Platelet glycoprotein IIb/IIIa inhibition in acute coronary syndromes

Gradient of benefit related to the revascularization strategy

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Aims To assess the efficacy of platelet glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndromes primarily medically managed.

Methods and Results We performed a meta-analysis of the randomized clinical trials of platelet glycoprotein IIb/IIIa inhibitor therapy in the medical management of non-ST-elevation acute coronary syndromes. Among 29,570 patients, IIb/IIIa integrin blockade was associated with a reduction in death or non-fatal myocardial infarction at 30 days, from 11.5% to 10.7% (odds ratio 0.91, \(P=0.02\)). Patients undergoing percutaneous coronary intervention during index hospitalization sustained a greater reduction in ischaemic events (odds ratio 0.82, \(P=0.01\)) than patients medically managed (odds ratio 0.95, \(P=0.27\)). Among patients undergoing intervention, the benefit was more pronounced if the procedure was performed during glycoprotein IIb/IIIa inhibitor infusion (odds ratio 0.74; \(P=0.02\)), than if revascularization was performed after drug discontinuation (odds ratio 0.87, \(P=0.17\)).

Conclusion This analysis, including the entire large-scale trial experience of intravenous glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndromes primarily medically managed, demonstrates an overall significant, albeit moderate, reduction in 30-day death or myocardial infarction associated with therapy. Although not based on a prospectively defined hypothesis, the findings suggest a gradient of benefit conferred by these agents depending on the revascularization strategy used.


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Introduction

Aspirin, and to a lesser extent heparin, have been shown to reduce subsequent myocardial infarction and death in acute coronary syndromes without ST-segment

elevation[1,2]. Nevertheless, patients remain at risk for recurrent ischaemic events. Newer strategies involving more potent platelet inhibition have focused on the platelet surface membrane IIb/IIIa integrin, the primary receptor in platelet activation and aggregation[3]. The benefit of these agents as adjunctive treatment for percutaneous coronary intervention has been substantial and consistently observed among trials, which have collectively enrolled over 19,000 patients. The observed reduction in 30-day ischaemic end-points (death, myocardial infarction, and urgent revascularization) ranged from 16% to 56%[4]. Conversely, the efficacy of IIb/IIIa inhibitors in the empiric medical management of
non-ST-segment elevation acute coronary syndromes has been less marked\(^8\), and their use has been controversial, particularly following the negative results of GUSTO IV\(^6\).

We performed a meta-analysis of the large-scale randomized trials investigating the use of IIb/IIIa integrin blockers in the medical management of non-ST-segment elevation acute coronary syndromes. The purposes of the study were to better characterize the overall benefit of these agents and to assess whether the reduction in ischaemic end-points associated with therapy was influenced by the revascularization strategy used.

**Methods**

**Trial selection**

Six randomized, double-blind, placebo-controlled trials of intravenous platelet glycoprotein IIb/IIIa antagonists evaluating the medical management of acute coronary syndromes in the absence of ST-segment elevation were identified through a MEDLINE search. Records between 1990 and 2001 were searched for the words ‘platelet,’ ‘intravenous,’ ‘unstable angina,’ ‘random‡’ and ‘inhibit‡ or block‡’, where ‡ was a wild card. Trials were included if the total number of patients exceeded 1000 and the duration of clinical follow-up was ≥30 days. Data from trials presented at major cardiology meetings were also considered. In all trials patients received aspirin.

The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial\(^9\) randomized 1915 patients to either tirofiban (0·6 \(\mu\)g \(\cdot\) kg\(^{-1}\) min\(^{-1}\) for 30 min followed by a 0·15 \(\mu\)g \(\cdot\) kg\(^{-1}\) min\(^{-1}\) infusion) or unfractionated heparin for 48 h. Invasive assessment was discouraged within the first 48 h of randomization, and the drug was discontinued if percutaneous revascularization was performed. The primary end-point was death, myocardial infarction, or refractory ischaemia at 48 h. Patients were followed for 30 days in a pre-defined exploratory analysis.

