

Bivalirudin and Provisional Glycoprotein IIb/IIIa Blockade Compared With Heparin and Planned Glycoprotein IIb/IIIa Blockade During Percutaneous Coronary Intervention

REPLACE-2 Randomized Trial

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UNFRACTIONATED HEPARIN HAS been the standard of adjunctive antithrombin therapy during percutaneous coronary intervention (PCI) for more than 25 years. Yet heparin is subject to important intrinsic limitations, including

For editorial comment see p 903.

Context The direct thrombin inhibitor bivalirudin has been associated with better efficacy and less bleeding than heparin during coronary balloon angioplasty but has not been widely tested during contemporary percutaneous coronary intervention (PCI).

Objective To determine the efficacy of bivalirudin, with glycoprotein IIb/IIIa (Gp IIb/IIIa) inhibition on a provisional basis for complications during PCI, compared with heparin plus planned Gp IIb/IIIa blockade with regard to protection from periprocedural ischemic and hemorrhagic complications.

Design, Setting, and Participants The Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial, a randomized, double-blind, active-controlled trial conducted among 6010 patients undergoing urgent or elective PCI at 233 community or referral hospitals in 9 countries from October 2001 through August 2002.

Interventions Patients were randomly assigned to receive intravenous bivalirudin (0.75-mg/kg bolus plus 1.75 mg/kg per hour for the duration of PCI), with provisional Gp IIb/IIIa inhibition (n=2999), or heparin (65-U/kg bolus) with planned Gp IIb/IIIa inhibition (abciximab or eptifibatide) (n=3011). Both groups received daily aspirin and a thienopyridine for at least 30 days after PCI.

Main Outcome Measures The primary composite end point was 30-day incidence of death, myocardial infarction, urgent repeat revascularization, or in-hospital major bleeding; the secondary composite end point was 30-day incidence of death, myocardial infarction, or urgent repeat revascularization.

Results Provisional Gp IIb/IIIa blockade was administered to 7.2% of patients in the bivalirudin group. By 30 days, the primary composite end point had occurred among 9.2% of patients in the bivalirudin group vs 10.0% of patients in the heparin-plus-Gp IIb/IIIa group (odds ratio, 0.92; 95% confidence interval, 0.77-1.09; $P=.32$). The secondary composite end point occurred in 7.6% of patients in the bivalirudin vs 7.1% of patients in the heparin-plus-Gp IIb/IIIa groups (odds ratio, 1.09; 95% confidence interval 0.90-1.32; $P=.40$). Prespecified statistical criteria for noninferiority to heparin plus Gp IIb/IIIa were satisfied for both end points. In-hospital major bleeding rates were significantly reduced by bivalirudin (2.4% vs 4.1%; $P<.001$).

Conclusions Bivalirudin with provisional Gp IIb/IIIa blockade is statistically not inferior to heparin plus planned Gp IIb/IIIa blockade during contemporary PCI with regard to suppression of acute ischemic end points and is associated with less bleeding.

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unpredictable pharmacokinetics, inhibition by plasma proteins, and the potential to activate platelets.¹⁻⁴ Considerable reductions in periprocedural complications have been achieved with

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administration of glycoprotein IIb/IIIa (Gp IIb/IIIa) antagonists in addition to heparin.⁵ These potent platelet inhibitors are not used universally, however, in part because of concerns about cost and increased bleeding risk.

The direct thrombin inhibitor bivalirudin was approved for clinical use in December 2000 as an alternative to heparin for patients with unstable angina during PCI, based primarily on the results of a randomized trial conducted between 1993 and 1994. In that study of 4312 patients, ischemic events were decreased by 22% and hemorrhagic complications by 62% with bivalirudin compared with heparin.^{6,7} The relevance of these data to current interventional practice is unknown, given that coronary artery stents, Gp IIb/IIIa inhibitors, low-dose heparin regimens, and thienopyridines were not used at the time of that trial. Two smaller more contemporary pilot studies did suggest, however, that by replacing heparin with bivalirudin during PCI, adjunctive Gp IIb/IIIa blockade might be used selectively rather than for all patients.^{8,9} If validated, such an approach might offer potential advantages with regard to cost, hemorrhagic risk, and procedural simplicity.

Our current randomized trial was therefore performed to determine if bivalirudin, with Gp IIb/IIIa inhibitors used in a provisional fashion if necessary during the procedure, could provide protection from ischemic and bleeding complications of PCI comparable with the current efficacy standard of low-dose heparin plus routine Gp IIb/IIIa blockade.

METHODS

Patient Population

The Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial was carried out at 233 hospitals in 9 countries. Patients were eligible for entry if they were older than age 21 years and were to undergo PCI with an approved device. Exclusion criteria included PCI performed as reperfusion therapy for acute myocardial infar-

tion, poorly controlled hypertension (blood pressure >180/110 mm Hg), unprotected left main trunk stenosis of more than 50% severity not protected by a patent bypass graft, pregnancy, PCI within the prior month or planned staged PCI within the subsequent month, active internal bleeding or bleeding diathesis, surgery, trauma or gastrointestinal or genitourinary tract bleeding within 6 weeks, prior intracranial bleeding or structural abnormality, platelet count less than $100 \times 10^3/\mu\text{L}$, or renal insufficiency with serum creatinine levels more than 4 mg/dL (353.6 $\mu\text{mol/L}$), or dependency on renal dialysis. Patients were also excluded if they required ongoing warfarin therapy or had been treated with unfractionated heparin within 6 hours (unless activated partial thromboplastin time [aPTT] was ≤ 50 seconds or activated clotting time [ACT] was ≤ 175 seconds), low-molecular-weight heparin within 8 hours, bivalirudin within 24 hours, abciximab within 7 days, or eptifibatid or tirofiban within 12 hours before randomization. The protocol was approved by the institutional review boards at each clinical site, and all patients gave written informed consent.

