Platelet glycoprotein IIb/IIIa receptor blockade in coronary artery disease
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Abstract
Glycoprotein IIb/IIIa inhibitors represent a new promising class of antiplatelet medications. Their use in acute coronary syndromes and for patients undergoing percutaneous coronary intervention has been the subject of a number of large controlled trials using both the intravenous and the oral forms. In this review, we present a systematic overview of these trials.

Keywords coronary artery disease, glycoprotein IIb/IIIa inhibitors, myocardial infarction, percutaneous coronary interventions

Platelets play a pivotal role in acute coronary syndromes [1,2]. Plaque rupture exposes highly thrombogenic components that induce platelet activation and initiate coagulation cascade. Platelet activation involves a conformational change in the membrane glycoproteins (GP) that are receptors for adhesive proteins [3]. The recent development of a new class of drugs that allow direct inhibition of platelet GP IIb/IIIa receptors, the ‘final common pathway’ of platelet activation, has raised the possibility that these potent agents may reduce thrombotic complications after percutaneous coronary interventions or in acute coronary syndromes [4]. In the following review, we summarize the trials conducted to evaluate the use of GP IIb/IIIa inhibitors in these clinical settings, and discuss issues of efficacy and safety.

Intravenous GP IIb/IIIa antagonists
Four intravenous GP IIb/IIIa antagonists have been investigated: abciximab (c7E3 Fab), eptifibatide (Integrilin), tirofiban (Aggrastat), and lamifiban (Ro 44-9883) (Table 1).

Percutaneous coronary interventions
The role of periprocedural intravenous GP IIb/IIIa inhibition in percutaneous coronary revascularization was established in nine placebo-controlled randomized trials and one comparative trial enrolling, in total, over 24,000 patients.
patients [5–19]. All trials were blinded throughout the follow-up period. Inclusion criteria varied (Table 2).

The EPIC trial
The Evaluation of c7E3 for Prevention of Ischemic Complications (EPIC) trial included only patients at higher risk than normal for ischemic complications [5]. The administration of an intravenous bolus and 12-hour infusion of abciximab resulted in a 35% reduction of relative risk of the primary endpoint and reduced the risk of procedure-related myocardial infarction (MI). This benefit was more pronounced in patients with unstable angina and those undergoing angioplasty for MI. The major limitation of the EPIC trial, however, was the existence of a substantially increased risk of bleeding subsequently attributed to the high heparin doses.

The EPILLOG trial
The Evaluation in PTCA to Improve Long-term Outcome with Abciximab GP IIb/IIIa Blockade (EPILLOG) trial extended the application of abciximab to all patients undergoing coronary angioplasty, using the same abciximab
IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial and the Enhanced Suppression of the Platelet Aggregation and Coronary Thrombosis — II (IMPACT II) trial assessed the efficacy of abciximab in patients undergoing coronary intervention in the Integrilin to Minimize Platelet Eptifibatide was evaluated in patients undergoing coronary intervention in the Randomized Eptifibatide was evaluated in patients undergoing routine stent implantation [13]. The patients were randomized to receive either eptifibatide in two 180 µg/kg boluses 10 min apart with a continuous infusion of 2.0 µg/g/min for 18–24 hours, or placebo. The results showed a significant reduction in the primary endpoints from 10.5 to 6.6% (P = 0.0017). There was a 38% reduction in the relative risk of death or MI at 30 days (6.3% versus 10.2%, P = 0.002), which was maintained throughout the 6-month follow-up period (7.5% versus 11.5%, P = 0.002, 95% confidence interval = 0.47–0.84) [14]. The higher dose of eptifibatide used in the ESPRIT trial resulted in more platelet inhibition (90–95%) than in the IMPACT II trial (50–60%) and may have contributed to a better outcome.

The GOLD study
The GOLD study was a prospective multicenter study to determine the optimal level of platelet inhibition with GPIIb/IIIa inhibitors in patients undergoing coronary intervention [15]. This study of GP IIb/IIIa inhibition in conjunction with percutaneous coronary intervention found that patients who achieved greater than 70% inhibition had much lower rates of major cardiac events than patients with lower levels of inhibition (12% versus 32%, P = 0.02).

