background antiplatelet therapy with aspirin. Whether these agents are better than aspirin alone will require the direct comparisons with aspirin being tested in a number of ongoing trials.

An upcoming trial, the Global Use of Strategies To Open occluded coronary arteries (GUSTO-IV) trial, will evaluate whether the monoclonal antibody fragment GP IIb/IIIa inhibitor, abciximab, benefits patients with non–ST-elevation acute coronary syndromes, as was suggested in subgroup analyses of the EPIC and CAPTURE trials. It will include patients with the entire spectrum of acute coronary syndromes, including unstable angina, non–ST-elevation myocardial infarction and acute ST-elevation myocardial infarction. If abciximab has the same magnitude of benefit in the non–ST-elevation acute coronary syndrome population as it does in the coronary intervention population, its use will represent a further advance in the treatment of such patients.

Patients who present with non–ST-elevation acute coronary syndromes continue to have high rates of death and nonfatal myocardial infarction long after their acute episode has resolved.[8,9] Aspirin, a relatively weak antiplatelet agent, has been shown to be of benefit in the secondary prevention of death and ischaemic complications in patients with coronary artery disease.[1,2] There are at least 12 oral GP IIb/IIIa inhibitors that have been developed and are now under investigation in clinical trials to de-

Table III. Comparison of the PRISM, PRISM-PLUS, PARAGON A, and PURSUIT trials

Study	Agent	No. patients	Patient population	Treatment	Primary end-point	Heparin	Outcome
PRISM[22]	Tirofiban	3232	UA/NQMI	Tirofiban *vs* heparin	48h death/MI/refractory ischemia	Control arm, open label	32% ↓ 48h death/MI/ischaemia*, 36% ↓ 30d death*
PRISM-PLUS[23]	Tirofiban	1915	High risk UA/NQMI	Tirofiban *vs* heparin *vs* tirofiban + heparin	7d death/MI/refractory ischemia	control arm (with/without), open label	28% ↓ 7d death/MI/ischaemia*, 27% ↓ 30d death/MI*
PARAGON A[25]	Lamifiban	2282	UA/NQMI	High lamifiban (± heparin) *vs* low lamifiban (± heparin) *vs* heparin	30d death/MI	Randomised, blinded	11% ↓ 30d death/MI, 28% ↓ 6mo death/MI*
PURSUIT[9]	Eptifibatide	10 948	UA/NQMI	Eptifibatide *vs* placebo	30d death/MI	MD discretion	9. 6% ↓ 30d death/MI*

d = day; **h** = hour; **MD** = medical doctor; **MI** = myocardial infarction; **mo** = month; **NQMI** = non–Q-wave myocardial infarction; **PARAGON-A** = Platelet IIb/IIIa Antagonist for the Reduction of Acute coronary syndrome events in a Global Organisation Network; **PRISM** = Platelet Receptor inhibition for Ischaemic Syndrome Management; **PRISM-PLUS** = Platelet Receptor inhibition for Ischaemic Syndrome Management in Patients Limited to very Unstable Signs and symptoms; **PURSUIT** = Platelet IIb/IIIa in Unstable angina Receptor Suppression Using Integrilin Therapy **UA** = unstable angina; * $p < 0.05$; ↓ = decrease.