Study Protocol

All patients received aspirin. Pretreatment with clopidogrel bisulfate, 300 mg, was strongly encouraged 2 to 12 hours before the interventional procedure, followed by daily administration of 75 mg for at least 30 days. Before each patient was randomized, physicians were required to specify on the study database whether abciximab or eptifibatid was to be used as the Gp IIb/IIIa inhibitor in the heparin group or as provisional administration in the bivalirudin group. Patients were randomized in a double-blind fashion by a central telephone system to receive either bivalirudin (with provisional Gp IIb/IIIa blockade) or heparin plus planned Gp IIb/IIIa blockade (FIGURE 1). Bivalirudin was administered as a bolus of 0.75 mg/kg prior to the start of the intervention, followed

by infusion of 1.75 mg/kg per hour for the duration of the procedure. Patients randomized to heparin plus Gp IIb/IIIa received a heparin bolus of 65 U/kg (maximum 7000 U) prior to PCI, with either abciximab (0.25 mg/kg bolus, 0.125 $\mu\text{g/kg}$ per minute [maximum of 10 $\mu\text{g/min}$] infusion for 12 hours) or eptifibatid (two 180- $\mu\text{g/kg}$ boluses 10 minutes apart, 2.0 $\mu\text{g/kg}$ per minute infusion for 18 hours). Double-blinding was maintained by using a double-dummy technique, wherein hospital research pharmacists dispensed identical bivalirudin or heparin bolus syringes, bivalirudin or placebo infusion bags, and a Gp IIb/IIIa inhibitor or placebo bolus and infusion. The ACT was measured on the Hemochron Jr device (ITC, Edison, NJ) 5 minutes after the study drug boluses were administered. An additional bivalirudin (0.3 mg/kg) or heparin (20 U/kg) bolus was given if the ACT was less than 225 seconds; a matching saline placebo bolus was administered if the ACT was 225 seconds or higher.

Provisional Gp IIb/IIIa blockade with the agent chosen prior to randomization could be administered for procedural or angiographic complications at any time during the PCI using a blinded bolus plus infusion of active drug (in the bivalirudin group) or placebo (in the heparin plus Gp IIb/IIIa group). Suggested indications for provisional Gp IIb/IIIa use included, but were not restricted to, abrupt or side-branch closure, obstructive dissection, new or suspected thrombus, impaired or slow coronary flow, distal embolization, persistent residual stenosis, unplanned stent placement, prolonged ischemia, or other clinical instability. Unless an approved closure device was used, vascular access sheaths were to be removed following the procedure once the ACT was 175 seconds or less or the aPTT was 50 seconds or less.

Study End Points

The primary end point was a quadruple composite of death, myocardial infarction, severe myocardial ischemia requiring urgent surgical or repeat per-

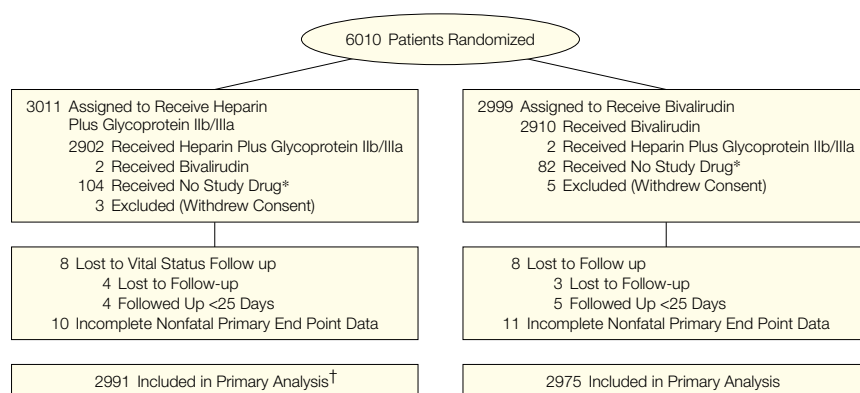
cutaneous coronary revascularization, or in-hospital major bleeding within 30 days of randomization. A secondary composite end point was confined to the triple ischemic components of death, myocardial infarction, or urgent revascularization by 30 days. End point myocardial infarction was defined by new significant Q waves in 2 or more contiguous electrocardiographic leads or elevation in creatine kinase (CK) levels or CK-MB (obtained in all patients every 8 hours for the 24 hours after the procedure) to 3 or more times the upper limit of local normal within 2 days of revascularization or to 2 or more times the upper limit of normal outside of the setting of revascularization.

Major bleeding was defined as intracranial, intraocular, or retroperitoneal hemorrhage, clinically overt blood loss resulting in a decrease in hemoglobin of more than 3 g/dL, any decrease in hemoglobin of more than 4 g/dL, or transfusion of 2 or more units of packed red blood cells or whole blood. Minor bleeding was defined as clinically overt bleeding that did not meet criteria for major bleeding. Bleeding was also classified according to the criteria of the Thrombolysis in Myocardial Infarction (TIMI) study group.¹⁰ To account for the influence of red blood cell transfusions, estimated decreases in hemoglobin were adjusted according to the technique described by Landefeld et al.¹¹ End point classifications were made by a blinded clinical events committee.

