

Small peptide GP IIb/IIIa receptor inhibitors as upstream therapy in non-ST-segment elevation acute coronary syndromes: results of the PURSUIT, PRISM, PRISM-PLUS, TACTICS, and PARAGON trials

Raymond G. McKay, MD, and William E. Boden, MD, FACC

The primary pathophysiologic mechanism underlying all non-ST-segment elevation acute coronary syndromes (NSTEMI/ACS) is the formation of platelet-rich coronary thrombi in response to spontaneous or intervention-induced endothelial damage with exposure of subendothelial substrates. Antagonists of the glycoprotein (GP) IIb/IIIa receptor ameliorate this process by blocking the final common pathway for platelet aggregation. Based upon collective data in over 24,000 patients, clinical trials have demonstrated that treatment of NSTEMI/ACS patients with GP IIb/IIIa agents results in an approximate 12% relative risk reduction in the incidence of death or myocardial infarction at 30 days. The magnitude of this clinical benefit is increased in patients who are troponin-positive and who are referred for early percutaneous intervention. Potential benefits of GP IIb/IIIa inhibitor use must be weighed against an increased risk of bleeding. Ongoing controversies exist concerning the relative efficacy of different GP IIb/IIIa antagonists, the accurate use of platelet function tests to define safe and efficacious drug dosing, the adjunctive use of additional anti-thrombotic agents, and the optimal timing of upstream therapy before diagnostic cardiac catheterization and revascularization. *Curr Opin Cardiol* 2001, 16:364–369 © 2001

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The Heart Center at Hartford Hospital, Hartford, Connecticut, USA.

Correspondence to Raymond G. McKay, MD, Clinical Professor of Medicine, Hartford Hospital, 80 Seymour Street, Hartford, CT 06102, USA; e-mail: rmckay@harthosp.org

Current Opinion in Cardiology 2001, 16:364–369

Abbreviations

CABG	coronary artery bypass grafting
GP	glycoprotein
MI	myocardial infarction
NSTEMI/ACS	non-ST-segment elevation acute coronary syndrome
PCI	percutaneous coronary intervention

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Myocardial ischemia associated with all non-ST-segment elevation acute coronary syndromes (NSTEMI/ACS) is predominantly initiated by the formation of a platelet-rich thrombus in a coronary artery in response to disruption of an atherosclerotic plaque, either occurring spontaneously or secondary to mechanical intervention [1–4]. Plaque disruption results in exposure of the thrombogenic plaque core and subendothelial matrix proteins to circulating platelets and coagulation factors, leading to platelet deposition and formation of an initial hemostatic plug. Upon deposition, adherent platelets are activated by both mechanical and chemical stimuli (*eg*, high shear stress, thrombin, collagen, adenosine diphosphate), resulting in changes in platelet morphology, activation of coagulant activity and thrombin synthesis, and release of mediators sequestered in platelet granules. The resultant local increase in thrombin and release of these mediators, including adenosine diphosphate and serotonin, further serve to recruit and activate additional platelets. The ultimate result of platelet activation is the conversion of the inactive platelet receptor glycoprotein (GP) IIb/IIIa to a ligand-receptive conformation capable of binding fibrinogen and von Willebrand factor [5]. Cross-linking of activated GP IIb/IIIa receptors on adjacent platelets using these adhesive plasma protein results in ongoing growth of the original platelet plug. As the membrane surface of the accumulating platelets increases, additional coagulation factors are bound and local thrombin and fibrin production is further accelerated. The resulting accumulation of platelets and fibrin forms a white thrombus, while red thrombus is formed with the subsequent trapping of red blood cells.

The ultimate clinical impact of plaque rupture depends upon the extent and duration of thrombus formation in the coronary vessel. Unstable angina and non-ST-segment myocardial infarction may develop as a result of an imbalance between myocardial oxygen supply and demand that results from vessel narrowing from a non-occlusive thrombus or by abnormal vasoconstriction. Additionally, embolization of platelet-rich thrombotic microparticles to the distal coronary microcirculation may reduce local myocardial perfusion and lead to myocardial necrosis and elevation of cardiac markers, including creatine kinase-myocardial band and cardiac troponin.

Recognition of the central role of the GP IIb/IIIa receptor in the pathogenesis of NSTEMI ACS has led to the development of both oral and parenteral GP IIb/IIIa inhibitors.

Approximately, 50,000 to 80,000 GP IIb/IIIa receptors are expressed on each platelet in the resting state [6]. Each receptor has a large extracellular region for cation-facilitated binding. Several extracellular domains have been characterized, including the KQAGDV binding site corresponding to the carboxyl-terminal of fibrinogen gamma-chain and the RGD binding site corresponding to the Arg-Gly-Asp sequence found in many protein ligands including fibrinogen [7–9].