The RESTORE trial
Tirofiban was evaluated in patients with unstable angina undergoing coronary intervention in the Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) trial [16]. A trend towards improvement in outcome at 30 days was observed in the tirofiban-treated patients when compared with placebo (10.3% versus 12.2%, P = 0.16). Furthermore, the bleeding rates were low and not significantly different from placebo.

The ADMIRAL trial
The Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-term follow-up (ADMIRAL) trial randomized patients suffering acute MI with ST elevation to either abciximab (0.25 mg/kg bolus, 0.125 µg/kg/min [10 µg/kg/min maximum] for 12 hours) plus stenting or placebo plus stenting [17]. The composite endpoint of death, reinfarction or urgent revascularization at 30 days was significantly lower in the abciximab group (6.0% versus 14.6%,
In conclusion, as an adjunct to percutaneous coronary interventions, GP IIb/IIIa inhibition results in a significant reduction in early ischemic events that is sustained throughout the 1-year follow-up period. Furthermore, this benefit is independent of the interventional devices used and of lesion complexities, and has been reported across all the aforementioned interventional trials. Hemorrhagic risk was reduced when the heparin dose was limited and the vascular sheath was removed early. Rates of intracranial hemorrhage were not increased by GP IIb/IIIa blockade. It unclear whether the superiority of abciximab over tirofiban is related to the differences in the mechanisms of antagonism of GP IIb/IIIa, the specific effects of abciximab in blocking interactions between platelets and endothelial cells and leukocytes, differences in doses, differences in patients, or statistical variation [21].

**Acute coronary syndromes**
The role of intravenous GP IIb/IIIa antagonists in the treatment of unstable ischemic syndromes, independent of the use of coronary revascularization, was tested in more than 31,000 patients in six placebo-controlled trials (Table 3) [22–26].

**The PRISM trial**
The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) trial randomized patients with unstable angina or non-Q-wave MI to receive either standard heparin or a 48-hour infusion of tirofiban [22]. At 48 hours, tirofiban was superior to heparin in reducing the composite endpoint of death, MI and refractory ischemia (3.8% versus 5.6%, \(P = 0.01\)), with a 36% reduction in relative risk.

**The PRISM-PLUS trial**
Patients in the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs (PRISM-PLUS) trial were randomized to receive either tirofiban alone, tirofiban with heparin, or heparin alone [23]. The tirofiban-only arm was subsequently discontinued because of a higher mortality rate than heparin alone. The combination of tirofiban and heparin was, however, superior to heparin in reducing the combined endpoint of death, MI and recurrent ischemia after 7 days (12.9% versus 17.9%, \(P = 0.004\)). This significant difference persisted throughout 6 months of follow-up (18.5% versus 22.3%, \(P = 0.03\)).

**The PURSUIT trial**
In the Platelet IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial, an eptifibatide infusion for 72 hours reduced the combined incidence of death or MI by 10% after 30 days (14.2% versus 15.7%, \(P = 0.04\)) [24].
The PARAGON trials

The Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome events in the Global Organization Network (PARAGON A [25] and PARAGON B [26]) trials, in contrast to PRISM, PRISM-PLUS and PURSUIT, failed to demonstrate an advantage of lamifiban over placebo. This failure did not include results in patients with elevated troponin-T levels (30-day composite endpoint, 11% versus 19.4%, \( P = 0.01 \)).

The GUSTO IV-ACS trial

Similarly disappointing results have recently been demonstrated in the Global Use of Strategies To Open Occluded Arteries – IV – Acute Coronary Syndrome (GUSTO IV-ACS) trial [27]. A total of 7800 patients with non-ST-elevation acute coronary syndromes, for whom percutaneous coronary interventions 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 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; not significant).