Statistical Analysis

The objective of this trial was to determine if bivalirudin with provisional Gp IIb/IIIa blockade was not inferior to the current efficacy standard of heparin plus Gp IIb/IIIa and was superior to heparin alone with regard to the primary quadruple composite end point. Given the strength of evidence supporting Gp IIb/IIIa blockade over heparin alone, it was considered unethical to randomize patients in this trial to receive heparin monotherapy. An indirect comparison of the bivalirudin group to an imputed heparin control was therefore made. Using a random-effects

Figure 1. Flow Diagram of Patients Through 30 Days of Follow-up



*Denotes patients received no blinded study drug due to no percutaneous intervention performed, physician preference, or other reasons; open-label agents were administered in some of these patients.

†Complete data were available for 2990, but bleeding data were available for 1 additional patient who reached the end point of the quadruple composite.

meta-analysis of the data sets from 2 recent trials of abciximab¹² or eptifibatid¹³ vs heparin during coronary stenting (with end point definitions consistent with those in our trial), a combined odds ratio (OR) of 0.68 (95% confidence interval [CI], 0.55-0.84) was calculated to represent the benefit of heparin plus Gp IIb/IIIa blockade vs heparin alone ($OR_{\text{heparin+Gp IIb/IIIa vs heparin}}$). From the results of the current REPLACE-2 trial, an OR comparing bivalirudin to heparin plus Gp IIb/IIIa was directly computed ($OR_{\text{bivalirudin vs heparin+Gp IIb/IIIa}}$). An imputed OR comparing bivalirudin with heparin monotherapy ($OR_{\text{bivalirudin vs heparin}}$) was then derived using the product¹⁴:

$$OR_{\text{bivalirudin vs heparin}} = \frac{OR_{\text{bivalirudin vs heparin+Gp IIb/IIIa}}}{OR_{\text{heparin+Gp IIb/IIIa vs heparin}}} \times$$

Two sequential tests were performed using the imputed OR of bivalirudin vs heparin. First, superiority of bivalirudin over heparin was assessed by observing if the upper 95% CI of the imputed $OR_{\text{bivalirudin vs heparin}}$ excluded unity. Second, noninferiority of bivalirudin vs heparin plus Gp IIb/IIIa was determined by whether bivalirudin preserved at least 50% of the effect of heparin plus Gp IIb/IIIa over heparin alone.¹⁴⁻¹⁶ For this second test, 50% of the benefit of heparin plus Gp IIb/

IIIa over heparin is described mathematically by the square root of the overall $OR_{\text{heparin+Gp IIb/IIIa vs heparin}}$ and is OR 0.82 (95% CI, 0.74-0.92). The upper CI for this estimate (0.92) defines the noninferiority boundary; thus, for bivalirudin to be regarded as noninferior to heparin plus Gp IIb/IIIa, the upper bound of the 95% CI of the imputed $OR_{\text{bivalirudin vs heparin}}$ could be no greater than 0.92. The secondary triple composite end point of the trial was subjected to analogous superiority and noninferiority testing, using the $OR_{\text{heparin+Gp IIb/IIIa vs heparin}}$ of 0.55 (95% CI, 0.43-0.71) and noninferiority boundary of 0.84 calculated from the meta-analysis. Two-sided *P* values are reported, and analyses included all patients for whom end point data were available. Analyses were performed using SAS statistical software, version 8.0 (SAS Inc, Cary, NC).

Sample size was based on pilot data suggesting an 8.0% primary quadruple end point event rate in the control (heparin plus Gp IIb/IIIa blockade) group and a 12.5% relative reduction in the bivalirudin arm.⁹ Using a 2-sided α level of .05 and 3000 patients per group, the trial had a 99% power to detect superiority over the imputed heparin control and a 92% power to satisfy noninferiority criteria relative to heparin plus Gp IIb/IIIa. An in-

terim safety analysis was performed by a data and safety monitoring board when data for the first 1500 patients were available.

RESULTS

Enrollment of 6010 patients was completed between October 10, 2001, and August 26, 2002. The 30-day database was finalized on November 4, 2002 (Figure 1). Baseline characteristics were balanced between the 2 treatment groups (TABLE 1). An index PCI was undertaken in 2953 (98.2%) of 3008 patients in the heparin plus Gp IIb/IIIa group and 2950 (98.5%) of 2994 patients in the bivalirudin group. Successful PCI of all attempted vessels was

achieved in 96.0% and 95.7% of patients randomized to receive heparin plus Gp IIb/IIIa and bivalirudin, respectively.