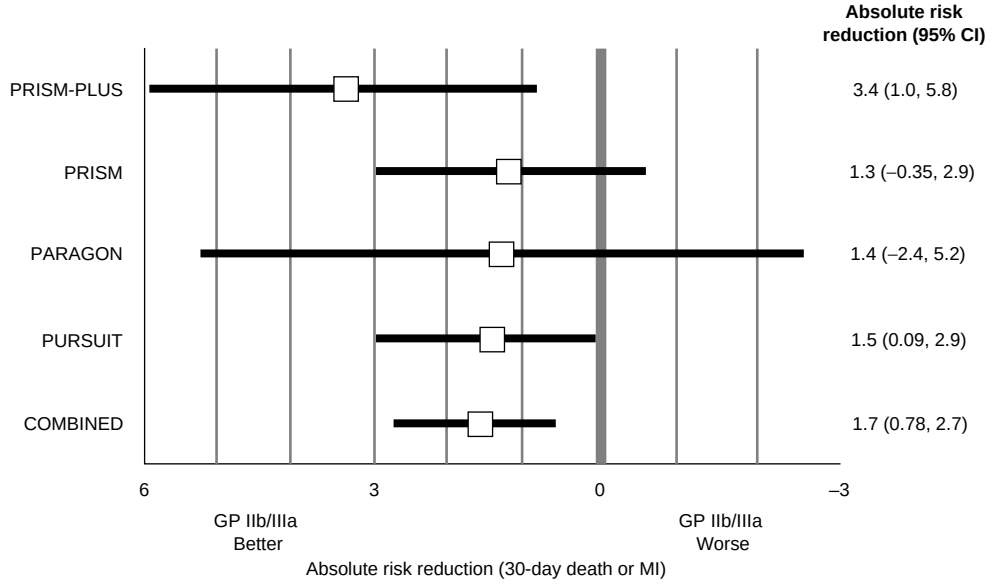

Fig. 5. Absolute reduction in 30-day death or myocardial infarction in the Platelet Receptor inhibition for Ischaemic Syndrome Management (PRISM),[22] Platelet Receptor inhibition for Ischaemic Syndrome Management in Patients Limited to very Unstable Signs and symptoms (PRISM-PLUS),[23] Platelet IIb/IIIa Antagonist for the Reduction of Acute coronary syndrome events in a Global Organisation Network (PARAGON-A)[25] and Platelet IIb/IIIa in Unstable angina Receptor Suppression Using Integrilin Therapy (PURSUIT)[9] trials of glycoprotein IIb/IIIa inhibitors in patients with non-ST-elevation acute coronary syndromes. **95% CI** = 95% confidence intervals; **RR** = risk reduction.

termine their role in secondary prevention.[29] Whether long term GP IIb/IIIa blockade will produce further reductions in death and other ischaemic complications will be determined in the next few years.

Glycoprotein IIb/IIIa inhibitors are revolutionising the care of patients with atherosclerotic coronary artery disease. Acute therapy with an intravenous GP IIb/IIIa inhibitor may soon be the cornerstone of management of patients with acute coronary syndromes. In the future, GP IIb/IIIa inhibitors may play as integral a role in the treatment of patients with coronary disease as aspirin does today.

References

1. Braunwald E, Mark D, Jones R, et al. Unstable angina: diagnosis and management. Clinical practice guideline: number 10 [publication 94-0602]. Rockville (MD): Agency for Health Care Policy and Research, 1994
2. Fuster V, Badimon L, Badimon J, et al. The pathogenesis of coronary artery disease and the acute coronary syndromes. N Engl J Med 1992; 326: 310-8, 342-50
3. Coller BS. Antiplatelet agents in the prevention and therapy of thrombosis. Ann Rev Med 1992; 43: 171-80
4. Fuster V, Dyken ML, Vokonas PS, et al. Aspirin as a therapeutic agent in cardiovascular disease. Circulation 1993; 87: 659-75
5. Ridker PM, Cushman M, Stampfer MJ, et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997; 336: 973-9
6. Antiplatelet Trialists Collaboration. Collaborative overview of randomised trials of antiplatelet therapy: I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994; 308: 81-106
7. Second International Study of Infarct Survival (ISIS-2) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988; 2: 349-59
8. Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. N Engl J Med 1996; 335: 775-82
9. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes without persistent ST-segment elevation. N Engl J Med 1998; 339: 436-43
10. Alexander JH, Harrington RA. Antiplatelet and antithrombin therapies in the acute coronary syndromes. Curr Opin Cardiol 1997; 12: 427-37

