Increased Mortality With Oral Platelet Glycoprotein IIb/IIIa Antagonists
A Meta-Analysis of Phase III Multicenter Randomized Trials
Derek P. Chew, MBBS; Deepak L. Bhatt, MD; Shelly Sapp, MS; Eric J. Topol, MD

Background—Numerous clinical trials have established the benefits of intravenous glycoprotein IIb/IIIa inhibition in the management of coronary artery disease. In contrast, the recent large-scale, placebo-controlled, randomized trials of the oral glycoprotein IIb/IIIa antagonists have failed to provide commensurate reductions in late composite ischemic end points despite potent inhibition of platelet aggregation.

Methods and Results—The ORs for death, myocardial infarction, urgent revascularization, and major bleeding from the 4 large-scale, placebo-controlled, randomized trials with oral glycoprotein IIb/IIIa inhibitors were calculated and combined. Stratification by low-dose or high-dose therapy and the use of concurrent aspirin was also undertaken. In 33 326 patients followed for >30 days, a consistent and statistically significant increase in mortality was observed with oral glycoprotein IIb/IIIa therapy (OR, 1.37; 95% CI, 1.13 to 1.66; \( P<0.001 \)). This effect was evident regardless of aspirin coadministration and treatment with either low-dose or high-dose therapy. Although a reduction in urgent revascularization was observed with oral glycoprotein IIb/IIIa inhibition, pooled analysis favored an increase in myocardial infarction that did not demonstrate statistical significance.

Conclusions—Although we found a highly significant excess in mortality consistent across 4 trials with 3 different oral glycoprotein IIb/IIIa inhibitor agents, this was associated with a reduction in the need for urgent revascularization and no increase in myocardial infarction. These findings suggest the potential for a direct toxic effect with these agents and argue against a prothrombotic mechanism. Further investigation to elucidate the cause of this increased fatality risk is warranted. (Circulation. 2001;103:201-206.)

Key Words: mortality ■ glycoproteins ■ trials

Collectively, the efficacy of the intravenous glycoprotein IIb/IIIa antagonists as adjunctive therapy for percutaneous coronary intervention (PCI) and as empiric therapy for acute coronary syndromes is well established.1 Nevertheless, ongoing ischemic events continue to occur in these patient populations and represent an important contributor to the morbidity and mortality from coronary artery disease. After episodes of coronary instability, heightened platelet activity persists and correlates with ongoing ischemia and mortality.2,3 In addition, relatively weak platelet antagonists, such as aspirin and the thienopyridines, have provided an ≈25% relative risk reduction in vascular events when administered as secondary prevention.4,5 These observations have persuasively argued that ongoing platelet activation plays an integral role in the pathophysiology of these late ischemic outcomes.

By blocking the fibrinogen receptor, the final common pathway of platelet aggregation,6 the intravenous glycoprotein IIb/IIIa antagonists provide potent platelet inhibition and have led to commensurate declines in ischemic events after spontaneous or mechanical coronary vascular injury. This success has spurred interest in the development of oral agents with the intention of extending these initial benefits to long-term care. To date, the experience with >33 000 patients in 4 large-scale, double-blind, placebo-controlled, clinical trials has been compiled. Individually, each trial has failed to document a reduction in long-term ischemic outcomes with the respective oral glycoprotein IIb/IIIa receptor antagonist studied, while a worrisome suggestion of increased mortality has been observed.7-9 Therefore, this article represents a meta-analysis of all the completed randomized clinical trials evaluating the impact of oral glycoprotein IIb/IIIa antagonists on mortality and myocardial infarction (MI).