More than 85% of patients received treatment with clopidogrel (or infrequently ticlopidine) before undergoing the interventional procedure (TABLE 2). In the heparin plus Gp IIb/IIIa group, median durations of Gp IIb/IIIa infusion were 18.0 hours (interquartile range [IQR], 16.5-18.1 hours) for eptifibatide or 12.0 hours (IQR, 11.9-12.2 hours) for abciximab. The median duration of bivalirudin administration was 0.73 hours (IQR, 0.43-1.33 hours). A Gp IIb/IIIa inhibitor (or matching placebo) was used on a pro-

visional basis in 157 (5.2%) patients randomized to the heparin plus Gp IIb/IIIa and 217 (7.2%) patients in the bivalirudin groups ($P = .001$; Table 2). The most common reasons cited for administering provisional Gp IIb/IIIa blockade were diminished or slow coronary flow (10.2% and 11.1% of provisional use in the heparin and bivalirudin groups, respectively), obstructive dissection (12.7% and 16.7%), new or suspected thrombus (17.2% and 17.1%), persistent residual stenosis (10.2% and 9.3%), and unplanned stent (11.5% and 8.8%). By 5 minutes after the study drug boluses, the median ACT was 41 seconds longer among patients treated with bivalirudin (358 seconds; IQR, 320-400 seconds) vs heparin plus Gp IIb/IIIa (317 seconds; IQR, 263-373 seconds; $P < .001$; FIGURE 2). At the end of the interventional procedure, median ACT values were 68 seconds higher with bivalirudin than with heparin plus Gp IIb/IIIa.

The primary quadruple composite end point of death, myocardial infarction, urgent repeat revascularization, or in-hospital major bleeding by 30 days occurred in 299 (10.0%) of 2991 patients in the heparin plus Gp IIb/IIIa inhibitor group vs 275 (9.2%) of 2975 patients in the bivalirudin group (OR, 0.92; 95% CI, 0.77-1.09; $P = .32$). Relative to heparin alone, the imputed OR was 0.62 (95% CI, 0.47-0.82), satisfying statistical criteria for noninferiority to heparin plus Gp IIb/IIIa blockade and superiority to heparin alone. The secondary triple composite end point of death, myocardial infarction, or urgent repeat revascularization was reached in 211 (7.1%) of 2990 patients in the heparin plus Gp IIb/IIIa inhibitor group vs 227 (7.6%) of 2975 patients in the bivalirudin group (OR, 1.09; 95% CI, 0.90-1.32; $P = .40$). The imputed OR relative to heparin alone was 0.61 (95% CI, 0.44-0.83), satisfying criteria for noninferiority to heparin plus Gp IIb/IIIa inhibition and superiority to heparin alone. Criteria for noninferiority with the quadruple and triple end points were also met among the per protocol population of 5785 pa-

Table 1. Baseline and Procedural Characteristics*

Characteristics	Heparin Plus Glycoprotein IIb/IIIa (n = 3008)	Bivalirudin (n = 2994)
Age, mean (SD), y	62.6 (11.0)	62.6 (10.8)
Age >75 y	412 (13.7)	394 (13.2)
Weight, mean (SD), kg	87.5 (18.1)	87.3 (18.2)
Women	779 (25.9)	758 (25.3)
White race	2775 (92.3)	2777 (92.8)
Diabetes mellitus	784 (26.1)	840 (28.1)
Prior myocardial infarction	1085 (36.7)	1099 (37.4)
Prior percutaneous intervention	1059 (35.3)	1029 (34.5)
Prior coronary artery bypass surgery	564 (18.8)	538 (18.0)
Smoking in last 12 mo	762 (26.0)	796 (27.2)
Hypertension	2040 (68.0)	1965 (66.0)
Prior congestive heart failure	198 (6.6)	217 (7.3)
Prior cerebrovascular accident	66 (2.2)	75 (2.5)
Indication for procedure		
Unstable angina, ≤48 h	434 (14.7)	421 (14.3)
Myocardial infarction, ≤7 d	248 (8.4)	248 (8.4)
Unstable angina, >48 h	619 (21.0)	599 (20.3)
Stable angina	722 (24.4)	770 (26.1)
Positive stress test result or other	930 (31.5)	912 (30.9)
Procedure type		
Stent	2578 (85.7)	2548 (85.1)
Atherectomy	114 (3.8)	114 (3.8)
Balloon only	209 (6.9)	237 (7.9)
Multivessel intervention attempted	443 (15.0)†	506 (17.2)†
Target vessel (not mutually exclusive)		
Left anterior descending artery	1282 (42.6)	1264 (42.2)
Left circumflex artery	865 (28.8)	883 (29.5)
Right coronary artery	1035 (34.4)‡	1115 (37.3)‡
Left main artery	39 (1.3)	36 (1.2)
Coronary bypass graft surgery	185 (6.2)	174 (5.8)

*Values expressed as number (percentage) unless otherwise noted. All percentages are of patients for whom data were available.

† $P < .05$.

‡ $P = .02$.

tients in whom PCI was attempted and the study drug administered. There were no apparent differences among various major subgroups of patients with regard to the effect of bivalirudin vs heparin plus Gp IIb/IIIa therapy on the primary quadruple end point (FIGURE 3) or the secondary triple end point. The timing of clopidogrel pretreatment did not influence the efficacy of bivalirudin relative to heparin plus Gp IIb/IIIa blockade.

Individual components of the composite end points are listed in TABLE 3. Rates of myocardial infarction were numerically higher in the bivalirudin group by an absolute 0.8%; this non-significant difference was confined to non-Q-wave infarctions, predominantly with a moderate-sized increase in CK-MB 5 to 10 times the upper limit of normal. In contrast to the absence of statistically significant differences between treatment groups with regard to the ischemic events, there was a 41% relative reduction in the major bleeding component of the primary end point among patients treated with bivalirudin (2.4% vs 4.1%; $P < .001$). The most frequent site of major bleeding was the vascular access puncture, for which the incidence of hemorrhage was 2.5% with heparin plus Gp IIb/IIIa vs 0.8% with bivalirudin. The rates of other hemorrhagic end points were also lower with bivalirudin (TABLE 4).

