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# Lack of Clopidogrel Pretreatment Effect on the Relative Efficacy of Bivalirudin With Provisional Glycoprotein IIb/IIIa Blockade Compared to Heparin With Routine Glycoprotein IIb/IIIa Blockade

## A REPLACE-2 Substudy

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**OBJECTIVES** The purpose of this study was to assess if clopidogrel pretreatment affects the relative efficacy of bivalirudin versus heparin with glycoprotein (GP) IIb/IIIa blockade for percutaneous coronary interventions (PCI).

**BACKGROUND** Although thienopyridine pretreatment may improve clinical outcomes with PCI, it is unknown if bivalirudin's efficacy compared with heparin is dependent upon such pretreatment.

**METHODS** The Randomized Evaluation in Percutaneous coronary intervention Linking Angiomax to reduced Clinical Events (REPLACE-2) trial was a double-blind, triple-dummy, randomized-controlled trial comparing heparin plus routine GP IIb/IIIa blockade (heparin group) with bivalirudin plus provisional GP IIb/IIIa blockade (bivalirudin group) during PCI. The primary end point was a composite of death, myocardial infarction (MI), urgent revascularization at 30 days, and major in-hospital bleeding. The secondary end point was a 30-day composite of death, MI, and urgent revascularization. Clopidogrel pretreatment was encouraged (300 mg loading, 75 mg/day).

**RESULTS** Of 6,010 patients enrolled, 5,893 received clopidogrel, with 85.8% in the bivalirudin and 84.6% in the heparin group receiving clopidogrel pretreatment. Bivalirudin (provisional GP IIb/IIIa blockade 7.2%) was noninferior to the heparin group for both primary and secondary end points. Clopidogrel pretreatment did not affect the relative efficacy of bivalirudin versus heparin with GP IIb/IIIa blockade, irrespective of pretreatment duration. Pretreatment was associated with significantly lower primary end point with bivalirudin (8.7% pretreatment vs. 12.9% no pretreatment, $p = 0.007$), and nonsignificantly with heparin (9.7% vs. 11.7%, respectively, $p = 0.20$). Multivariable models showed a trend toward lower primary and secondary end points with clopidogrel pretreatment.

**CONCLUSIONS** Clopidogrel pretreatment at the doses and time administered in this trial did not influence the relative efficacy of bivalirudin versus heparin plus GP IIb/IIIa blockade for PCI. However, pretreatment was associated with a trend towards lower clinical events after PCI. (J Am Coll Cardiol 2004;44:1194–9) © 2004 by the American College of Cardiology Foundation

The combination of antiplatelet and antithrombin therapy is crucial during percutaneous coronary interventions (PCI). Randomized-controlled trials have established that triple antiplatelet therapy (aspirin, thienopyridine, and glycoprotein [GP] IIa/IIIb blockade) is efficacious and safe with PCI in conjunction with a thrombin inhibitor. Furthermore, recent evidence supports enhanced benefit with thienopyridine treatment before PCI in reducing short- and long-term clinical events (1–4). Bivalirudin, a direct thrombin inhibitor, is an alternative to heparin that was approved by the U.S. Food and Drug Administration in 2000 for patients with unstable angina undergoing PCI. More recently, the Randomized Evaluation in Percutaneous coronary intervention Linking Angiomax to Reduced Clinical Events (REPLACE-2) trial demonstrated bivalirudin with provisional use of a GP IIb/IIIa antagonist to be superior to heparin alone and noninferior to the combination of heparin and routine GP IIb/IIIa blockade during PCI (5). All patients in this trial received aspirin and a thienopyridine. Prior trial data supporting the important role of platelet inhibition during PCI raised the question of whether thienopyridine pretreatment (to attain a higher degree of platelet inhibition during PCI) was essential for the strategy of bivalirudin with provisional GP IIb/IIIa inhibition to achieve efficacy comparable with heparin with planned GP IIb/IIIa blockade. We, therefore, performed a post-hoc analysis of the REPLACE-2 trial to evaluate if clopidogrel

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**Abbreviations and Acronyms**

| | |
|---|---|
| GP | = glycoprotein |
| MI | = myocardial infarction |
| OR | = odds ratio |
| PCI | = percutaneous coronary intervention |
| REPLACE-2 | = Randomized Evaluation in Percutaneous coronary intervention Linking Angiomax to reduced Clinical Events |

pretreatment affects the relative efficacy of bivalirudin compared with heparin plus GP IIb/IIIa blockade.