Two predominant pharmacologic approaches have been employed in the design of GP IIb/IIIa inhibitors, including irreversible blocking of the receptor site with a monoclonal antibody (eg, abciximab) and reversible inhibition with small-molecule, competitive antagonists that mimic physiologic ligands. The potential role of abciximab in treating NSTEMI ACS patients has been examined in the CAPTURE trial [10] and in the GUSTO IV-ACS trial [11], and will be discussed later in this journal. Three small molecule, competitive inhibitors, eptifibatid, tirofiban, and lamifiban, have been extensively tested in multiple NSTEMI ACS trials, and will be the subject of the remainder of this review.

Eptifibatid

Eptifibatid is a synthetic, cyclic heptapeptide containing six amino acids and one mercaptopropionyl residue [12,13]. The drug was developed based on the structure of barbourin, a peptide found in the venom of the Southeastern pygmy rattlesnake (*Sistrurus m. barbouri*). The binding specificity of eptifibatid to the GP IIb/IIIa receptor is due to the peptide sequence lysine-glycine-aspartate (KGD), which differs by one amino acid from the RGD sequence present in integrin ligands. The drug has a high affinity and a high specificity for the GP IIb/IIIa receptor, as well as a rapid rate of dissociation. As a result, with a short half-life of elimination, platelet inhibition with eptifibatid is readily reversible with a return of platelet function to baseline within 2 to 4 hours of stopping drug infusion. Unlike abciximab, eptifibatid is not immunogenic, with an observed frequency of thrombocytopenia similar to unfractionated heparin.

The efficacy of eptifibatid in treating patients with NSTEMI ACS has been documented in the PURSUIT trial (Platelet IIb/IIIa Receptor to Suppress Unstable Angina Ischemic Events Trial) [14]. The PURSUIT trial enrolled 10,948 patients with NSTEMI ACS from North America, Western Europe, Eastern Europe, and Latin America, representing the largest clinical trial ever conducted in patients with unstable angina and non-ST-elevation myocardial infarction. Entry criteria for ran-

domization included a history of chest pain lasting longer than 10 minutes with either ischemic ECG changes or elevated plasma levels of CK-MB. All patients were treated with aspirin and standard unfractionated heparin (PTT 50–70 secs), and then randomized to receive either placebo or one of two dosing regimens of eptifibatid (180 ug/kg bolus plus either 1.3 ug/kg/min or 2.0 ug/kg/min). The decision to proceed to diagnostic cardiac catheterization and either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) was left to the discretion of individual investigators. Placebo and eptifibatid infusions were continued until hospital discharge or CABG surgery, up to 72 hours. In patients who were referred for PCI in the period between 48 and 72 hours of random assignment, infusions were continued for 24 hours after the intervention. Early in the study, the low-dose eptifibatid infusion was discontinued after a pre-specified interim analysis demonstrated an acceptable safety profile for the high dose.

The primary end-point of the study, a composite of death or nonfatal myocardial infarction at 30 days, was reduced from 15.7% in the placebo group to 14.2% in the eptifibatid group ($P = 0.042$). A reduced composite event rate was maintained at 6 months, with a rate of death or investigator-determined myocardial infarction of 13.6% in the placebo group and 12.1% in the eptifibatid group ($P = 0.021$). Of interest, the benefit of eptifibatid was observed both in patients who were referred for early invasive procedures (diagnostic catheterization, PCI, CABG) within 72 hours of randomization, and in patients who were treated only with medical therapy. Although the incidence of thrombocytopenia was the same for both the placebo and eptifibatid groups, major bleeding rates were higher in patients treated with eptifibatid, primarily due to an increase in bleeding from the femoral arteriotomy site in patients referred for catheterization and PCI.

Tirofiban

Tirofiban is a nonpeptide tyrosine derivative with a molecular structure similar to that of the RGD sequence of the snake venom echistatin [15]. Like eptifibatid, tirofiban has a high affinity and specificity for the GP IIb/IIIa receptor, with a rapid rate of dissociation. After discontinuation of drug infusion, platelet function returns to baseline within 2 to 4 hours. Tirofiban has a higher incidence of thrombocytopenia than eptifibatid, but less than abciximab.

Three major trials have examined the potential benefit of tirofiban in treating patients with NSTEMI ACS, including the PRISM trial (Platelet Receptor Inhibition for Ischemic Syndrome Management) [16], the PRISM-PLUS trial (Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Very Un-

stable Signs and Symptoms) [17], and the TIMI-18 TACTICS trial (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy) [18].