The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Angina: Receptor Suppression Using Integrin Therapy (PURSUIT)\(^10\) randomized 10 948 patients to eptifibatide 180 \(\mu\)g \(\cdot\) kg\(^{-1}\) bolus and 1·3 \(\mu\)g \(\cdot\) kg\(^{-1}\) min\(^{-1}\) infusion, or bolus and 2·0 \(\mu\)g \(\cdot\) kg\(^{-1}\) min\(^{-1}\) infusion, or placebo for up to 72 h. Adjunctive unfractionated heparin was encouraged but not required. The protocol mandated the discontinuation of the lower-dose arm after documentation of an acceptable safety profile of the higher dose in the interim analysis. Accordingly, the patients randomized to either placebo or higher-dose of eptifibatide were included in the analysis (n=9461). Coronary angiography and revascularization were performed at the discretion of the physician. In patients undergoing early percutaneous intervention, the drug was continued for at least 24 h. The primary end-point was a composite of death or myocardial infarction at 30 days.

The Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON) A trial\(^9\) randomized 2282 patients to lamifiban 300 \(\mu\)g bolus followed by a 1·0 \(\mu\)g min\(^{-1}\) infusion, or 750 \(\mu\)g bolus followed by a 5·0 \(\mu\)g min\(^{-1}\) infusion, or placebo for 3 to 5 days. All patients in the placebo arm received heparin, whereas by factorial design, heparin therapy was randomized among patients receiving lamifiban. Invasive assessment was discouraged. In patients undergoing early percutaneous coronary intervention, the study drug was continued for additional 12 to 24 h. The primary end-point was a composite of death or myocardial infarction at 30 days.

The Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON) B trial\(^10\) randomized 5225 patients to lamifiban (500 \(\mu\)g bolus followed by an infusion of 1·0 to 2·0 \(\mu\)g min\(^{-1}\) according to estimated renal function) or placebo for 72 h or until hospital discharge. All patients received heparin. Coronary angiography and revascularization were discouraged in the first 24 h and then performed according to local standards of practice. In patients undergoing early percutaneous revascularization, the study infusion was continued for an additional 18 to 48 h. The primary end-point was death, myocardial infarction, or severe recurrent ischaemia at 30 days.

The Global Utilization of Strategies To Open Occluded Coronary Arteries (GUSTO IV)\(^6\) randomized 7800 patients to either abciximab 0·25 \(\mu\)g \(\cdot\) kg\(^{-1}\) bolus and 0·125 \(\mu\)g \(\cdot\) kg\(^{-1}\) min\(^{-1}\) (max. 10 \(\mu\)g min\(^{-1}\)) infusion for 24 h, or bolus and infusion for 48 h, or placebo. All patients received either heparin or low-molecular-weight heparin. Early invasive assessment was strongly discouraged. Most of the patients undergoing intervention received either blinded crossover therapy or abciximab on an open-label basis. The primary end-point was death or myocardial infarction at 30 days. For the purpose of this analysis, the 24 h-infusion and 48 h-infusion groups were pooled.
End-points and statistical analysis

Death, and death or non-fatal myocardial infarction, were assessed at 30 days based on an intention-to-treat analysis. The enzyme definitions of myocardial infarction were creatine kinase or creatine kinase-MB greater than the upper limit of normal in PURSUIT; creatine kinase or creatine kinase-MB greater than twice the upper limit of normal in PRISM, PRISM-PLUS, PARAGON A and PARAGON B; and creatine kinase-MB greater than three times the upper limit of normal in GUSTO IV. In addition, PRISM-PLUS, PARAGON B, and PURSUIT defined myocardial infarction post percutaneous intervention as creatine kinase or creatine kinase-MB greater than three times the upper limit of normal. Odds ratios and corresponding 95% confidence intervals were calculated for individual study populations. The Mantel–Haenszel statistic (SAS 6.12, SAS Institute Inc.) was used to test the significance of treatment effect within each study. Heterogeneity of the odds ratios across the trials was tested with the Breslow–Day statistic. If the resulting P-value was non-significant, individual event rates were weighted and pooled. A Pearson chi-square test was applied to the pooled event rates to assess overall significance of treatment effects. A value of P<0·05 was considered statistically significant.

Results

The study involved six trials and 29 570 patients. The aggregate analysis showed a significant reduction of death or myocardial infarction at 30 days associated with platelet glycoprotein IIb/IIIa inhibition, from 11·5% to 10·7% (odds ratio 0·91, 95% confidence interval (CI) 0·85–0·99; P=0·02) (Fig. 1). With the exception of GUSTO IV, the benefit was consistent across the trials in the absence of significant heterogeneity (Breslow–Day P=0·19), and reached statistical significance independently in PRISM-PLUS (odds ratio 0·70; P=0·03) and PURSUIT (odds ratio 0·89; P=0·04). The reduction in mortality associated with glycoprotein IIb/IIIa inhibition (from 3·7% to 3·4%) was of a similar proportion but did not reach statistical significance (odds ratio 0·90, 95% CI 0·80–1·03, P=0·12).