## METHODS

**The REPLACE-2 trial design.** The design, methods, and primary results of the REPLACE-2 trial have been described in detail (5). Briefly, 6,010 patients undergoing urgent or elective PCI with approved devices were enrolled in this double-blind, triple-dummy, randomized-controlled trial between October 2001 and August 2002 from 233 hospitals in 9 countries. Patients were randomized to the reference standard of heparin (65 U/kg, maximum 7,000 U) plus routine GP IIb/IIIa blockade (either abciximab or eptifibatide) (heparin group) or bivalirudin (0.75 mg/kg bolus, 1.75 mg/kg/h infusion) with provisional GP IIb/IIIa blockade (bivalirudin group) during PCI. The primary end point was a composite of death, myocardial infarction (MI), urgent revascularization, or major in-hospital bleeding by 30 days. The secondary end point was a 30-day composite of death, MI, and urgent revascularization. The MI end point was defined as new significant Q waves in ≥2 contiguous electrocardiogram leads, or creatine kinase/creatine kinase-MB elevation ≥3× upper limit of normal. Major bleeding was defined as clinically significant hemorrhage (intracranial, intraocular, retroperitoneal, or with hemoglobin decrease >3 g/dl), any hemoglobin decrease >4 g/dl, or transfusion of ≥2 U of blood. Minor bleeding was any clinically overt bleeding that did not meet major bleeding criteria.

All patients were to be treated with aspirin. Clopidogrel treatment (300 mg orally) was encouraged up to 24 h before PCI, followed by 75 mg/day for at least 30 days, although ticlopidine was permitted instead. The timing of clopidogrel treatment was documented in the case report form. The effects of clopidogrel pretreatment duration on efficacy (primary and secondary) and safety (major and minor bleeding) end points were examined for both the bivalirudin and heparin groups.

**Statistics.** Analyses included all patients with available end point data, excluding those who received ticlopidine instead of clopidogrel. Hypothesis testing was done using two-sided tests at the 5% significance level. Baseline characteristics were compared using chi-square and Fisher exact tests for discrete variables, and *t* test or Wilcoxon rank-sum for continuous variables. Odds ratio (OR) with corresponding 95% confidence interval were provided. Multivariable logistic models for the primary and secondary end points were developed to evaluate the effect of clopidogrel pretreatment after adjusting for these variables: age, diastolic blood pressure ≥60 mm Hg, body mass index <31, diabetes mellitus, low-molecular-weight heparin use before PCI within 48 h, provisional drug use, enrollment sites (Canada, Europe, Middle East, Northeast U.S., Southeast U.S.), and actual treatment group. A propensity analysis of clopidogrel pretreatment was performed (C-statistic 0.68 for this model), and the probability of having received clopidogrel was incorporated into the adjusted logistic models. The interaction between clopidogrel pretreatment and study drug was also tested in the model. Analyses were performed using SAS statistical software (version 8.2, SAS Institute, Cary, North Carolina).

## RESULTS

**Patient characteristics.** A total of 5,997 patients in the REPLACE-2 trial were treated with a thienopyridine, with 5,893 receiving clopidogrel (the 104 who received ticlopidine were excluded from our analysis). Of these, 5,052 received at least one dose of clopidogrel before the PCI (85.8% in bivalirudin group, 84.6% heparin group). Baseline demographics are described in Table 1. There were higher incidences of diabetes mellitus, female gender, provisional GP IIb/IIIa blockade, and stenting in the clopidogrel pretreatment group. Clopidogrel pretreatment timing was recorded in 97.7% of patients; GP IIb/IIIa blockade was administered to all patients in the heparin group and 7.2% (on a provisional basis) of patients in the bivalirudin arm.