Summary

In conclusion, high-risk patients (patients with ST depression or elevated troponin levels) should receive GP IIb/IIIa inhibitors (either tirofiban or eptifibatide) in addition to the usual antithrombotic regimen.

Adjuvants to reperfusion therapy

Several completed and ongoing studies are evaluating the role of GP IIb/IIIa inhibitors as an adjunct to thrombolytic therapy.

The TAMI 8 trial

The Thrombolysis and Angioplasty in MI (TAMI 8) trial was a preliminary dose-ranging trial, testing abciximab combined with thrombolytic therapy [28]. Sixty patients with acute MI receiving recombinant tissue-type plasminogen activator (rt-PA) also received a bolus injection of abciximab. The infarct-related artery was patent in 56% of control patients and 92% of the GP IIb/IIIa inhibitor patients. The incidence of major bleeding was increased in the control group (abciximab, 25% versus control, 50%).

The PARADIGM trial

The Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in MI (PARADIGM) trial studied patients with acute MI who received treatment with either alteplase or streptokinase [29]. The patients were randomly assigned treatment with either adjunctive lamifiban or placebo. Despite the higher patency of the infarct-related artery in the lamifiban group when compared with placebo (75% versus 62.5%), the clinical outcomes in the lamifiban and placebo groups were not significantly different (death, 2.1% versus 2.6%; reinfarc-

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**Table 3**

| Trial (number of patients) | Agent tested | Entry criteria | Primary endpoints |
|---------------------------|--------------|----------------|------------------|
| PURSUIT (10,948)          | Eptifibatide | CP at rest or minimal exertion within 24 hours and either ischemic ECG changes* or CK-MB elevations | Death, and non-fatal MI, at 30 days |
| PRISM-PLUS (1915)         | Tirofiban   | CP at rest or minimal exertion within 12 hours and either ischemic ECG changes* or CK-MB elevations | Death, MI, or refractory ischemia, at 7 days |
| PRISM (3232)              | Tirofiban   | CP at rest or minimal exertion within 24 hours and ischemic ECG changes* or CK-MB elevations or history of CAD or positive stress test | Death, MI or refractory ischemia, at 48 hours |
| PARAGON A (2282)          | Lamifiban   | CP at rest within 12 hours and ischemic ECG changes* | Death, and non-fatal MI, at 30 days |
| PARAGON B (5225)          | Lamifiban   | Patients within 12 hours of symptoms of acute myocardial ischemia and ECG changes* | The composite incidence of death, MI, or SRI, at 30 days |
| GUSTO IV-ACS (7800)       | Abciximab   | ACS within last 24 hours; > 5 min anginal symptoms at rest, and either + troponin I/T, or ST depression ≥ 0.5 mm | All-cause mortality, composite endpoint of death, or MI, at 30 days |

ACS, Acute coronary syndromes; CAD, coronary artery disease; CK-MB, creatine kinase MB isoenzyme; CP, Chest pain; ECG, electrocardiogram; MI, myocardial infarction; SRI, severe refractory ischemia. * ST depression, T inversion or transient ST elevation.
tion, 8.9% versus 6.0%; refractor ischemia, 6.4% versus 8.5%; and revascularization, 11.4% versus 12.0%). Furthermore, there was more bleeding associated with lamifiban (transfusions, 16% versus 10.3%; major bleeding, 3.0% versus 1.7%).

The IMPACT-AMI trial
The Integrilin to Minimize Platelet Aggregation and Prevent Coronary Thrombosis AMI (IMPACT-AMI) trial was a randomized, placebo-controlled, dose-ranging trial in which 132 patients who received accelerated alteplase (rt-PA) were randomized to eptifibatide (Integrilin) or placebo [30]. Patients treated with the highest eptifibatide dose achieved 90-min 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%).