COMMENT

This large-scale randomized multicenter trial tested the efficacy of the direct thrombin inhibitor bivalirudin as a replacement for heparin during the contemporary practice of PCI. A broad spectrum of more than 6000 patients undergoing urgent or elective stent, angioplasty, or atherectomy procedures was evaluated. Bivalirudin, with a Gp IIb/IIIa inhibitor administered provisionally in approximately 7% of patients, provided protection from periprocedural ischemic events that was not inferior to that of the current standard of low-dose heparin plus planned Gp IIb/IIIa blockade, with less associated major hemorrhage. Bivalirudin with a

provisional Gp IIb/IIIa inhibitor was superior to heparin alone by an imputed comparison. These findings validate bivalirudin with selective Gp IIb/IIIa blockade as an effective and safe anticoagulation strategy during PCI, with advantages with regard to bleeding risk, cost, and ease of administration.

Heparin provides incomplete protection from periprocedural ischemic events and has a clear propensity for

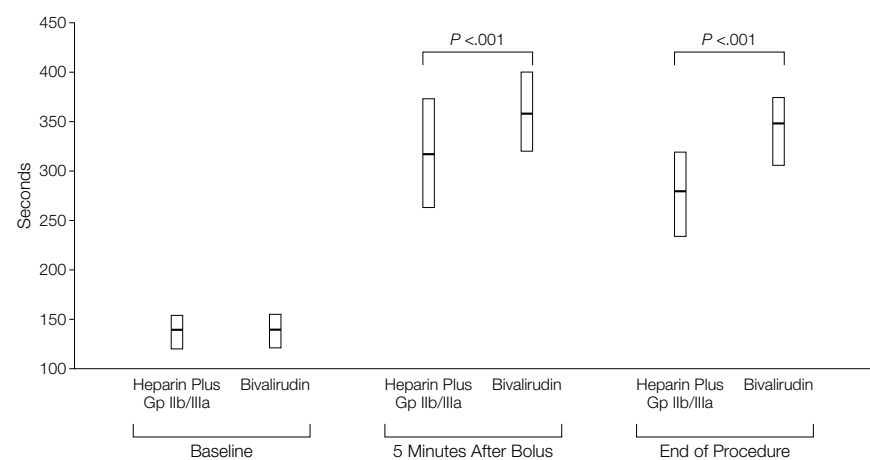
greater bleeding risk as doses are increased to improve efficacy.¹⁷ Although adjunctive administration of platelet Gp IIb/IIIa inhibitors is unquestionably effective in reducing the incidence of acute ischemic complications,^{12,13} with evidence of long-term suppression of mortality as well with abciximab,¹⁸⁻²⁰ therapy with these agents is not without limitations. Bleeding has been an issue of particular concern since

Table 2. Thienopyridine and Glycoprotein IIb/IIIa Inhibitor Use*

Variables	Heparin Plus Glycoprotein IIb/IIIa (n = 3008)	Bivalirudin (n = 2994)
Thienopyridine pretreatment	2566 (85.4)	2593 (86.7)
Clopidogrel	2511 (83.6)	2541 (84.9)
Ticlopidine	53 (1.8)	51 (1.7)
Duration of thienopyridine pretreatment, h		
<2	784 (26.1)	797 (26.6)
2 to 48	1685 (56.1)	1702 (56.9)
>48	34 (1.1)	34 (1.2)
Unknown	63 (2.1)	60 (2.0)
Thienopyridine postprocedure	2748 (91.5)	2748 (91.9)
Planned glycoprotein IIb/IIIa inhibitor use	2902 (96.5)	...
Eptifibatide	1605 (53.4)	...
Abciximab	1289 (42.9)	...
Provisional glycoprotein IIb/IIIa inhibitor use	157 (5.2)†	217 (7.2)†
Eptifibatide	...	111 (3.7)
Abciximab	...	106 (3.5)
Placebo	157 (5.2)	...

*Values expressed as number (percentage). All percentages are of patients for whom data were available. Ellipses indicate not applicable.
† $P = .001$. All other P values not significant.

Figure 2. Activated Clotting Times



Activated clotting times (ACTs) were measured in the heparin plus glycoprotein IIb/IIIa (Gp IIb/IIIa) and bivalirudin groups at baseline, 5 minutes after study drug bolus, and at the end of the interventional procedure. Plotted are medians and interquartile ranges.