Methods

Trial Selection
Randomized, double-blind, placebo-controlled trials of the oral glycoprotein IIb/IIIa antagonists were identified through a MEDLINE search. Records between 1990 and 2000 were searched for the words “platelet,” “oral,” “random$,” and “inhibit$ or block$,” where
Overview of Randomized Placebo-Controlled Trials With Oral Glycoprotein IIb/IIIa Inhibitors

<table>
<thead>
<tr>
<th>Indication</th>
<th>EXCITE (n=7232)</th>
<th>OPUS (n=10 302)</th>
<th>SYMPHONY (n=9169)</th>
<th>2nd SYMPHONY (n=6637)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study drug</td>
<td>Xemilofiban 10 or 20 mg</td>
<td>Orbofiban 50 mg BID or 50 mg BID</td>
<td>Sibrafiban 3, 4, or 6 mg BID</td>
<td>Sibrafiban 3, 4, or 6 mg BID</td>
</tr>
<tr>
<td>Primary end point</td>
<td>Death, MI, and recurrent ischemia, or stroke</td>
<td>Death, MI, and recurrent ischemia, or stroke</td>
<td>Death, MI, and severe recurrent ischemia</td>
<td>Death, MI, and severe recurrent ischemia</td>
</tr>
<tr>
<td>Concurrent aspirin</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes (low dose only)</td>
</tr>
<tr>
<td>Ticlopidine in stented patients</td>
<td>Randomized</td>
<td>Randomized</td>
<td>Low-dose arm</td>
<td>Low-dose arm</td>
</tr>
<tr>
<td>Low dose, anticipated ADP inhibition, %</td>
<td>30–60</td>
<td>40–60</td>
<td>&gt;25</td>
<td>&gt;25</td>
</tr>
<tr>
<td>High dose, anticipated ADP inhibition, %</td>
<td>50–80</td>
<td>60–80</td>
<td>&gt;50</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Follow-up duration, d</td>
<td>182</td>
<td>300</td>
<td>90</td>
<td>90</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome.

$S$ is a wild card. Trials were included if the total number of patients enrolled exceeded 1000 and the duration of the clinical follow-up was $\geq 30$ days. Data from more recent trials presented at major cardiology meetings were also included. Results from phase II dose-ranging studies were not included in this analysis.

Four trials were identified and included: 3 enrolling patients presenting with acute coronary syndromes and 1 with patients undergoing PCI. Three different agents have been studied: xemilofiban, orbofiban, and sibrafiban, although each agent is a prodrug with the active compound mediating inhibition via the Arg-Gly-Asp (RGD) peptide binding sequence, one of several binding domains on the glycoprotein IIb/IIIa receptor (the Table).

The Evaluation of Xemilofiban in Controlling Thrombotic Events (EXCITE) trials studied xemilofiban 10 or 20 mg compared with placebo administered 3 times a day for 2 weeks followed by twice-daily dosing for an additional 2 weeks in 7232 patients undergoing PCI. All patients received concurrent aspirin therapy, and stented patients were randomized to ticlopidine or xemilofiban. The primary end point was death, recurrent MI, and urgent intervention and was reported at 30 and 182 days. The 30-day outcomes were used in this analysis.

The Orbofiban in Patients With Unstable Coronary Syndromes Thrombolysis in Myocardial Infarction (OPUS TIMI) 16 trial randomized 10 302 patients presenting with acute coronary syndromes to 50 mg orbofiban twice daily for 6 months, 50 mg orbofiban twice daily for 30 days followed by 30 mg twice daily for 5 months, or placebo. All patients received concurrent aspirin, whereas patients receiving stents were randomized to orbofiban or ticlopidine. This trial was stopped prematurely because of a statistically significant increase in mortality observed with orbofiban therapy. The primary end point was death, recurrent MI, and urgent intervention and was reported at 30 days and 10 months. The 30-day outcomes were used in this analysis.

The Sibrafiban Versus Aspirin to Yield Maximum Protection From Ischemic Heart Events Post Acute Coronary Syndromes (SYMPHONY) and 2nd SYMPHONY trials studied sibrafiban individualized by weight and serum creatinine in acute coronary syndrome patients. SYMPHONY randomized 9233 patients to low-dose sibrafiban, high-dose sibrafiban, or aspirin therapy for 90 days. Patients receiving sibrafiban did not receive concurrent aspirin, but patients undergoing coronary stenting were administered ticlopidine concurrently if randomized to the low-dose sibrafiban arm. The 2nd SYMPHONY trial compared the same low-dose regimen of sibrafiban with aspirin or high-dose sibrafiban without aspirin to aspirin therapy alone for 90 days. This trial was terminated prematurely at 6637 patients (planned enrollment, 9000) when the results of the SYMPHONY trial were known. For both studies, the primary end point was death, MI, and severe recurrent ischemia requiring revascularization at 90 days.