**Primary 30-day end point (death/MI/urgent revascularization/major bleeding).** In the overall REPLACE-2 trial, bivalirudin was not inferior to heparin plus GP IIb/IIIa blockade with regard to the composite 30-day quadruple end point (9.2% vs. 10.0%, respectively, OR = 0.92, p = 0.32). Pretreatment with clopidogrel, irrespective of the timing of preadministration, did not affect the relative efficacy of bivalirudin compared with heparin (Fig. 1). Among patients randomized to bivalirudin, clopidogrel pretreatment was associated with lower primary event rates compared with no pretreatment, with a similar nonsignificant trend in those randomized to heparin (Fig. 2). In the multivariable model including the propensity score, clopidogrel pretreatment demonstrated a trend toward lower primary events (OR = 0.82, p = 0.119). The interaction test between clopidogrel pretreatment and study drug randomization was not significant (p = 0.47), indicating no difference in primary end point outcomes between treatment groups, regardless of clopidogrel pretreatment.

**Secondary 30-day end point (death/MI/urgent revascularization).** In the overall REPLACE-2 trial population, the secondary end point of death, MI, or urgent revascularization was noninferior with bivalirudin compared with heparin plus routine GP IIb/IIIa blockade (7.6% vs. 7.1%, respectively, OR = 1.09, p = 0.396). Similarly, clopidogrel

**Table 1.** Baseline Demographics for Patients Receiving Clopidogrel in the REPLACE-2

| | No Clopidogrel Pretreatment (n = 841) | Clopidogrel Pretreatment (n = 5,052) | p Value |
|---|---|---|---|
| Age, mean (SD), yrs | 63.2 (11.1) | 62.5 (10.9) | 0.101 |
| Female, n (%) | 239 (28.4) | 1,272 (25.2) | 0.046 |
| Weight, mean (SD), kg | 88.2 (18.7) | 87.4 (18.1) | 0.216 |
| BMI, mean (SD), $kg/m^2$ | 29.7 (6.6) | 29.7 (5.9) | 0.806 |
| Caucasian race, n (%) | 786 (93.5) | 4,661 (92.3) | 0.223 |
| Clinical history, n/N (%) | | | |
| Prior myocardial infarction | 289/832 (34.7) | 1,860/4,957 (37.5) | 0.125 |
| Prior PCI | 320/839 (38.1) | 1,742/5,028 (34.6) | 0.050 |
| Prior CABG | 161/841 (19.1) | 922/5,047 (18.3) | 0.544 |
| History of angina | 643/832 (77.3) | 3,808/4,992 (76.3) | 0.529 |
| Prior cerebrovascular accident | 22/837 (2.6) | 118/5,046 (2.3) | 0.610 |
| History of hypertension | 560/837 (66.9) | 3,395/5,036 (67.4) | 0.771 |
| Prior congestive heart failure | 59/838 (7.0) | 353/5,007 (7.1) | 0.992 |
| Smoking during past year | 222/825 (26.9) | 1,300/4,956 (26.2) | 0.682 |
| Diabetes mellitus | 197/839 (23.5) | 1,408/5,044 (27.9) | 0.008 |
| Intervention attempted, n/N (%) | | | |
| PCI | 791/841 (94.1) | 4902/5,052 (97.0) | < 0.001 |
| Stent | 672/836 (80.4) | 4,365/4,999 (87.3) | < 0.001 |
| Balloon only | 89/836 (10.6) | 375/4,999 (7.5) | 0.002 |
| Atherectomy | 34/831 (4.1) | 195/4,983 (3.9) | 0.807 |
| Provisional GPIIb/IIIa inhibitors | 40/841 (4.8) | 333/5,052 (6.6) | 0.043 |

