Platelet Glycoprotein IIb/IIIa Inhibitors Reduce Mortality in Diabetic Patients With Non–ST-Segment-Elevation Acute Coronary Syndromes

Marco Roffi, MD; Derek P. Chew, MBBS; Debabrata Mukherjee, MD; Deepak L. Bhatt, MD; Jennifer A. White, MS; Christopher Heeschen, MD; Christian W. Hamm, MD; David J. Moliterno, MD; Robert M. Califf, MD; Harvey D. White, DSc; Neal S. Kleiman, MD; Pierre Théroux, MD; Eric J. Topol, MD

Background—Diabetes mellitus is a major risk factor for adverse outcomes after acute coronary syndromes (ACS). Because this disease may be associated with increased platelet aggregation, we investigated whether diabetic patients with ACS derive particular benefit from platelet glycoprotein (GP) IIb/IIIa receptor inhibition.

Methods and Results—We performed a meta-analysis of the diabetic populations enrolled in the 6 large-scale platelet GP IIb/IIIa inhibitor ACS trials: PRISM, PRISM-PLUS, PARAGON A, PARAGON B, PURSUIT, and GUSTO IV. Among 6458 diabetic patients, platelet GP IIb/IIIa inhibition was associated with a significant mortality reduction at 30 days, from 6.2% to 4.6% (OR 0.74; 95% CI 0.59 to 0.92; \( p = 0.007 \)). Conversely, 23,072 nondiabetic patients had no survival benefit (3.0% versus 3.0%). The interaction between platelet GP IIb/IIIa inhibition and diabetic status was statistically significant (\( p = 0.036 \)). Among 1279 diabetic patients undergoing percutaneous coronary intervention (PCI) during index hospitalization, the use of these agents was associated with a mortality reduction at 30 days from 4.0% to 1.2% (OR 0.30; 95% CI 0.14 to 0.69; \( p = 0.002 \)).

Conclusions—This meta-analysis, including the entire large-scale trial experience of intravenous platelet GP IIb/IIIa inhibitors for the medical management of non–ST-segment-elevation ACS, shows that these agents may significantly reduce mortality at 30 days in diabetic patients. Although not based on a randomized assessment, the survival benefit appears to be of greater magnitude in patients undergoing PCI. Therefore, the use of platelet GP IIb/IIIa inhibitors should be strongly considered in diabetic patients with ACS. (Circulation. 2001;104:2767-2771.)

Key Words: diabetes mellitus ■ angina ■ platelets ■ glycoproteins ■ angioplasty

Diabetes mellitus is a major risk factor for cardiovascular morbidity and mortality. The burden of cardiovascular disease associated with this condition will increase dramatically, because the prevalence of diabetes is estimated to double by the year 2025.1 Diabetic patients suffer increased mortality in the setting of ST-segment-elevation myocardial infarction (MI)2,3 and non–ST-segment-elevation acute coronary syndromes (ACS).4

See p 2759

In vitro and ex vivo data suggest that diabetes may be associated with increased platelet aggregation.5,6 The clinical relevance of these observations, however, remains unclear. To investigate whether diabetic patients with ACS derive particular benefit from platelet glycoprotein (GP) IIb/IIIa receptor inhibition, we performed a meta-analysis of the diabetic populations within all large-scale placebo-controlled randomized trials.

Methods

Trial Selection
Six randomized, double-blind, placebo-controlled trials of intravenous platelet GP IIb/IIIa antagonists evaluating the medical management of ACS 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. Six trials testing 4 different agents were identified and included in the analysis. In all the trials, patients received aspirin.
For the purpose of this analysis, patients were assigned to the diabetic or nondiabetic subgroup on the basis of the presence or absence of a history of diabetes mellitus at study enrollment, as identified by the study investigators in the case report forms. The assignment was validated by review of the source documents by the study monitors.

The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) trial randomized 3232 patients to either tirofiban (0.6 µg·kg⁻¹·min⁻¹ for 30 minutes followed by a 0.15-µg·kg⁻¹·min⁻¹ infusion) or unfractionated heparin for 48 hours. Invasive assessment was discouraged within the first 48 hours of randomization. If percutaneous coronary intervention (PCI) was performed, it was recommended that the study drug be discontinued. The primary end point was death or MI at 30 days. Patients were followed up for 30 days in a predefined exploratory analysis. The trial enrolled 687 diabetic patients (21%) of the total population.