In the PRISM trial, a total of 3232 patients with unstable angina or non-ST-elevation myocardial infarction were randomly assigned to receive either heparin alone (5000 U bolus plus 1000 U/h infusion) or tirofiban alone (0.6 mg/kg per minute for 30 minutes loading dose plus 0.15 mg/kg per minute infusion). The study drug was continued for 48 hours, during which time invasive procedures were discouraged. At 48 hours, the composite end-point of death, myocardial infarction, and refractory ischemia was significantly reduced from 5.6% in the heparin group to 3.8% in the tirofiban group ($P = 0.01$). This reduction was primarily due to a decrease in recurrent ischemia without a significant effect on the incidence of death or MI. Additionally, the difference in composite outcomes was not statistically significant at 30 days. Tirofiban was also associated with a higher incidence of both moderate and severe thrombocytopenia.

The PRISM-PLUS trial initially randomized 1915 patients with unstable angina and non-ST-segment elevation myocardial infarction to one of three treatment strategies. Patients received either standard dose unfractionated heparin alone, tirofiban alone (0.6 ug/kg/min loading infusion for 30 minutes plus 0.15 ug/kg/min maintenance infusion), or combination heparin and tirofiban ((0.4 ug/kg/min loading infusion for 30 minutes plus 0.1 ug/kg/min maintenance infusion). The study protocol encouraged a modified early invasive treatment approach, with recommended performance of diagnostic catheterization and interventional procedures between 48 and 96 hours after randomization.

After an early interim analysis, the tirofiban-only arm was discontinued because of an increased mortality rate at 7 days compared with the heparin-only group. For the remaining two groups, the rate of composite events (death, MI or recurrent ischemia) was reduced at 7 days from 17.9% in the heparin-only group to 12.9% in the tirofiban plus heparin group ($P = 0.004$). This benefit was primarily derived from a reduction in MIs (3.9 vs 7.0% in the heparin-only group, $P = 0.006$) and recurrent ischemia (9.3 vs 12.7% in the heparin-only group, $P = 0.02$), with no significant difference in mortality (1.9% in both groups). The difference in composite events between the two groups was less at 30 days, and the prespecified requirement for statistical significance ($P < 0.025$) was not achieved. In terms of safety, major bleeding and thrombocytopenia both occurred more frequently in the tirofiban plus heparin group.

Diagnostic cardiac catheterization was performed in approximately 90% of PRISM-PLUS patients, with use of

PCI in 30.5% and CABG in 23.3%. Reduced rates of death or MI at 30 days were observed in PCI patients, as well as in patients who were managed medically with and without diagnostic catheterization. None of these differences, however, was statistically significant.

The TACTICS trial was designed to evaluate the upstream use of tirofiban in NSTEMI ACS patients in combination with an "early invasive" approach of diagnostic catheterization and PCI. The trial included 2200 patients with unstable angina or non-ST-elevation infarction who had either ECG changes, elevated cardiac markers and/or a prior history of coronary artery disease. All patients were initially treated with aspirin, heparin and tirofiban, and then randomized either to early diagnostic catheterization within 4 to 48 hours and revascularization as indicated, or to a more conservative approach with invasive procedures performed only if the patient had objective evidence of recurrent ischemia or positive stress test. The rate of the primary end point of the study (composite of death, MI or re-hospitalization for an acute coronary syndrome at 6 months) was reduced from 19.4% in the conservative group to 15.9% in the early invasive strategy ($P = 0.025$), with a similar significant reduction in death or MI from 9.5% to 7.3% ($P = 0.0498$). This benefit of an early invasive approach was confined to patients who were troponin-positive or who had ST-segment depression on their admission electrocardiogram.

Lamifiban

Like tirofiban, lamifiban is a nonpeptide GP IIb/IIIa receptor antagonist based on the RGD motif. It is a highly selective, competitive inhibitor with a half-life of approximately 90 minutes. Return of platelet function after discontinuation of drug infusion is similar to eptifibatid and tirofiban [19].

The potential impact of lamifiban on NSTEMI ACS patients has been evaluated in the Canadian Lamifiban Study [19], the PARAGON trial (Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network) [20], and the more recent PARAGON B trial [21,22]. The Canadian Lamifiban Study was a dose-ranging pilot study, which randomized 365 patients with unstable angina to placebo or to four different doses of lamifiban. Treatment was administered for 72 to 120 hours. During the infusion period, lamifiban (all doses combined) reduced the risk of death, MI or need for urgent revascularization from 8.1% to 3.3% ($P = 0.04$). At 30 days, the risk of death or MI was reduced from 8.1% in the placebo group to 2.5% in the patients treated with the two highest doses of lamifiban ($P = 0.03$).