Each study included a low-dose and high-dose trial design. Because the range of target inhibition determined by ADP-induced platelet aggregometry for low-dose therapy (30% to 60%) and high-dose therapy (50% to 80%) was comparable among the respective studies, the event rates in the low-dose treatment arms were pooled, as were the high-dose treatment arms, and each was compared with aspirin alone. However, both the low- and high-dose treatment groups of the OPUS TIMI-16 study were included in the high-dose analysis because all patients in this study received the high-dose orbofiban for the first 30 days, and this end point was used in the analysis.

The protocol of each trial varied with respect to the use of concurrent aspirin therapy. To determine whether a potential effect of combined aspirin and oral glycoprotein IIb/IIIa therapy could be observed, the treatment arms from EXCITE and OPUS TIMI-16 and the low-dose arm of the 2nd SYMPHONY study, which included concurrent aspirin therapy, were pooled and compared with aspirin alone. Conversely, both low- and high-dose treatment arms of the SYMPHONY study and the high-dose arm of the 2nd SYMPHONY study did not include concurrent aspirin and therefore were pooled and compared with aspirin alone.

Clinical End Points
The clinical end-point definitions were similar among the trials, enabling the use of protocol-defined death, MI, urgent revascularization, and major bleeding within this meta-analysis. The number of patients experiencing events in the treatment and control arms were compiled at this “30 day or greater” end point. The event rates for each treatment arm reflect the number of events observed divided by the number of patients enrolled, according to intention to treat.

Statistical Analysis
Based on the treatment group sample sizes and event rates for each trial, pooled ORs adjusting for the trial sample sizes and the corresponding 95% CIs were calculated for death, MI, urgent revascularization, and major bleeding. The Cochran-Mantel-Haenszel statistic (SAS 6.12, SAS Institute Inc) was used to evaluate the association between treatment and outcome, adjusting for trial. The homogeneity of the ORs across the trials was assessed by Breslow-Day test. A value of $P<0.05$ was considered statistically significant.

Results
Mortality
In total, 33 340 patients were enrolled in the 4 randomized trials, of which 33 326 patients have available follow-up.
Overall, each trial reported an increased risk of mortality during the follow-up period. This increased mortality risk was statistically significant in the EXCITE trial (OR, 2.1; 95% CI, 0.99 to 4.46; \( P = 0.048 \)), OPUS TIMI-16 trial (OR, 1.4; 95% CI, 1.00 to 1.95; \( P = 0.047 \)), and 2nd SYMPHONY trial (OR, 1.54; 95% CI, 1.02 to 2.34; \( P = 0.038 \)). Pooled results confirm an increase in mortality with the use of any oral glycoprotein IIb/IIIa antagonist regimen, with an OR of 1.37 (95% CI, 1.13 to 1.67; \( P = 0.001 \); Figure 1A).

**Myocardial Infarction**

Compared with placebo, randomization of any oral glycoprotein IIb/IIIa antagonists favored an increased risk of MI in both SYMPHONY trials but was not observed in EXCITE or OPUS TIMI-16. No trial demonstrated a statistically significant effect on MI, and this lack of effect was confirmed on pooled analysis of the all the trials (OR, 1.04; 95% CI, 0.93 to 1.16; \( P = 0.481 \); Figure 1B).

**Urgent Revascularization**

Conversely, the need for urgent revascularization was reduced in each study except the EXCITE trial (OR, 1.06; 95% CI, 0.80 to 1.41; \( P = 0.688 \)). A statistically significant reduction in urgent revascularization was observed in both the OPUS TIMI-16 (OR, 0.60; 95% CI, 0.48 to 0.75; \( P < 0.001 \)) and 2nd SYMPHONY (OR, 0.74; 95% CI, 0.56 to 0.99; \( P = 0.039 \)) trials. Pooled results of all the oral glycoprotein IIb/IIIa treatment arms indicated a statistically significant reduction in urgent revascularization, with an OR of 0.77 (95% CI, 0.66 to 0.87; \( P < 0.001 \); Figure 1C).