The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial randomized 1915 patients to either tirofiban (0.6 µg·kg⁻¹·min⁻¹ for 30 minutes and 0.15-µg·kg⁻¹·min⁻¹ infusion), tirofiban (0.4 µg·kg⁻¹·min⁻¹ for 30 minutes and 0.1-µg·kg⁻¹·min⁻¹ infusion) with heparin, or unfractionated heparin alone, for a duration of ≥48 hours. The arm of the study not including heparin (n=345) was discontinued before completion of the trials and was not included in this analysis. Invasive assessment was deferred for the first 48 hours. In patients undergoing early PCI, the study drug was continued for 12 to 24 hours after intervention. The primary end point was the composite of death, MI, and refractory ischemia at 7 days. A total of 362 patients (23% of the studied population) had diabetes.

The Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON) A trial randomized 2282 patients to lamifiban 300 µg bolus followed by a 1.0-µg·min⁻¹ infusion or 750 µg bolus followed by a 5.0-µg·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 PCI, the study drug was continued for an additional 12 to 24 hours. The primary end point was a composite of death or MI at 30 days. The trial enrolled 412 diabetics (18%).

The PARAGON B trial randomized 5225 patients to lamifiban 500 µg bolus followed by an infusion (1.0 to 2.0 µg·min⁻¹) adjusted for estimated renal function for 72 hours or until discharge, or placebo. All patients received heparin. Coronary angiography and revascularization were performed according to local standards of practice. In patients undergoing early PCI, the study infusion was continued for an additional 18 to 48 hours. The primary end point was death, MI, or severe recurrent ischemia at 30 days. A total of 1157 patients (22%) had diabetes.

Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) randomized 10948 patients to either abciximab 0.25 µg/kg bolus followed by a 0.125-µg·kg⁻¹·min⁻¹ infusion (maximum 10 µg/min) infusion for 24 hours, bolus and infusion for 48 hours, or placebo. All patients received either heparin or low-molecular-weight heparin. Early invasive assessment was strongly discouraged. The primary end point was death or MI at 30 days. The trial enrolled 1677 patients with diabetes (21%). For the purpose of this analysis, the 24-hour-infusion and 48-hour-infusion groups were pooled.

**End Points and Statistical Analysis**

Death and death or nonfatal MI were assessed at 30 days on the basis of an intention-to-treat analysis. The enzyme definitions of MI were creatine kinase (CK) or CK-MB greater than the upper limit of normal (ULN) in PURSUIT; CK or CK-MB >2× ULN in PRISM, PRISM-PLUS, PARAGON A, and PARAGON B; and CK-MB >3× ULN in GUSTO IV. ORs and corresponding 95% CIs 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 ORs across the trials was examined with the Breslow-Day statistic. If the resulting P value was nonsignificant, individual event rates were pooled into an overall rate. A Pearson χ² 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. Logistic regression modeling assessed the interaction of diabetic status with treatment as follows: Log odds=α+β₁X₁+β₂X₂+β₃X₃, where X₁ is the GP IIb/IIIa inhibitor treatment versus placebo, X₂ is diabetic status (yes/no), and X₃ is interaction between treatment and diabetic status. Two-sided, 95% confidence interval CIs were constructed, and an α-level of 0.05 was used to declare statistical significance of the interaction term.

**Results**

The meta-analysis involved a total of 6458 diabetic patients with non-ST-segment-elevation ACS, corresponding to 22% of the enrolled population. Platelet GP IIb/IIIa inhibition was associated with a significant reduction of the aggregate 30-day mortality in diabetic patients, from 6.2% to 4.6% (OR 0.74; 95% CI 0.59 to 0.92; P=0.007) (Figure 1). Within the individual trials, mortality was significantly reduced in GUSTO IV (OR 0.62; P=0.022). The greatest survival benefit was observed in PRISM (OR 0.42), although it did not reach statistical significance (P=0.07). In contrast, among 23 072 nondiabetic patients, platelet GP IIb/IIIa inhibition conferred no survival benefit (3.0% versus 3.0%) (Figure 2).

Logistic regression analysis demonstrated that the interaction between diabetic status and treatment was significant with respect to 30-day mortality (adjusted OR 0.75; P=0.036; Figure 3). Diabetic patients had a significantly higher 30-day mortality (adjusted OR 2.05; P<0.0001).
Treatment was not associated with survival benefit in the overall ACS population (adjusted OR 1.01; \( P = 0.85 \)). The most marked benefit from active therapy was documented in 1279 diabetic patients undergoing PCI during the index hospitalization (20% of the diabetic population). The pooled mortality was 1.2% in patients randomized to active treatment versus 4.0% in patients who received placebo (OR 0.30; 95% CI 0.14 to 0.69; \( P = 0.002 \)) (Figure 4). The lack of heterogeneity of treatment effect across the trials with respect to mortality was demonstrated with Breslow-Day statistics for all the analyses (probability values reported in the figures).