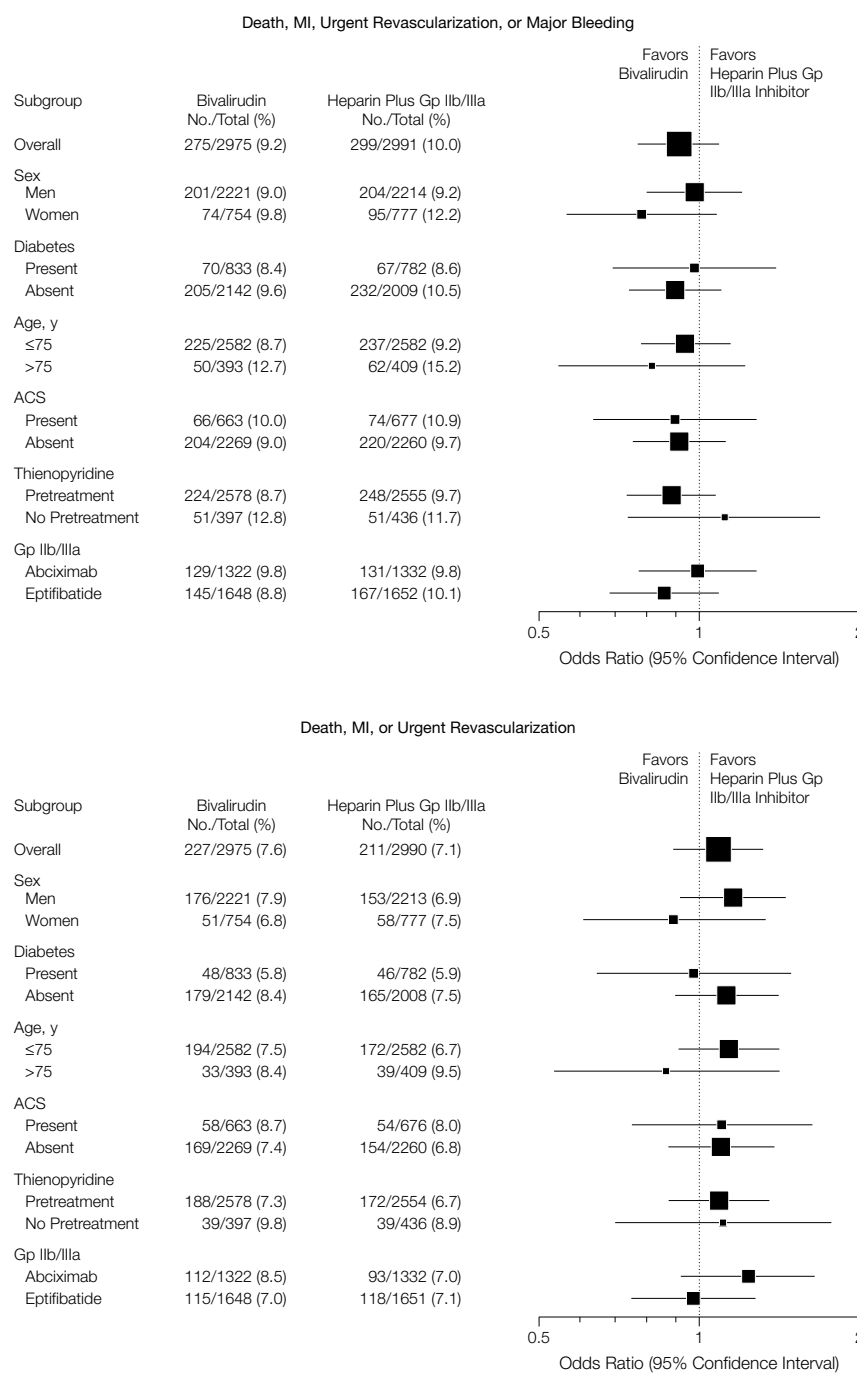
the first Gp IIb/IIIa interventional trial, in which treatment with abciximab was associated with a doubling of the rates of bleeding and transfusions.²¹ Reduction and weight-adjustment of concomitant heparin dosing with Gp IIb/

IIIa inhibition have substantially reduced, but not eliminated, this bleeding risk.²² Thrombocytopenia, at times profound, occurs in 1% to 3% of patients during Gp IIb/IIIa blockade, particularly with abciximab.^{12,13} Although reversible, thrombocytopenia in this setting is associated with bleeding and ischemic sequelae, blood product transfusions, and prolonged hospitalizations.^{23,24} Moreover, economic considerations discourage use of Gp IIb/IIIa agents, given the wholesale acquisition costs for an average (87 kg in REPLACE-2) patient of approximately \$1300 for abciximab or \$615 for eptifibatid. In addition, the prescribed 12- or 18-hour infusion durations for abciximab or eptifibatid, respectively, may prolong hospitalization and patient immobilization times in an era of expedited care following PCI.

Bivalirudin directly inhibits the fibrinogen recognition and catalytic sites of the thrombin molecule. Unlike heparin, this agent can neutralize clot-bound thrombin, does not require a cofactor, is not inactivated by circulating inhibitors, and does not bind to plasma proteins.^{1,26} Furthermore, in contrast to the platelet-activating effect of heparin, bivalirudin may inhibit thrombin-mediated platelet activation.²⁷ Prior to our trial, clinical data supporting bivalirudin as an alternative to heparin during PCI were particularly noteworthy for evidence of substantial reductions in bleeding complications in conjunction with diminished ischemic events.^{6,8}

Several features of the design of REPLACE-2 deserve comment. We chose to use bivalirudin as a monotherapy with provisional rather than planned Gp IIb/IIIa blockade. This decision was based in part on pilot data suggesting that the advantage of bivalirudin with regard to bleeding may be attenuated by concomitant Gp IIb/IIIa inhibition,⁹ as well as considerations of the additive costs of these therapies. Additionally, the antiplatelet effect of bivalirudin may be clinically relevant in combination with thienopyridines and aspirin. These considerations, coupled

Figure 3. Subgroups and Primary End Point by Treatment Assignment



ACS indicates acute coronary syndrome, defined as unstable angina within preceding 48 hours or myocardial infarction (MI) within the prior 7 days; Gp, glycoprotein. The size of the data markers are approximately proportional to the size of the subgroup.

with the observation of low rates of periprocedural myocardial infarction with bivalirudin monotherapy in prior studies,⁷⁻⁹ suggested that the risk of ischemic complications with this agent might be comparable with that of heparin plus Gp IIb/IIIa blockade. A noninferiority trial design was therefore used, based on the hypothesis that by virtue of its lower cost, short duration of administration, and potential to reduce hemorrhagic complications, bivalirudin would be an attractive treatment alternative if its efficacy approximated that of heparin plus Gp IIb/IIIa inhibition.