**Major Bleeding**

A statistically significant increase in bleeding was observed in each trial individually, with the most substantial increase observed in the EXCITE trial, which investigated the role of oral glycoprotein IIb/IIIa antagonism in the setting of PCI. Pooled analysis of the 4 trials reiterates this increased bleeding risk, with an OR of 1.74 (95% CI, 1.52 to 2.00; \( P < 0.001 \); Figure 1D).

**Low-Dose Versus High-Dose Therapy**

A total of 15 431 patients were treated with either low-dose glycoprotein IIb/IIIa inhibition (with or without aspirin) or aspirin alone. Compared with aspirin, pooled analysis of the low-dose arms indicates a significant increase in mortality, with an OR of 1.32 (95% CI, 1.01 to 1.73; \( P = 0.046 \)). As with the overall analysis, with low-dose therapy the risk of MI was increased while the need for urgent revascularization was reduced, although both analyses did not demonstrate statistical significance. Analysis of patients randomized to high-dose therapy (with or without aspirin) compared with aspirin alone involves 25 614 patients and indicates an even greater effect on mortality than observed with low-dose therapy. Mortality was increased by an OR of 1.40 (95% CI, 1.14 to 1.73; \( P = 0.002 \)) with high-dose oral glycoprotein IIb/IIIa therapy. On pooled analysis, a significant effect on MI was not evident; a more prominent benefit with respect to urgent revascularization was observed with high-dose therapy (OR, 0.71; 95% CI, 0.62 to 0.82; \( P < 0.001 \); Figure 2).

**Aspirin Versus No Aspirin**

A total of 13 574 patients were included in the analysis of oral glycoprotein IIb/IIIa antagonist without aspirin compared with aspirin alone. In the absence of concurrent aspirin...
therapy, the risks of death and MI are significantly increased with oral glycoprotein IIb/IIIa inhibitor therapy, with ORs of 1.34 (95% CI, 1.04 to 1.74; \(P = 0.026\)) and 1.18 (95% CI, 1.16 to 1.37; \(P = 0.030\)), respectively. Oral glycoprotein IIb/IIIa inhibition without concurrent aspirin therapy provided a reduction in urgent revascularization (OR, 0.80; 95% CI, 0.65 to 0.98; \(P = 0.031\)). Pooled comparison of oral glycoprotein IIb/IIIa therapy and concurrent aspirin arms with those receiving aspirin alone includes 21,983 patients. Increased mortality was observed in the patients receiving combined antplatelet therapy (OR, 1.44; 95% CI, 1.11 to 1.86; \(P = 0.005\)), but a significant increase in MI (OR, 0.95; 95% CI, 0.83 to 1.09; \(P = 0.483\)) was no longer evident. As with the previous analyses, urgent revascularization was reduced with the combined regimens of aspirin and oral glycoprotein IIb/IIIa inhibition (OR, 0.75; 95% CI, 0.64 to 0.87; \(P < 0.001\); Figure 3).

**Heterogeneity**

The Breslow-Day statistic revealed no significant heterogeneity within the analyses of death, MI, or urgent revascularization except for the overall and concurrent aspirin analyses of urgent revascularization (\(P = 0.016\) and \(P = 0.008\), respectively). A nonstatistically significant increase in the urgent revascularization rate within the EXCITE trial is responsible for this effect and was no longer observed when the analysis of urgent revascularization was stratified by dose. Heterogeneity was also evident in the analysis of major bleeding (Breslow-Day statistic, \(P = 0.027\)), again because of the greater OR of bleeding risk observed in the EXCITE trial.