BMI = body mass index; CABG = coronary artery bypass surgery; GP = glycoprotein; PCI = percutaneous coronary interventions; REPLACE-2 = Randomized Evaluation in PCI Linking Angiomax to reduced Clinical Events trial.

pretreatment, irrespective of timing of preadministration, did not affect the relative efficacy of bivalirudin compared with heparin (Fig. 3). Among those randomized to bivalirudin or heparin, there was a trend toward lower secondary end point events among patients who received clopidogrel pretreatment compared with no pretreatment (Fig. 2). In the multivariable analysis including the propensity score, clopidogrel pretreatment demonstrated a nearly significant trend toward lower secondary events (OR = 0.78, p = 0.076). The individual end points of death, MI, urgent revascularization, or death/MI were not different between treatment groups according to clopidogrel pretreatment (Table 2).

**Bleeding.** Randomization to bivalirudin was associated with reduced major bleeding (2.4% vs. 4.1%, respectively, $p < 0.001$), minor bleeding (13.4% vs. 25.7%, respectively, $p < 0.001$), and transfusion requirements (1.6% vs. 2.5%, respectively, $p = 0.023$) compared with heparin in the entire REPLACE-2 trial population. Clopidogrel pretreatment duration (≥6 or <6 h) did not affect the benefit of bivalirudin compared with heparin for both major and minor bleeding events (Table 3).

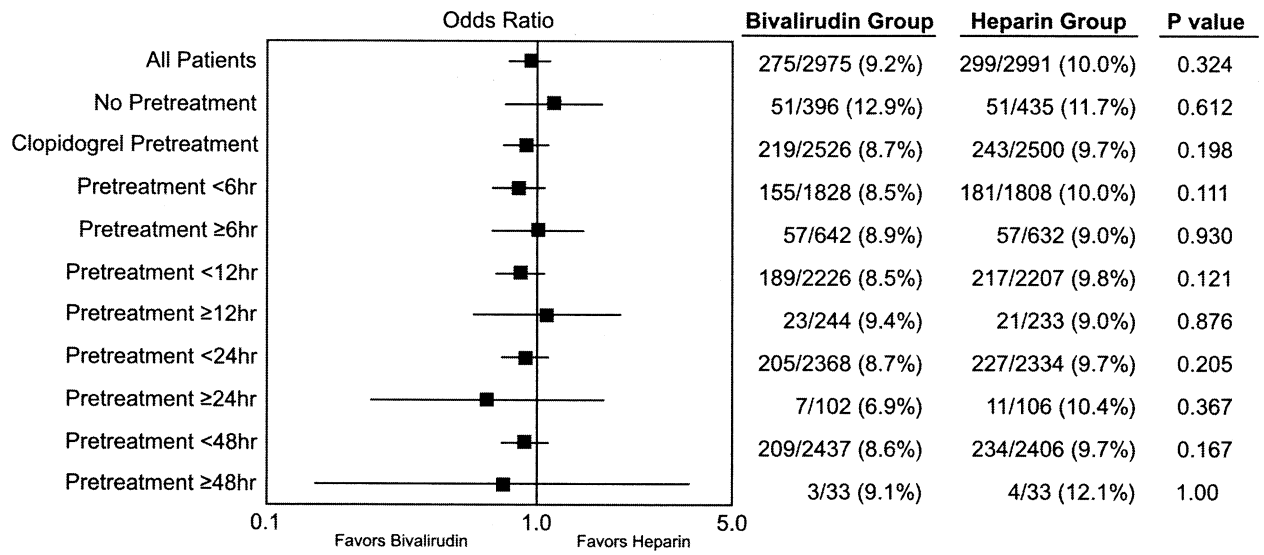


**Figure 1.** Comparison of bivalirudin with provisional glycoprotein (GP) IIb/IIIa blockade versus heparin with routine GP IIb/IIIa blockade with respect to the primary composite end point of death, myocardial infarction, urgent revascularization, and in-hospital major bleeding by 30 days in the Randomized Evaluation in Percutaneous coronary intervention Linking Angiomax to reduced Clinical Events (REPLACE-2) trial.