The statistical approach to establishing noninferiority in this trial was rigorous²⁸ because we used a formal noninferiority margin. Although no standard or universally-accepted basis exists for choosing such a margin,^{14,16} a noninferiority boundary preserving at least 50% of the standard drug effect as used in this study, has precedent^{15,29,30} and is clinically relevant.¹⁶ The findings of the imputed CI method prespecified for REPLACE-2 were confirmed by 3 other techniques (calculations not shown). Hasselblad and Kong¹⁴ have proposed an alternative in which the “proportion of active control effect retained” may be estimated; using their technique, bivalirudin with provisional Gp IIb/IIIa preserves at least 75% and 51% of the effect of heparin plus Gp IIb/IIIa blockade with respect to the quadruple and triple end points, respectively. A “two confidence interval procedure” described by Rothmann and colleagues³¹ provides 99.7% and 96.3% confidence that the quadruple and triple end points, respectively, preserve at least 50% of the effect of heparin plus Gp IIb/IIIa inhibition. In addition, both the quadruple and triple end points meet the requirements of another method that assesses whether the CI for the benefit of a new therapy falls within the limits of the “minimum treatment effect” of the standard therapy.³²

The control group of REPLACE-2 reflects the current state of best clinical practice during PCI. Both abciximab and eptifibatide have been proven in

placebo-controlled trials to reduce periprocedural ischemic events in this setting relative to heparin alone¹² or heparin and provisional Gp IIb/IIIa.¹³ The REPLACE-2 design therefore permitted either abciximab or eptifibatide to be chosen, and the ratio in the trial (0.55:0.45 eptifibatide:abciximab) was

similar to current-use patterns. The heparin dose prescribed in the control group was 65 U/kg, midway between the reduced, weight-adjusted doses of 70 U/kg and 60 U/kg used in the recent Evaluation of Platelet Inhibition in Stenting (EPISTENT)¹² and Enhanced Suppression of the Platelet IIb/IIIa Re-

Table 3. Primary End Point Components by 30 Days*

Variables	Heparin Plus Glycoprotein IIb/IIIa	Bivalirudin	P Value
Quadruple composite (death, MI, urgent revascularization, or major bleeding)	299/2991 (10.0)†	275/2975 (9.2)	.32
Triple composite (death, MI, or urgent revascularization)	211/2990 (7.1)	227/2975 (7.6)	.40
Death	12/3000 (0.4)	7/2986 (0.2)	.26
MI	185/2990 (6.2)	207/2975 (7.0)	.23
Q-wave MI	13/2990 (0.4)	12/2975 (0.4)	.43‡
Non-Q-wave MI	172/2990 (5.8)	195/2975 (6.6)	
CK-MB <3 × control	3/2987 (0.1)	3/2971 (0.1)	.41‡
CK-MB >3 to 5 × control	76/2987 (2.5)	70/2971 (2.4)	
CK-MB >5 to 10 × control	52/2987 (1.7)	72/2971 (2.4)	
CK-MB >10 × control	38/2987 (1.3)	43/2971 (1.4)	
Urgent revascularization	42/2990 (1.4)	35/2975 (1.2)	.44
Urgent percutaneous revascularization	27/2990 (0.9)	22/2975 (0.7)	.49
Urgent surgical revascularization	16/2990 (0.5)	14/2975 (0.5)	.73
Major bleeding	123/3008 (4.1)†	71/2993 (2.4)	<.001

Abbreviations: CK-MB, creatine kinase MB isoenzyme; MI, myocardial infarction.
 *Values are expressed as number/total (percentage). Denominators are corrected for missing values or follow-up of less than 25 days.
 †Complete data were available for 2990, but bleeding data were available for 1 additional patient who reached the end point of the quadruple composite.
 ‡P value for trends in MI type or CK-MB elevation.

Table 4. Hemorrhagic End Points*

Variables	Heparin Plus Glycoprotein IIb/IIIa	Bivalirudin	P Value
Major bleeding	123/3008 (4.1)	71/2993 (2.4)	<.001
Intracranial	2/3008 (0.1)	1/2993 (0)	>.99
Retroperitoneal	16/3008 (0.5)	7/2993 (0.2)	.06
Vascular access puncture	74/3008 (2.5)	25/2993 (0.8)	<.001
Gastrointestinal	18/3008 (0.6)	4/2993 (0.1)	.003
Genitourinary	6/3008 (0.2)	1/2993 (0)	.13
Related to cardiac surgery	18/3008 (0.6)	17/2993 (0.6)	.88
Minor bleeding	772/3008 (25.7)	400/2993 (13.4)	<.001
TIMI bleeding criteria†			
Major bleeding	26/3008 (0.9)	19/2993 (0.6)	.30
Minor bleeding	91/3008 (3.0)	39/2993 (1.3)	<.001
Any transfusion	76/3008 (2.5)	50/2993 (1.7)	.02
Transfusion ≥2 U	58/3008 (1.9)	39/2993 (1.3)	.06
Red blood cell	57/3008 (1.9)	43/2993 (1.4)	.17
Whole blood	4/3008 (0.1)	1/2993 (0)	.38
Platelets	18/3008 (0.6)	10/2993 (0.3)	.13
Thrombocytopenia			
Platelets <100 × 10 ³ /μL	50/2863 (1.7)	20/2868 (0.7)	<.001
Platelets <50 × 10 ³ /μL	19/2863 (0.7)	8/2868 (0.3)	.03