The TIMI 14 trial
In the Thrombolysis in MI (TIMI 14) trial, 888 patients who suffered a MI with ST elevation were randomized to receive either 100 mg accelerated-dose alteplase (control), abciximab alone, or abciximab in combination with either reduced doses of alteplase (20, 35, or 65 mg) or streptokinase (500,000 U–1.5 MU) [31]. Excessive bleeding was noted with the highest dose of streptokinase plus abciximab, and this arm was discontinued after five patients were enrolled. The most promising regimen was the combination of abciximab and a 50 mg dose of alteplase, which resulted in 77% TIMI grade 3 flow at 90 min compared with 62% for alteplase alone (P = 0.02). This improvement in reperfusion with alteplase occurred without an increase in the risk of major bleeding.

The SPEED trial
The Strategies for Patency Enhancement in the Emergency Department (SPEED) trial was a dose escalation trial testing the combination of abciximab and reteplase in patients with acute MI [32,33]. All patients received a full-dose of abciximab (0.25 mg/kg bolus, 0.125 µg/kg/min [10 µg/kg/min maximum] for 12 hours) and were randomly assigned in a 4:1 ratio to receive either reteplase (5, 7.5, 10, or 5 + 5 U) with abciximab, or abciximab alone. TIMI 3 flow in the various groups at 60 min was 19% (abciximab alone), 52% (5 U reteplase plus abciximab), 48% (7.5 U reteplase plus abciximab), 51% (10 U reteplase plus abciximab) and 62% (5 + 5 U reteplase plus abciximab).

The GUSTO V trial
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 elevation were randomized to receive two bolus doses of reteplase (10 U) or two half-boluses of reteplase (5 U) with a full dose of abciximab (0.25 mg/kg bolus, 0.125 µg/kg/min [10 µg/kg/min maximum] for 12 hours) [34]. The medication was administered on an open label basis. The combination of half-dose reteplase and abciximab has failed to show a significant reduction in mortality at 30 days compared with full-dose reteplase alone (5.6% versus 6.9%, P = 0.43). The trial did, however, show that the combination was ‘non-inferior’ to the fibrinolytic alone. There were, however, fewer deaths or reinfarctions with the combination (7.4% versus 8.8%, P = 0.001) and less need for urgent revascularization, but more non-cranial bleeds (severe bleeding, 1.1% versus 0.5%, P < 0.0001; moderate bleeding, 3.5% versus 1.8%, P < 0.0001; transfusion, 5.7% versus 4.0%, P < 0.0001).

Summary
In conclusion, the combination of intravenous GP IIb/IIIa antagonists and fibrinolytic therapy results in more rapid reperfusion than conventional therapy. The incidence of 30-day mortality was not reduced, however, and its use was associated with more non-cranial bleeds. There are other ongoing trials; both angiographic (i.e. looking at effects on TIMI flow) with TNKase and each of the three GP IIb/IIIa inhibitors (such as the Integrilin and Tenecteplase for Acute Myocardial Infarction [INTEGRITI] trial), and larger mortality trials (such as Assessment of the Safety and Efficacy of a New Thrombolytic – III [ASSENT III]) with TNKase and abciximab. These ongoing trials are exploring further the potential role of GP IIb/IIIa inhibitors combined with reduced doses of thrombolytic therapy and may further clarify its role as an adjunct to reperfusion therapy.

Oral platelet GP IIb/IIIa antagonists
Prodrugs with RGD specificity (Arg-Gly-Asp sequence) now include oral GP IIb/IIIa receptor blockers, such as xemilofiban, orofiban, sibrafiban and lotrafiban, which have longer half-lives and are excreted renally. Five trials evaluated the use of these agents in patients with acute coronary syndrome or undergoing percutaneous coronary intervention. Four of these trials enrolled patients presenting with acute coronary syndromes and one trial enrolled patients undergoing percutaneous coronary interventions (Table 4).