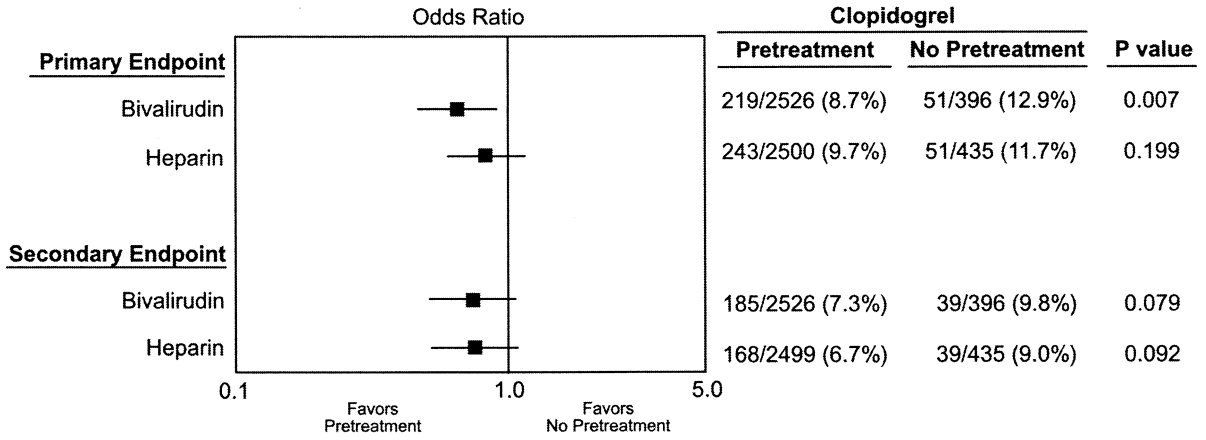


**Figure 2.** Comparison of clopidogrel pretreatment versus no pretreatment with respect to 30-day primary (death, myocardial infarction, urgent revascularization, and in-hospital major bleeding) and secondary (death, myocardial infarction, and urgent revascularization) end points in patients randomized to bivalirudin plus provisional glycoprotein (GP) IIb/IIIa blockade or heparin plus routine GP IIb/IIIa blockade.

**Analysis including patients who received ticlopidine.** Reanalysis of outcomes with the inclusion of patients who received ticlopidine in the "no clopidogrel pretreatment" group showed no difference in any of the end points (data not shown).

## DISCUSSION

The REPLACE-2 trial validated bivalirudin plus provisional GP IIb/IIIa blockade as an alternative anticoagulant regimen to heparin plus planned GP IIb/IIIa blockade during urgent or elective PCI. This substudy of the REPLACE-2 trial focused on the role of clopidogrel pretreatment with both these treatment strategies. Although administration of clopidogrel before PCI was associated with a trend toward lower rates of periprocedural ischemic events for patients who received either bivalirudin or heparin plus GP IIb/IIIa blockade, bivalirudin with provisional GP IIb/IIIa blockade was noninferior to heparin plus planned GP IIb/IIIa blockade in all subgroups irrespective of pretreatment or the duration of pretreatment. Moreover, there was no evidence that clopidogrel pretreatment attenuated the reduction in bleeding complications by bivalirudin. Therefore, clopidogrel pretreatment appears to improve clinical outcomes without compromising safety, but is not required for bivalirudin to achieve efficacy similar to heparin plus GP IIb/IIIa blockade.