**Discussion**

Contrasting the unquestionable benefits of intravenous glycoprotein IIb/IIIa antagonists, the randomized, placebo-controlled trials with oral glycoprotein IIb/IIIa inhibitors demonstrate a 31% increase in mortality (\(P = 0.001\)) when the entire 33,326-patient clinical experience is combined. In contradistinction, when glycoprotein IIb/IIIa inhibitors are administered with concurrent aspirin, an overall impact on recurrent MI after coronary interventions or in patients presenting with acute coronary syndromes is not observed. Considering the increased bleeding events, which underscores the antiplatelet effect of these agents, these results not only indicate a paradoxical dissociation between inhibition of platelet aggregation and provocation of late adverse events but also demonstrate an isolated increase in mortality, implying the presence of clinically relevant “toxic” mechanisms.

After the initial disappointing results from these trials, several putative explanations have been suggested, including inadequate plasma levels between oral doses, diversity in patient-specific factors, and the lack of concurrent aspirin in some study arms.\(^9\,14\) Compared with intravenous administration, fluctuation in plasma levels with oral dosing may provide subtherapeutic platelet inhibition for a large proportion of the treatment period.\(^11\,12\) Experience with the intrave-
nous glycoprotein IIb/IIIa antagonists clearly supports the association between a high level of platelet inhibition at the time of thromboembolic risk and efficacy with this class of agents.\textsuperscript{15,16} In contrast, compared with the low-dose arms in this analysis, high-dose oral glycoprotein IIb/IIIa inhibition is associated with an even greater fatality risk. Therefore, increased dosing cannot necessarily be expected to deliver superior clinical efficacy.

Individual variation in dose-response may also confound the appropriate therapeutic dosing of these agents.\textsuperscript{11,12} Although the factors contributing to interindividual and intran- duval diversity of dose-response are not well characterized, variation in patient acuity, intrinsic platelet competence, antecedent medications,\textsuperscript{17} and renal function\textsuperscript{12} are likely sources of this diversity. Of particular note, although an increased rate of bleeding may be expected and is reported in patients with reduced renal function, an association with mortality has also been observed with orbofiban therapy.\textsuperscript{7} Nevertheless, attempts to dose according to weight and renal function with sibrafiban have failed to provide superior efficacy and safety over aspirin therapy alone.\textsuperscript{9} Likewise, although patients at increased risk of recurrent coronary events (defined by troponin elevation) derive a greater benefit from intravenous glycoprotein IIb/IIIa inhibition,\textsuperscript{18,19} the oral antagonist trials have not consistently replicated this experience. Subgroup analysis of the Fibrinogen Receptor Occupancy Study Trial (FROST)\textsuperscript{20} showed a greater reduction in cardiac events associated with lefradafiban therapy in patients presenting with troponin elevation. Contrasting this are the large-scale trials in which no incremental benefit was evident in high-risk patients, such as those with unstable angina undergoing PCI in the EXCITE trial\textsuperscript{8} and post-MI patients in the SYMPHONY trial.\textsuperscript{9} Unfortunately, outcomes stratified by troponin elevation at enrollment are currently unavailable in these studies.

Similarly, the increase in mortality was also evident regardless of aspirin coadministration. The increase in MI observed in the treatment arms without concurrent aspirin therapy compared with those receiving concurrent aspirin attests to the importance of aspirin in the treatment of coronary artery disease. Furthermore, without concurrent aspirin, the greater rate of MI may be interpreted by some as evidence for the suggested prothrombotic effects associated with glycoprotein IIb/IIIa inhibitors, corroborating the observation of mortality associated with an increase in thrombotic events reported from OPUS TIMI-16.\textsuperscript{6} Recently, several intravenous and oral glycoprotein IIb/IIIa inhibition–induced prothrombotic mechanisms have been proposed. Although platelet glycoprotein IIb/IIIa blockade effectively prevents platelet aggregation, other platelet functions, such as secretion, procoagulant activity, and platelet-leukocyte interactions, are not necessarily equally impaired and may be potentiated.\textsuperscript{21,22} As with endogenous ligands, binding by these agents induces “outside-to-inside” signals within the receptor-cell membrane complex that influence receptor conformational status and competency, membrane fluidity, and calcium metabolism.\textsuperscript{23} Contrasting the endogenous ligands, these synthetic agents are able to bind both quiescent and competent receptors, thereby possibly contributing to glyco-

protein IIb/IIIa receptor activation, continued procoagulant activity, and P-selectin expression.\textsuperscript{24,25} Continued or augmented prothrombotic activity may therefore explain the synergistic benefit of heparin when combined with orbofiban therapy observed in OPUS TIMI-16.\textsuperscript{7} Adding to this complexity is the finding that the site of binding within the receptor determines, at least in part, the specific secondary signals induced by specific antagonists.\textsuperscript{23} Therefore, these outside-to-inside signals are subclass specific and may even be agent specific, raising the possibility that the negative results observed in the current trials are confined to antagonists of the RGD binding site.