The EXCITE trial
The Evaluation of Xemilofiban in Controlling Thrombotic Events (EXCITE) trial compared xemilofiban (10–20 mg, administered 3 times a day for 2 weeks) with placebo in 7232 patients undergoing percutaneous coronary interventions [35]. The primary endpoint was death, recurrent MI, and urgent revascularization at 30 and 182 days. The incidence of death, MI, and urgent revascularization within 182 days was comparable among the three groups (13.5% in placebo, 13.9% in those receiving 10 mg xemilofiban, and 12.7% in those receiving 20 mg xemilofiban).
The OPUS-TIMI 16 trial
The Orofiban in Patients with Unstable Coronary Syndromes Thrombolysis in MI (OPUS-TIMI 16) trial randomized 10,302 patients presenting with acute coronary syndromes [36]. They received either 50 mg orofiban twice daily for 6 months, 50 mg orofiban for 30 days followed by 30 mg twice daily for 6 months, 50 mg orofiban twice daily for 5 months, or placebo. The primary endpoint was death, recurrent MI, non-Q-wave MI, and UA, in preceding 72 hours with either ECG changes, enzyme elevation, or prior CAD. This trial was stopped prematurely because of a statistically significant increase in mortality observed after 30 days with orofiban therapy (2.0% versus 1.4%, \(P = 0.02\)).

The SYMPHONY trials
The Sibrafiban Versus Aspirin to Yield Maximum Protection From Ischemic Heart Events Post Acute Coronary Syndromes (SYMPHONY [37] and SECOND SYMPHONY [38]) trials studied sibrafiban, with doses adjusted to weight and serum creatinine, in acute coronary syndrome patients. The SYMPHONY trial randomized 9233 patients to low-dose sibrafiban, high-dose sibrafiban, or aspirin therapy for 90 days. The SECOND SYMPHONY trial compared the same low-dose regimen of sibrafiban with aspirin or high-dose sibrafiban without aspirin with aspirin therapy alone for 90 days. The primary endpoint for both studies was death, MI, and severe recurrent ischemia requiring rehospitalization or revascularization, and stroke, at 30 days and at 10 months. This trial was stopped prematurely because of a statistically significant increase in mortality observed after 30 days with sibrafiban therapy (9.8% versus 1.4%, \(P = 0.02\)).

The BRAVO trial
The Blockade of the GP IIb/IIIa Receptor to Avoid Vascular Occlusion (BRAVO) trial studied the role of lotrafiban in patients who had suffered a recent MI, unstable angina, transient ischemic attack or a stroke, or patients who presented at any time after a diagnosis of peripheral vascular disease [39]. The trial was stopped when it was found at an interim analysis that lotrafiban had a higher mortality than placebo (2.7% versus 2.0%, \(P = 0.022\), more major bleeding (4.2% versus 1.3%, \(P < 0.022\)) and a greater incidence of serious thrombocytopenia (2.2% versus 0.5%) [26].

Summary
Overall, each trial reported an increased risk of mortality during the follow-up period, with an overall 31% increase in mortality. Furthermore, high-dose GP IIb/IIIa inhibition is associated with an even greater fatality risk. No trial demonstrated a statistically significant effect on MI. Conversely, the need for urgent revascularization was reduced in each study except in the EXCITE trial. Moreover, a statistically significant increase in bleeding was observed in each trial. In a meta-analysis of the first four published trials, Chew et al demonstrated that there was a consistent and statistically significant increase in mortality with oral GP IIb/IIIa therapy (odds ratio = 1.37, 95% confidence interval = 1.13–1.66, \(P = 0.001\)) [40].

Conclusion
Intravenous GP IIb/IIIa inhibition used as an adjunct to percutaneous coronary interventions results in significant reduction in early ischemic events that may be sustained for 1 year. This benefit is independent of the interventional devices used and independent of lesion complexities. Abciximab seems to provide better results than eptifibatide.
batide. Preliminary data suggest that intravenous GP IIb/IIIa inhibition may be a useful adjunct to conventional thrombolytic therapy by accelerating the process of fibrinolysis. However, this awaits confirmatory evidence on the efficacy and safety of this combination regimen from ongoing megatrails.

In contrast to the beneficial effects of intravenous GP IIb/IIIa inhibitors, oral GP IIb/IIIa inhibitors were associated with a significant increase in mortality. Further investigation to elucidate the cause of this increased fatality risk is warranted.

Competing interests
None declared.

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