Our substudy is concordant with previous studies (post-hoc analyses or randomized trials) suggesting the benefit of thienopyridine pretreatment for PCI. Steinhubl and colleagues (1) showed that ticlopidine pretreatment reduced the composite of death, MI, or target vessel revascularization at one year (adjusted hazard ratio 0.73, p = 0.036) in

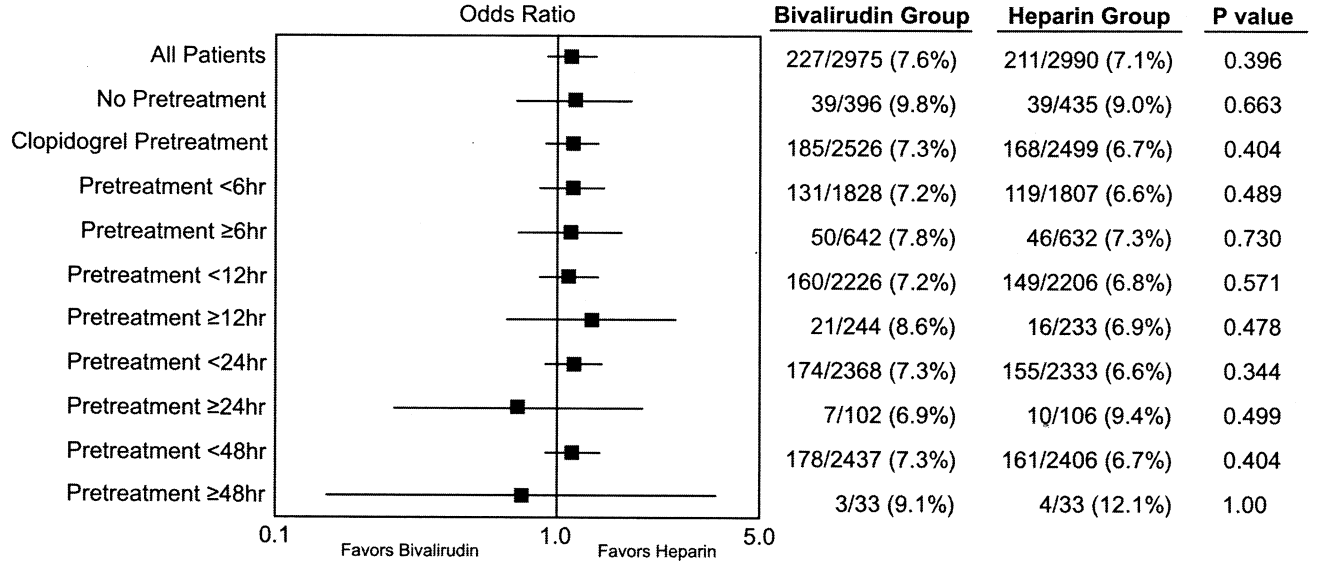


**Figure 3.** Comparison of bivalirudin with provisional glycoprotein (GP) IIb/IIIa blockade versus heparin with routine GP IIb/IIIa blockade with respect to the secondary composite end point of death, myocardial infarction, and urgent revascularization at 30 days in the Randomized Evaluation in Percutaneous coronary intervention Linking Angiomax to reduced Clinical Events (REPLACE-2) trial.