A total of 6337 patients (21%) underwent percutaneous revascularization during index hospitalization. In this setting, glycoprotein IIb/IIIa inhibition was associated with a significant reduction in 30-day death or myocardial infarction, from 12·7% to 10·7% (odds ratio 0·82, 95% CI 0·71–0·96, P=0·01) (Fig. 2). The benefit was consistent across the trials in the absence of heterogeneity (Breslow–Day P=0·79), but did not reach statistical significance in individual studies. The odds ratios for the composite end-point associated with therapy ranged between 0·61 (P=0·09) in PRISM-PLUS and 0·91 (P=0·63) in GUSTO IV. Mortality at 30 days was reduced from 1·9% to 1·4% (odds ratio 0·73, 95% CI 0·49–1·09, P=0·12).

The greatest reduction in death or myocardial infarction was observed among patients undergoing percutaneous revascularization while still receiving the glycoprotein IIb/IIIa inhibitor infusion. Among these 2249 patients, the death or myocardial infarction composite was lowered from 13·6% to 10·5% (odds ratio 0·74, 95% CI 0·57–0·96, P=0·02) by IIb/IIIa integrin blockade (Fig. 3). The benefit was observed across the trials in the absence of significant heterogeneity (Breslow–Day P=0·78). Within the individual
studies the ischaemic end-points reduction associated with therapy reached statistical significance only in PARAGON B (OR 0·58; \( P = 0·04 \)). Patients enrolled in PRISM were excluded from this analysis since protocol mandated drug discontinuation prior to revascularization. The few patients undergoing early percutaneous revascularization in GUSTO IV had high event rates, probably due to the restrictive requirements for early invasive assessment (i.e. recurrent or continuing ischaemia at rest with ECG changes refractory to medical management). Of note, the treatment effect in patients undergoing percutaneous intervention in GUSTO IV could not be adequately assessed because most patients received either blinded placebos or IIb/IIIa inhibitors.

**Figure 2** Odds ratio with 95% confidence intervals (CI) and corresponding \( P \)-values for treatment effect on 30-day death or myocardial infarction (MI) in patients undergoing percutaneous coronary intervention (PCI) during index hospitalization. Values to left of 1·0 indicate a benefit of platelet glycoprotein IIb/IIIa inhibition.

**Figure 3** Odds ratio with 95% confidence intervals (CI) and corresponding \( P \)-values for treatment effect on 30-day death or myocardial infarction (MI) in patients undergoing percutaneous coronary intervention (PCI) while on study drug. Patients enrolled in PRISM were excluded from this analysis as protocol mandated drug discontinuation prior to revascularization. Values to left of 1·0 indicate a benefit of platelet glycoprotein IIb/IIIa inhibition.
crossover therapy or abciximab on an open-label basis.

Patients undergoing percutaneous intervention after drug discontinuation had a moderate event decrease associated with therapy that did not reach statistically significance, from 12.3% to 10.9% (odds ratio 0.87, 95% CI 0.72–1.06, P = 0.17) (Fig. 4). The degree of efficacy ranged from a significant event reduction in PRISM-PLUS (odds ratio 0.39) to a minimal event increase in PARAGON B (odds ratio 1.03).

A marginal event reduction was observed among patients treated conservatively (n = 20,054). The incidence of death or myocardial infarction at 30 days was 9.7% in the placebo group and 9.3% in patients treated with platelet glycoprotein IIb/IIIa inhibitors (odds ratio 0.95, 95% CI 0.86–1.04, P = 0.27) (Fig. 5). Within the individual trials, a significant event reduction associated with therapy was observed in PRISM (odds ratio 0.57) only. The mortality at 30 days was 4.0% in the placebo group and 3.7% in the active treatment group (OR 0.91; 95% CI 0.79–1.06, P = 0.23).