The larger PARAGON study randomized 2282 patients from 20 countries with unstable angina and non-ST-

elevation myocardial infarction to one of five treatments, including heparin alone, low dose lamifiban (300 ug bolus with 1 ug/min infusion) with and without heparin, and high dose lamifiban (750 ug bolus with 5 ug/min infusion) with and without heparin. At 30 days, neither dose of lamifiban was statistically better than placebo with respect to the composite of death or MI at 30 days (heparin alone 11.7%, low dose lamifiban 10.6%, high dose lamifiban 12.0%). By 6 months, however, there was a 30% significant reduction in the composite endpoint in the group receiving low dose lamifiban and heparin, compared to heparin alone ($P=0.025$). Of note, the combination of high-dose lamifiban and heparin resulted in more intermediate and major bleeding (12.1 *vs* 5.5% in heparin alone, $P = 0.002$).

The more recent PARAGON B trial randomized 5200 patients with unstable angina or non-ST-elevation myocardial infarction to renal-dose lamifiban or to placebo. Unlike PARAGON A, the study's primary composite endpoint at 30 days included recurrent ischemia as well as death and myocardial infarction. The overall results of the study demonstrated a nonsignificant effect of lamifiban across the entire spectrum of patients. However, a PARAGON B substudy assessing the effect of lamifiban in troponin T-positive patients has recently been published [22]. Interestingly, lamifiban was associated with a significant reduction in the 30-day composite endpoint (19.4% for placebo *vs* 11.0% for lamifiban, $P = 0.01$) in troponin-positive patients, but not among troponin-negative patients (11.2% for placebo *vs* 10.8% for lamifiban, $P = NS$).

Overview of clinical trials

Based upon the clinical trials that have been performed to date, several important conclusions can be drawn. First, intravenous GP IIb/IIIa inhibition has been incontrovertibly proven to be a clinically effective adjunct therapy in the treatment of patients with unstable angina and non-ST-elevation myocardial infarction. Collectively, with over 24,000 patients studied in the various NSTEMI ACS trials, use of these agents has resulted in an approximate 12% risk reduction in 30-day death or MI [23,24]. Current AHA/ACC guidelines list the use of eptifibatid or tirofiban in combination with aspirin and unfractionated heparin as a 1A classification for the treatment of patients with ongoing ischemia or other high-risk features, and in patients in whom PCI is planned. Based upon the CAPTURE trial, abciximab is similarly classified for 12-24 hour use in NSTEMI ACS patients in whom PCI is planned within the following 24 hours [25].

Second, based upon the PRISM, PRISM-PLUS, PARAGON-B and CAPTURE studies, it seems clear that the treatment effects of GP IIb/IIIa antagonists are magnified in patients who are troponin-positive. Multiple previous studies have demonstrated that elevated troponin

levels in NSTEMI ACS patients are predictive of an increased risk of mortality and nonfatal myocardial infarction [26,27]. Such patients have been shown to have more extensive coronary artery disease with more complex lesions often containing thrombus [28]. Use of GP IIb/IIIa agents in troponin-positive patients resulted in relative reduction of the composite of death or MI by 74% in the PRISM trial, 71% in the PRISM-PLUS trial, 70% in the CAPTURE trial and 42% in the PARAGON-B trial. Similarly, reduced or no benefit has been shown in these trials in troponin-negative patients [24].

Third, based upon the PURSUIT, PRISM PLUS and PARAGON B trials, the benefit of GP IIb/IIIa agents also appears magnified in NSTEMI ACS patients referred for early cardiac catheterization and PCI. Comparing the composite outcome of 30-day death or MI among patients referred for PCI versus those who did not undergo intervention, the relative risk reduction with GP IIb/IIIa use was 31% *vs* 6% for PURSUIT, 42% versus 12% for PRISM-PLUS, and 35% versus 7% for PARAGON B [24].

Finally, based upon both NSTEMI ACS and PCI trials, there appears to be a strong relationship between the level of inhibition of platelet aggregation and clinical outcomes. For both eptifibatid and tirofiban, it has been shown that use of a calcium-chelating citrate anticoagulant in *ex vivo* platelet aggregation assays overestimates the *in vivo* inhibitory effect of the GP IIb/IIIa antagonist. Since these assays were utilized to determine the dosing regimens for various trials, it appears that the desired more than 80% inhibition of platelet aggregation was often not achieved [29]. Thus, the higher doses of eptifibatid that were utilized in the PURSUIT and ESPRIT [30] trials may explain the more robust clinical benefit that was seen with lower eptifibatid doses used in IMPACT-II [31]. Similarly, it has been postulated for dosing levels for tirofiban with varying levels of platelet inhibition may explain both the positive results of the PRISM-PLUS trial and the negative findings of the RESTORE [32] and TARGET [33] Trials.