Platelet GP IIb/IIIa inhibition was also associated with a reduction in the composite of death or MI at 30 days in diabetics, reaching statistical significance in PRISM (OR 0.50; \( P = 0.038 \)) and PRISM-PLUS (OR 0.27; \( P = 0.001 \)). Pooling of the ORs led to a statistically significant reduction in the combined end point. Because the Breslow-Day analysis demonstrated heterogeneity (\( P = 0.024 \)), however, the pooled results were not reported (Figure 5). In diabetic patients undergoing PCI, active therapy was associated with a significant reduction of death or MI at 30 days, from 15.8% to 9.9% (OR 0.58; 95% CI 0.41 to 0.82; \( P = 0.002 \)), in the absence of heterogeneity.

GP IIb/IIIa receptor inhibition was associated with similar proportionate reduction in mortality for patients treated with insulin and those on diet or oral hypoglycemic drugs. Accordingly, mortality was reduced from 6.9% to 5.2% (OR 0.74; \( P = 0.14 \)) among 1799 patients on insulin and from 5.8% to 4.3% (OR 0.74; \( P = 0.028 \)) among 4551 diabetics on diet or oral hypoglycemic drugs.

**Discussion**

The burden of cardiovascular morbidity and mortality associated with diabetes is substantial and is likely to steadily increase, because the prevalence of diabetes is estimated to double during the first quarter of the 21st century.\(^1\) Despite control for other risk factors, individuals with diabetes have a 3- to 5-fold greater risk of developing coronary artery disease than nondiabetics.\(^13\) In addition, coronary artery disease associated with diabetes has a more aggressive course. Accordingly, diabetic patients with no history of heart disease have the same risk for cardiovascular death as nondiabetics.\(^14\) In addition, up to 75% of individuals with diabetes will ultimately die of coronary artery disease,\(^13\) and up to 33% of patients with insulin-dependent disease will die by the age of 50 years.\(^15\)

Diabetic patients have increased mortality in the setting of both ST-segment-elevation MI\(^2,3\) and non–ST-segment-elevation ACS.\(^4\) In vitro and ex vivo studies have demonstrated that diabetic patients have increased platelet aggrega-

![Figure 2. OR with 95% CI and corresponding \( P \) values for treatment effect on 30-day mortality among nondiabetic patients with ACS. Values to left of 1.0 indicate a survival benefit.](http://circ.ahajournals.org/)

![Figure 3. Adjusted OR with 95% CIs and corresponding \( P \) values for 30-day mortality by diabetes status, treatment assignment, and their interaction. Values to left of 1.0 indicate a survival benefit.](http://circ.ahajournals.org/)

![Figure 4. OR with 95% CIs and corresponding \( P \) values for treatment effect on 30-day mortality among diabetic patients with ACS undergoing PCI. Values to left of 1.0 indicate a survival benefit of platelet GP IIb/IIIa inhibition.](http://circ.ahajournals.org/)

![Figure 5. OR with 95% CIs and corresponding \( P \) values for treatment effect on 30-day death or MI among diabetic patients with ACS. Values to left of 1.0 indicate a benefit of platelet GP IIb/IIIa inhibition. Because Breslow-Day analysis demonstrates heterogeneity (\( P = 0.024 \)), pooled results are not reported.](http://circ.ahajournals.org/)
tion, although the mechanisms remain unclear. One putative pathway is the oxidation of amino groups by glucose, which ultimately results in the formation of advanced glycation end products. Glycation end products have been shown to enhance the aggregation of human platelets in vitro. In addition, diabetics have larger platelets, an increased number of GP IIb/IIIa receptors on each platelet, and an increased population of activated circulating platelets expressing, among other substances, P-selectin and thrombospondin. These adhesion molecules mediate platelet-leukocyte interactions and therefore are potential triggers of inflammatory response and thrombosis. In addition, the metabolic constellation typical of type 2 diabetes, including hyperglycemia, hypertriglyceridemia, and hyperinsulinemia, has been associated with impaired fibrinolysis. The clinical relevance of these observations, however, remains unclear. Despite baseline increased platelet aggregation, administration of the platelet GP IIb/IIIa inhibitor abciximab led to the same degree of platelet inhibition in diabetics and nondiabetics. From a clinical perspective, encouraging data came from PRISM-PLUS, which demonstrated a significant reduction in death or MI at 30 days associated with the platelet GP IIb/IIIa inhibitor tirofiban in 362 diabetic patients presenting with ACS.