Discussion

This meta-analysis, including the entire large-scale clinical trial experience of intravenous platelet glycoprotein IIb/IIIa inhibitors for the medical management of acute coronary syndromes, demonstrates a significant, albeit moderate (odds ratio 0.91, P = 0.02) overall reduction in death or myocardial infarction at 30 days associated with therapy. This translates into eight ischaemic events prevented per 1000 patients treated. Although the trials were primarily designed to test this drug class in medically managed patients, a proportion of patients underwent percutaneous revascularization. Our analysis suggests a gradient of benefit associated with platelet glycoprotein IIb/IIIa inhibition as adjunct treatment for acute coronary syndromes depending upon strategy and timing of revascularization (Fig. 6). Among patients undergoing intervention during the index hospitalization, those randomized to IIb/IIIa integrin blockade experienced a significant reduction in death or myocardial infarction at 30 days, corresponding to 20 events prevented per 1000 patients treated (odds ratio 0.82, P = 0.01). The mortality benefit was of even greater proportion, albeit not reaching statistical significance due to lower event rates. When stratified by timing of revascularization, a significant reduction in terms of death or myocardial infarction was observed only in individuals undergoing revascularization while receiving glycoprotein IIb/IIIa inhibitors (odds ratio 0.74, P = 0.02). This translates to 31 deaths or myocardial infarctions prevented for 1000 patients treated. If percutaneous intervention was performed after discontinuation of study drug, the benefit was less marked (odds ratio 0.87, P = 0.17), corresponding to 14 ischaemic events prevented for 1000 patients treated. In patients solely medically managed, IIb/IIIa integrin blockade was associated with marginal ischaemic event reduction (odds ratio 0.95, P = 0.27), equal to four events prevented per 1000 patients treated. The proportion of mortality reduction, as expressed by the odds ratio, was similar as to the combined end-point, but did not reach statistical significance in any of the subgroups addressed.
While not based on a randomized assessment and derived from a post-hoc analysis, this observation suggests that maximal efficacy of platelet glycoprotein IIb/IIIa inhibition in unstable patients may be achieved if pharmacological and mechanical stabilization occur simultaneously, whereas the benefit conferred by pharmacological stabilization may decrease if both therapy modalities occur sequentially, and only a modest benefit may be observed if sole aggressive platelet inhibition is pursued. These findings should be considered hypothesis-generating and require independent validation. Ideally, validation would involve a randomized assessment of patients with acute coronary syndromes either medically managed, or started on glycoprotein IIb/IIIa integrin blockade and then undergoing early invasive assessment, or undergoing initial glycoprotein IIb/IIIa-based medical management and then undergoing percutaneous intervention. However, such a trial would be ethically questionable. In fact, the superiority of an early invasive strategy over a conservative treatment in the setting of IIb/IIIa integrin blockade with tirofiban has been convincingly demonstrated in the

Table 1

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Odds ratio and 95% CI</th>
<th>Placebo IIb/IIIa</th>
<th>P-value</th>
<th>Placebo IIb/IIIa</th>
<th>P-value</th>
</tr>
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<td>PRISM</td>
<td>1999</td>
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<td>PRISM-PLUS</td>
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<td>10·4% 10·5%</td>
<td>0·97</td>
<td></td>
<td>10·8%</td>
<td>0·71</td>
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<td>0·71</td>
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<tr>
<td>PARAGON B</td>
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<td>0·30</td>
<td></td>
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<tr>
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<td>12·7% 11·9%</td>
<td>0·36</td>
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<tr>
<td>GUSTO IV</td>
<td>5834</td>
<td>6·6% 7·4%</td>
<td>0·30</td>
<td></td>
<td>9·7% 9·3%</td>
<td>0·27</td>
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<tr>
<td>Pooled</td>
<td>20 054</td>
<td>9·7% 9·3%</td>
<td>0·27</td>
<td></td>
<td>9·7% 9·3%</td>
<td>0·27</td>
</tr>
</tbody>
</table>

Breslow-Day P = 0·12

Figure 5 Odds ratio with 95% confidence intervals (CI) and corresponding P-values for treatment effect on 30-day death or myocardial infarction (MI) in patients medically managed. Values to left of 1·0 indicate a benefit of platelet glycoprotein IIb/IIIa inhibition.