Ongoing considerations

A number of unanswered questions remain concerning the use of IIb/IIIa inhibitors in patients with NSTEMI ACS. Despite of the overall benefit a 12% relative risk reduction in 30-day death or MI among the collective 24,000 patients studied, it is notable that the individual trials report a much higher range of risk reductions varying from 8% to 27% [24]. It is unclear whether this heterogeneity is related to inherent differences in individual drug efficacy, dosing considerations with lack of desired levels of platelet inhibition, diversity of patient acuity, or the uncertain timing of thrombo-occlusive events within the study populations. Ongoing head-to-head trials between different agents and improved platelet function

assays that may result in better patient-specific dosing may help clarify issues.

Apart from the observed clinical benefits with GP IIb/IIIa inhibitors, the advantageous use of these agents must be weighed against an increased risk of bleeding [34]. Excessive bleeding complications associated with GP IIb/IIIa agents that were noted in early NSTEMI ACS and PCI studies have been significantly reduced with the use of reduced-dosing, weight-adjusted heparin, avoidance of post-procedural heparin, and early removal of vascular access site sheaths. A recent meta-analysis of six NSTEMI ACS trials, however, demonstrated a 32% increased risk of moderate to severe hemorrhage with GP IIb-IIIa use [35]. The potential for serious bleeding emphasizes the need for a better understanding of the drug dose-clinical response relationship with potential for more patient-specific dosing. Additionally, given the large numbers of patients who present annually for evaluation of chest pain and the predominant efficacy of GP IIb/IIIa agents in those who are at high risk (*eg*, troponin positive), there is the need for appropriate risk stratification to determine who would benefit from this therapy and who would not.

Another area of confusion concerns the optimal adjunctive use of anticoagulants and additional platelet inhibitors, including unfractionated heparin, low molecular weight heparin, and the thienopyridines. With respect to unfractionated heparin, the PARAGON trial reported a significantly higher rate of intermediate and major bleeding when heparin was combined with high-dose lamifiban, while the PRISM-PLUS trial found that tirofiban use without heparin resulted in worse clinical outcomes including a higher mortality rate. This issue is further clouded by the PRISM trial, which demonstrated a beneficial effect of tirofiban alone. Current ACC/AHA recommendations include the combined use of eptifibatid or tirofiban with weight-adjusted heparin. With respect to low molecular weight heparin, the ACUTE I pilot study has demonstrated the safe combined administration of enoxaparin and tirofiban in 55 patients with NSTEMI ACS [36]. Larger studies, including the unpublished ACUTE II Trial and the ongoing A-Z Trial, will ultimately provide useful information on the combined use of these agents.

Finally, the optimal timing of upstream use of GP IIb/IIIa agents before diagnostic catheterization and PCI needs further clarification. Conventional therapy for unstable angina and non-ST-segment elevation myocardial infarction has predominantly involved the rapid initiation of intensive medical management and the subsequent risk stratification of patients into those who need urgent catheterization and possible revascularization versus those who should undergo additional noninvasive testing. The rationale for this approach has evolved pri-

marily from previous randomized trials (*ie*, TIMI-III [37], VANQUISH [38]) which failed to demonstrate an improvement in clinical outcomes with a routine "early invasive" strategy compared to an "ischemia-guided" or a "selective invasive" approach.

In contrast to previous studies, the TACTICS trial presented convincing data that the combined use of tirofiban in combination with an "early invasive" strategy provides benefit in NSTEMI ACS patients over a conventional "conservative" approach. The potential benefit of this combined pharmacologic and interventional approach was most apparent in the extremely low (*eg*, 4.7%) absolute rate of death or MI at 30 days in the TACTICS "early invasive" group. A critical component of this outcome was the lack of a significantly increased early rate of death and MI associated with percutaneous intervention. In particular, compared to TIMI-III and VANQUISH (both of which showed an excess MI and death/MI rate within the first 7 days in the "early invasive" group), there was no early hazard observed with early intervention in the TACTICS patients. This suggests that the adverse in-hospital outcomes in the earlier studies might have been a consequence of inadequate platelet inhibition, or from lack of a complementary combination of GP IIb/IIIa inhibitor and stent use. Additional studies will be needed to further corroborate this postulate and to document the potential benefit of an early invasive approach with other GP IIb/IIIa agents.

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