Our analysis, comprising the entire large-scale clinical trial experience of intravenous platelet GP IIb/IIIa inhibitors for the medical management of ACS, demonstrates that these agents significantly reduce mortality at 30 days among diabetic patients. This translates to 1 life saved for every 63 patients treated. The consistency of the survival benefit for diabetics is supported by the lack of heterogeneity of ORs across the trials. Furthermore, the significant interaction between diabetes status and platelet GP IIb/IIIa treatment strongly suggests an independent link between the disease and therapeutic effect. The most marked survival advantage conferred by platelet GP IIb/IIIa inhibitors is observed in diabetic patients undergoing PCI during index hospitalization. This translates to 1 life saved for every 36 patients revascularized percutaneously.

It remains speculative whether the increased platelet aggregation described in diabetic patients is related to the survival advantage observed in our analysis. Other than aspirin, no antithrombotic therapy or revascularization strategy has been associated with a survival benefit in non-ST-segment-elevation ACS. Previous analyses have shown that abciximab reduced mortality in all patients randomized to coronary stenting, and particularly in diabetics. The 1-year follow-up of EPISTENT reported a mortality reduction from 2.4% to 1.0% associated with abciximab in patients randomized to coronary stenting (P=0.037). A pooled analysis of EPIC, EPILOG, and EPISTENT showed a mortality reduction from 4.5% to 2.5% (P=0.031) at 1 year in diabetic patients undergoing PCI. Importantly, our data expand these observations to the field of ACS and to other platelet GP IIb/IIIa inhibitors. The weight of evidence that this meta-analysis adds to the existing literature is outlined by the large number of patients and events (339 deaths) involved.

The lack of mortality reduction seen in nondiabetics should not lead to the conclusion that GP IIb/IIIa receptor inhibitor use in the medical management of non-ST-segment-elevation ACS should be limited to diabetic patients. Other subgroups, such as patients presenting with troponin elevation, have been shown to derive particular benefit from these agents in some, albeit not all, trials. Future research should be devoted to identifying other subgroups of ACS patients who may derive greater benefit from these potent and efficacious drugs.

Limitations
Inherent to all meta-analyses, the included trials differed in design, inclusion criteria, therapeutic agents, regimens, and access to percutaneous revascularization, among others. The Breslow-Day test, however, which provides information about the validity of pooling the results from different trials, failed to demonstrate significant heterogeneity among treatment effects with respect to mortality reduction. The enzyme definition of MI was not uniform across the trials, and we cannot exclude the possibility that different cutoff points for enzyme elevation may have influenced the incidence of events and possibly the extent of therapeutic benefit. Despite that, the end-point definitions of the trials were respected so as to consider only adjudicated events. Of note, in PRISM, the primary end points were assessed at 48 hours and in PRISM-PLUS, at 7 days. In both trials, however, all 30-day events were adjudicated.

Finally, our report carries the limitations of subgroup analysis. Accordingly, the clinical trials addressed were not designed to evaluate treatment in diabetic patients. The present study represents a univariate analysis, focusing on diabetes, and should therefore be considered as exploratory. In addition, because the revascularization strategy was not randomized, the survival advantage associated with platelet GP IIb/IIIa inhibitors in patients undergoing PCI may have been influenced by selection bias. Therefore, this finding should be considered hypothesis-generating, and it requires independent validation.

Conclusions
This meta-analysis, including the entire large-scale trial experience of intravenous platelet GP IIb/IIIa inhibitors in the medical management of non-ST-segment-elevation ACS, demonstrates that these agents may significantly reduce mortality at 30 days among diabetic patients. Although not based on a randomized assessment, the survival advantage appears to be particularly marked in patients undergoing PCI. Therefore, the use of platelet GP IIb/IIIa inhibitors should be strongly considered in diabetic patients with ACS.

Acknowledgments
Dr Roffi was supported by a research grant from the Swiss National Science Foundation. The authors would like to acknowledge Peter M. DiBattiste, MD, and Steven Snapinn, PhD, Merck Research Laboratories, West Point, Pa, for providing the data from PRISM and PRISM-PLUS; Suzanne Turner, Cardiovascular Graphics Department, The Cleveland Clinic Foundation, for providing assistance with graphics; and Donna Bressan, The Cleveland Clinic Foundation, for editorial assistance.
References
Platelet Glycoprotein IIb/IIIa Inhibitors Reduce Mortality in Diabetic Patients With Non–ST-Segment-Elevation Acute Coronary Syndromes

Marco Roffi, Derek P. Chew, Debabrata Mukherjee, Deepak L. Bhatt, Jennifer A. White, Christopher Heeschen, Christian W. Hamm, David J. Moliterno, Robert M. Califf, Harvey D. White, Neal S. Kleiman, Pierre Théroux and Eric J. Topol

Circulation. 2001;104:2767-2771
doi: 10.1161/hc4801.100029

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/104/23/2767

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/