However, contrary to the clinical experience with intravenous glycoprotein IIb/IIIa blockade in which reductions in ischemic end points (death, MI, and urgent revascularization) have paralleled each other,\textsuperscript{1} the impact of oral glycoprotein IIb/IIIa inhibition on these end points is incongruous, both in the trials individually and in the collective analysis. Therefore, these results are not necessarily consistent with prothrombosis and ischemia as the primary basis for this increased mortality risk. The 16% increase in MI observed with oral glycoprotein IIb/IIIa blockade without concurrent aspirin therapy compared with those receiving aspirin alone is commensurate with the expected =25% to 30%\textsuperscript{4,5} increase in these events in the absence of any effective antiplatelet therapy. If clinically relevant prothrombotic mechanisms were to account for the 31% mortality risk, an even greater increase in MI would be expected. Therefore, combined with the reduction in the need for urgent revascularization, unanticipated toxic effects unrelated to platelet activation may provide a more adequate explanation and are supported by evolving evidence. Binding sites for the RGD sequence have been defined in many proteins, including procaspase-3, the precursor to caspase-3, a central signal for cellular apoptosis. Animal studies\textsuperscript{26,27} have documented time- and dose-dependent increases in caspase-3 expression and cardiomyocyte apoptosis when incubated with the RGD peptides, xemilofiban, or orbofiban; this effect is augmented by hypoxic conditions. These effects were not observed with epftibatide or abciximab, suggesting that these nonplatelet toxic effects are specific to the RGD peptide subclass. The role of apoptosis in the fatality risk associated with these agents warrants further investigation.

**Study Limitations**

As inherent in all meta-analyses, heterogeneity among protocols, therapeutic agents studied, and patient populations may be of sufficient diversity to make the results of a comparison among trials inaccurate. However, the Breslow-Day test, which examines the statistical heterogeneity among ORs and therefore assesses the validity of pooling the results from these trials, fails to demonstrate significant diversity among the analyses apart from the pooled urgent revascularization and bleeding analyses. For both of these analyses, the source of heterogeneity appears to be the EXCITE trial, with the neutral effect on urgent revascularization and increased bleeding potentially reflecting the fact that all patients in this study received percutaneous revascularization.
Follow-up duration reported by each study also varies. Nevertheless, the event rates among the studies are similar and consistent with the relatively small accumulation of events between the 30- and 90-day follow-up observed in recent intravenous glycoprotein IIb/IIIa trials. In addition, the ORs for mortality reported by each trial at the differing durations of follow-up are remarkably consistent, and mechanisms contributing to the increased hazard observed with these agents are unlikely to be preferentially operative in the early or late follow-up period.

Conclusions

The disparity between the oral and intravenous glycoprotein IIb/IIIa inhibitor trials is perplexing and requires reconciliation. This analysis indicates a worrisome increase in mortality with the oral agents, which is in stark contrast to the unquestionable benefits provided by short-term intravenous glycoprotein IIb/IIIa therapy. This isolated fatality risk points toward toxic effects rather than prothrombotic mechanisms that have been unanticipated and remain largely unexplained. It is, however, important to consider that each of the current oral glycoprotein IIb/IIIa antagonists studied mediates inhibition via the RGD binding site, and the detrimental effects observed with these agents may not extend to the antagonists binding to alternative sites within the glycoprotein IIb/IIIa receptor. Nevertheless, further understanding of the biological consequences of oral glycoprotein IIb/IIIa blockade should be sought before continued clinical testing is undertaken.

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References

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