**Table 2.** Odds Ratios of Individual and Composite End-Points According to Clopidogrel Pretreatment

| End Points | All Patients (n = 6,002) | No Clopidogrel Pretreatment (n = 841) | Clopidogrel Pretreatment (n = 5,052) |
|---|---|---|---|
| Death | | | |
| Bivalirudin | 7/2,986 (0.2%) | 0/399 (0.0%) | 7/2,538 (0.3%) |
| Heparin/GP IIb/IIIa | 12/3,000 (0.4%) | 1/439 (0.2%) | 11/2,507 (0.4%) |
| Odds ratio | 0.59 | 0.37 | 0.63 |
| p value | 0.26 | 1.00 | 0.33 |
| MI | | | |
| Bivalirudin | 207/2,975 (7.0%) | 35/397 (8.8%) | 170/2,533 (6.7%) |
| Heparin/GP IIb/IIIa | 185/2,990 (6.2%) | 35/439 (8.0%) | 146/2,505 (5.8%) |
| Odds ratio | 1.13 | 1.12 | 1.16 |
| p value | 0.23 | 0.66 | 0.20 |
| Urgent Revascularization | | | |
| Bivalirudin | 35/2,975 (1.2%) | 6/397 (1.5%) | 28/2,533 (1.1%) |
| Heparin/GP IIb/IIIa | 42/2,990 (1.4%) | 3/439 (0.7%) | 38/2,505 (1.5%) |
| Odds ratio | 0.84 | 2.23 | 0.73 |
| p value | 0.44 | 0.32 | 0.20 |
| Death/MI | | | |
| Bivalirudin | 209/2,392 (7.1%) | 35/397 (8.8%) | 174/2,533 (6.9%) |
| Heparin/GP IIb/IIIa | 186/2,947 (6.3%) | 36/439 (8.2%) | 150/2,505 (6.0%) |
| Odds ratio | 1.14 | 1.08 | 1.16 |
| p value | 0.21 | 0.75 | 0.20 |
| Death/MI/urgent revascularization | | | |
| Bivalirudin | 227/2,975 (7.6%) | 39/396 (9.8%) | 185/2,526 (7.3%) |
| Heparin/GP IIb/IIIa | 211/2,990 (7.1%) | 39/435 (9.0%) | 168/2,499 (6.7%) |
| Odds ratio | 1.09 | 1.11 | 1.10 |
| p value | 0.4 | 0.66 | 0.40 |
| Death/MI/urgent revascularization/major bleed | | | |
| Bivalirudin | 275/2,975 (9.2%) | 51/396 (12.9%) | 219/2,526 (8.7%) |
| Heparin/GP IIb/IIIa | 299/2,991 (10.0%) | 51/435 (11.7%) | 243/2,500 (9.7%) |
| Odds ratio | 0.92 | 1.11 | 0.88 |
| p value | 0.32 | 0.61 | 0.20 |

GP = glycoprotein; MI = myocardial infarction.

a retrospective analysis of the Evaluation of Platelet IIb/IIIa Inhibition in Stenting (EPISTENT) trial. The Percutaneous Coronary Intervention-Clopidogrel in Unstable angina to prevent Recurrent Events (PCI-CURE) was a prespecified subgroup analysis of the CURE trial that suggested that clopidogrel pretreatment (median 10 days before PCI) was beneficial in patients with non–ST-segment elevation MI who underwent PCI (reduction of cardiovascular death, MI, or urgent target-vessel revascularization by 30% within 30 days of PCI, p = 0.03) (2). However, the Clopidogrel for

**Table 3.** Bleeding Complications

| | Bivalirudin Group | Heparin Group | p Value |
|---|---|---|---|
| Major bleeding, n/N (%) | | | |
| All REPLACE-2 patients | 71/2,993 (2.4) | 123/3,008 (4.1) | < 0.001 |
| No pretreatment | 19/400 (4.8) | 19/441 (4.3) | 0.758 |
| Clopidogrel pretreatment | 50/2,540 (2.0) | 102/2,511 (4.1) | < 0.001 |
| Pretreatment <6 h | 37/1,838 (2.0) | 80/1,813 (4.4) | < 0.001 |
| Pretreatment ≥6 h | 10/645 (1.6) | 19/638 (3.0) | 0.085 |
| Minor bleeding, n/N (%) | | | |
| All REPLACE-2 patients | 400/2,993 (13.4) | 772/3,008 (25.7) | < 0.001 |
| No pretreatment | 55/400 (13.8) | 116/441 (26.3) | < 0.001 |
| Clopidogrel pretreatment | 344/2,540 (13.5) | 645/2,511 (25.7) | < 0.001 |
| Pretreatment <6 h | 251/1,838 (13.7) | 478/1,813 (26.4) | < 0.001 |
| Pretreatment ≥6 h | 91/645 (14.1) | 161/638 (25.2) | < 0.001 |
| Transfusions, n/N (%) | | | |
| All REPLACE-2 patients | 48/2,940 (1.6) | 73/2,952 (2.5) | 0.023 |
| No pretreatment | 8/400 (2.0) | 9/441 (2.0) | 0.966 |
| Clopidogrel pretreatment | 40/2,540 (1.6) | 64/2,511 (2.5) | 0.015 |
| Pretreatment <6 h | 32/1,838 (1.7) | 48/1,813 (2.6) | 0.061 |
| Pretreatment ≥6 h | 6/645 (0.9) | 14/638 (2.2) | 0.068 |