Figure 6 Odds ratio with 95% confidence intervals (CI) and corresponding P-values for treatment effect on 30-day death or myocardial infarction (MI) according to revascularization strategy. Values to left of 1·0 indicate a benefit of platelet glycoprotein IIb/IIIa inhibition.
The acute coronary syndrome population. Designs and populations enrolled. No conclusive data
glycoprotein IIb/IIIa inhibitors due to di
the Breslow–Day test, which
mens, and access to percutaneous revascularization,
in some[17,18], albeit not all [6], trials.
derive particular benefit from IIb/IIIa integrin blockade
addition, troponin-positive patients have been shown to
derive significant benefit from IIb/IIIa integrin
blockade. Accordingly, an analysis of the diabetic popu-
lative event reduction associated with platelet glycoprotein IIb/IIIa inhibitors observed in
this analysis had prolonged glycoprotein IIb/IIIa inhibi-
tor infusion prior to revascularization. Therefore, while
this analysis supports the concept that the benefit with
these agents is closely related to the revascularization
procedure, part of the ischaemic event reduction may
have occurred prior to percutaneous intervention. Such
upstream benefit has been described for CAPTURE,
PURSUIT and PRISM PLUS[15]. No conclusion can be
drawn from our analysis on the use of these drugs
immediately prior to percutaneous intervention, as none
of the trials addressed such a strategy. The limited
benefit of glycoprotein IIb/IIIa inhibitors observed in
this analysis among patients solely medically managed
should not lead to the conclusion that these agents are
indicated only in patients undergoing percutaneous cor-
nary intervention. In fact, specific subgroups of un-
stable patients primarily medically managed have been
shown to derive significant benefit from IIb/IIIa integrin
blockade. Accordingly, an analysis of the diabetic popu-
lations enrolled in the same six glycoprotein IIb/IIIa trials
demonstrated that the use of these agents was
associated with a significant mortality reduction[10]. In
addition, troponin-positive patients have been shown to
derive particular benefit from IIb/IIIa integrin blockade
in some[17,18], albeit not all[6], trials.
Based on the present study, as well as on the subgroup
analyses just mentioned, glycoprotein IIb/IIIa inhibitors
should be strongly considered in patients presenting with
troponin elevation, in diabetics, and in patients under-
going an early invasive strategy. Our analysis does not
allow efficacy comparison among different platelet
glycoprotein IIb/IIIa inhibitors due to differences in trial
designs and populations enrolled. No conclusive data
are available in the absence of direct comparisons within
the acute coronary syndrome population.

Limitations

Inherent to all meta-analyses, the included trials differed
in design, inclusion criteria, therapeutic agents, regi-
mens, and access to percutaneous revascularization,
among others. However, the Breslow–Day test, which
examines the statistical heterogeneity among odds
ratios, and therefore provides information about the
validity of pooling the results from different trials, failed
to demonstrate significant diversity among the analyses.
In addition, since the revascularization strategy was not
randomized, the ischaemic event reduction associated
with platelet glycoprotein IIb/IIIa inhibitors in patients
undergoing PCI may have been influenced by selection
bias. Therefore, this finding should be considered
hypothesis-generating and requires independent vali-
dation. In addition, the enzyme definition of myocardial
infarction was not uniform across the trials, and we
cannot rule out that different cut-offs for enzyme eleva-
tion may have influenced the incidence of events and
possibly the extent of therapeutic benefit. However, this
factor should have been mitigated as the statistical
analysis was based on a comparison of treatment groups
within each trial. In order to consider only adjudicated
events the end-point definitions of the trials were
respected. Finally, in PRISM the primary end-points
were assessed at 48 h and PRISM-PLUS at 7 days.
However, in both trials all 30-day events were
adjudicated.

Conclusions

The aggregate analysis of the entire large-scale clinical
trial experience of intravenous platelet glycoprotein IIb/
IIIa inhibitors for the medical management of non-ST-
segment acute coronary syndromes, demonstrates that
the use of these agents is associated with an overall
significant, albeit moderate, reduction in death or myo-
cardial infarction at 30 days. Although not based on a
prospectively defined hypothesis, our findings suggest a
gradient of benefit conferred by these agents depending
upon the revascularization strategy used. Accordingly,
patients undergoing percutaneous coronary intervention
while on platelet glycoprotein IIb/IIIa inhibitor derived
a significant benefit, while patients undergoing revascu-
larization after drug discontinuation demonstrated a
moderate event reduction that did not reach statistically
significance, and only a marginal benefit was observed
among patients medically managed.

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References

[1] Collaborative overview of randomised trials of antiplatelet
therapy — I: Prevention of death, myocardial infarction, and
stroke by prolonged antiplatelet therapy in various categories

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