11. Coller BS, Peerschke EI, Scudder LE, et al. A murine monoclonal antibody that completely blocks the binding of fibrinogen to platelets produces a thromboasthenic-like state in normal platelets and binds to glycoproteins IIb and/or IIIa. J Clin Invest 1983; 72: 325-38
12. Kleiman NS, Ohman M, Califf RM, et al. Profound inhibition of platelet aggregation with monoclonal antibody 7E3 Fab after thrombolytic therapy: results of the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI-8) pilot study. J Am Coll Cardiol 1993; 22: 381-9
13. EPIC Investigators. Use of a monoclonal antibody-directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 1993; 330: 956-61
14. EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. N Engl J Med 1997; 336: 1689-96
15. CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. Lancet 1997; 349: 1429-35
16. Tcheng JE, Harrington RA, Kottke-Marchant K, et al. Multicenter, randomized, double-blind, placebo-controlled trial of the platelet integrin glycoprotein IIb/IIIa blocker integrelin in elective coronary intervention. Circulation 1995; 91: 2151-7
17. IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Lancet 1997; 349: 1422-8
18. Harrington RA, Kleiman NS, Kottke-Marchant K, et al. Immediate and reversible platelet inhibition after intravenous administration of a peptide glycoprotein IIb/IIIa inhibitor during percutaneous coronary intervention. Am J Cardiol 1995; 76: 1222-7
19. Ohman EM, Kleiman NS, Gacioch G, et al. Combined accelerated tissue-plasminogen activator and platelet glycoprotein IIb/IIIa integrin receptor blackade with integrilin in acute myocardial infarction: results of a randomised, placebo-controlled, dose-ranging trial. Circulation 1997; 95: 846-54
20. Schulman SP, Goldschmidt-Clermont PJ, Topol EJ, et al. Effects of integrilin, a platelet glycoprotein IIb/IIIa inhibitor in unstable angina: a randomised multicenter trial. Circulation 1996; 94: 2083-9
21. RESTORE Investigators. 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. Circulation 1997; 96: 1445-53
22. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. N Engl J Med 1998; 338: 1498-505
23. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. N Engl J Med 1998; 338: 1488-97
24. Theroux P, Kouz S, Roy L, et al., on behalf of the Investigators. Platelet membrane receptor glycoprotein IIb/IIIa antagonism in unstable angina: the Canadian Lamifiban Study. Circulation 1996; 94: 899-905
25. PARAGON Investigators. International, randomised, controlled trial of lamifiban (a platelet glycoprotein IIb/IIIa inhibitor), heparin or both in unstable angina. Circulation 1998; 97: 2386-95
26. PARADIGM Investigators. Combining thrombolysis with the platelet glycoprotein IIb/IIIa inhibitor lamifiban: results of the Platelet Aggregation Receptor Antagonist Dose Investigation and reperfusion Gain in Myocardial Infarction (PARADIGM) trial. J Am Coll Cardiol. In press
27. Lincoff MA, Califf RM, Anderson KM, et al., for the EPIC Investigators. Evidence for prevention of death and myocardial infarction with platelet membrane glycoprotein IIb/IIIa receptor blockade by abciximab (c7E3 Fab) among patients with unstable angina undergoing percutaneous coronary revascularization. J Am Coll Cardiol 1997; 30: 149-56
28. Topol EJ, Ferguson JJ, Weisman HF, et al. Long-term protection from myocardial ischemic events in a randomized trial of brief integrin B_3 blockade with percutaneous coronary intervention. JAMA 1997; 278: 479-84
29. Theroux P. Oral inhibitors of platelet membrane recpetor glycoprotein IIb/IIIa in clinical cardiology: issues and opportunities. Am Heart J 1998; 135 (Pt 2 Suppl.): S107-12

Correspondence and reprints: Dr *John H. Alexander*, Duke Clinical Research Institute, 2400 Pratt Street, Room 0311 Terrace Level, Durham, NC 27705, USA.
E-mail: Alexa017@mc.duke.edu