REPLACE-2 = Randomized Evaluation in Percutaneous coronary interventions Linking Angiomax to reduced Clinical Events trial.

the Reduction of Events During Observation (CREDO) trial did not show a significant reduction in the 28-day composite of death, MI, and target vessel revascularization with clopidogrel pretreatment compared with placebo pretreatment, although a post-hoc analysis of those who received clopidogrel ≥6 h before PCI demonstrated a 39% reduction in the 28-day events ($p = 0.051$) (3). Because bivalirudin produces less intense inhibition of platelet aggregation than a regimen of heparin plus GP IIb/IIIa blockade, the results of the REPLACE-2 trial raised the question of whether clopidogrel pretreatment is necessary for bivalirudin to be noninferior to heparin plus GP IIb/IIIa blockade. Our study suggests that clopidogrel pretreatment is beneficial for both patients who receive bivalirudin or heparin plus GP IIb/IIIa blockade, but clopidogrel pretreatment does not affect the relative efficacy of these two therapeutic regimens.

Possible mechanisms of bivalirudin's clinical efficacy include better antithrombin activity (ability to inhibit both fibrin-bound and fluid-phase thrombin) and inhibition of thrombin-mediated platelet aggregation and activation (6,7). Possibly more important in this setting is that it does not produce dose-dependent augmentation of platelet activation and aggregation. In contrast, heparin does not inhibit fibrin-bound thrombin, and in vitro studies have shown that heparin can induce platelet aggregation (8).

A potential pitfall in our REPLACE-2 substudy is the probable suboptimal dosing and timing of clopidogrel administration before coronary intervention. The recent Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment (ISAR-REACT) trial (9) demonstrated that a 600-mg loading dose of clopidogrel was as effective compared with GP IIb/IIIa blockade (using abciximab) in a randomized trial of low-risk patients undergoing PCI. Before this trial these investigators (10) had shown that a 600-mg dose of clopidogrel achieved maximal ADP-induced platelet aggregation much more rapidly compared with a 300-mg dose used in our study. Further analysis of the CREDO trial also showed that, with a 300-mg loading dose, maximal platelet inhibition was not achieved until 15 h after initiation (11). Accordingly, the results of the current study have to be viewed in the context of suboptimal dosing and inadequate clopidogrel pretreatment timing before PCI.

Our study also has other limitations inherent to a retrospective, observational, post-hoc analysis. Pretreatment with clopidogrel was not randomized and is, therefore, subjected to selection bias. There were notable baseline differences, including more diabetics in the clopidogrel pretreatment group. However, multivariable models were performed to adjust for baseline characteristics. Importantly, the REPLACE-2 trial excluded patients who had an MI or unstable angina requiring ongoing GP IIb/IIIa blockade or low-molecular-weight heparin. Thus, our findings regarding the role of thienopyridine pretreatment on the relative effectiveness of bivalirudin should not be extrapolated to these patients at high-risk for thrombotic complications. Furthermore, our study was underpowered to assess the interaction between clopidogrel pretreatment and randomized treatment. However, the bivalirudin group trended to have similar outcome compared with the heparin group, regardless of clopidogrel pretreatment.

In conclusion, clopidogrel pretreatment appears to be associated with lower ischemic events and is a desirable treatment strategy, if possible, before PCI. The choice of bivalirudin versus heparin plus GP IIb/IIIa blockade, however, need not be influenced by whether clopidogrel pretreatment was administered, as the outcomes with these two pharmacologic regimens are comparable irrespective of thienopyridine pretreatment.

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