Abbreviation: TIMI, Thrombolysis in Myocardial Infarction trial.¹⁰
 *Values are expressed as number/total (percentage). Denominators are corrected for missing values.
 †TIMI major and minor bleeding are mutually exclusive classifications.

ceptor with Integrilin Therapy (ESPRIT)¹³ trials of abciximab and eptifibatide, respectively. Although heparin doses lower than 60 U/kg may be given by some operators in clinical practice, such doses have not been validated in a controlled trial setting, have not been demonstrated to provide adequate protection against ischemic events or reduce bleeding complications, and would not have been an appropriate control therapy in this trial.

The median peak ACT value in the heparin plus Gp IIb/IIIa group of REPLACE-2 was 317 seconds vs 314 seconds in EPISTENT and 273 seconds in ESPRIT.^{12,13} Given the similar weight-adjusted heparin doses and identical abciximab and eptifibatide regimens in the 3 trials, differences in ACT levels likely reflect variations in instrumentation and reagents over the years between the trials rather than true differences in degree of anticoagulation. Previous investigators have highlighted the difficulties in comparing ACT results obtained from different generations of the Hemochron device or different cuvettes by documenting substantial variations (by as much as ≥ 110 seconds) in ACT values.³³ Moreover, the incidences of hemorrhage were actually quite comparable in the heparin plus Gp IIb/IIIa groups of EPISTENT, ESPRIT, and REPLACE-2. By the TIMI definitions used in the earlier 2 trials, rates of major or minor bleeding (similar to the definition of "major bleeding" in REPLACE-2) were 4.4% in EPISTENT,¹² 4.0% in ESPRIT,¹³ and 3.9% in REPLACE-2 (Table 4).

Although statistical criteria for non-inferiority to heparin plus Gp IIb/IIIa were satisfied in REPLACE-2, there was a statistically nonsignificant 0.5% excess of ischemic events (predominantly non-Q-wave infarction) in the bivalirudin group. Previous studies have demonstrated an association between myocardial infarction during PCI and impaired long-term (≥ 1 year) survival,^{34,35} but the late mortality risk attributable to relatively small differences in infarction rates remains unknown. Long-term follow-up (6 month and 1 year) is under-

way in REPLACE-2 to examine the consequences of a disparity in early ischemic events, but it is relevant to note that even larger differences in early infarction rates have not consistently translated into detectable differences in 1-year mortality in other trials.^{15,36} On the other hand, major bleeding, transfusions, and thrombocytopenia are also clinically relevant complications, associated with patient discomfort, prolonged hospitalization, infection risk from blood products, and increased cost. The significant absolute 1.7 major bleeding events, 1 thrombocytopenia episode, or 0.8 transfusions prevented for every 100 patients treated with bivalirudin in this trial may be a reasonable balance against a nonsignificant 0.5% ischemic risk (1 additional event for every 200 patients treated). Moreover, although a formal health economic analysis of REPLACE-2 is underway, it is likely that bivalirudin therapy (wholesale acquisition cost of \$395 per patient on average in this trial²⁵) might prove to be economically attractive. The logistics of adjunctive drug administration and early hospital discharge may also be simplified by the brief duration (typically < 1 hour) of bivalirudin infusion.

On the basis of this trial then, what is an appropriate role for bivalirudin in the clinical practice of PCI? REPLACE-2 enrolled a representative cross-section of patients undergoing urgent or elective revascularization, and thereby establishes bivalirudin with provisional Gp IIb/IIIa blockade as a suitable alternative to heparin plus a Gp IIb/IIIa inhibitor in these settings. It is reassuring that preliminary analyses did not suggest heterogeneity in outcome with these 2 therapeutic strategies among different subsets of patients (Figure 3) although it must be recognized that any individual subgroup within the trial is insufficiently powered to support definitive conclusions regarding noninferiority. Moreover, patients with acute myocardial infarction or unstable ischemic syndromes requiring empiric Gp IIb/IIIa inhibition were not included in REPLACE-2, and the results of this trial should not be interpreted to suggest that

Gp IIb/IIIa blockade should be supplemented in those patients. Selection of adjunctive antithrombotic therapy during PCI must take into account the expected benefit vs hazard in individual patients, based on the findings of REPLACE-2 in the context of an existing body of trial data regarding Gp IIb/IIIa blockade. Glycoprotein IIb/IIIa inhibitors should therefore be withheld only with caution in those with high-risk characteristics (such as acute ischemic syndromes or treated diabetes), which have been correlated with distinctive acute benefit or long-term survival advantage from these agents.³⁷

Certainly, the sizable number of patients with low- or moderate-risk characteristics for periprocedural or long-term ischemic complications of PCI are appropriate candidates for bivalirudin with provisional Gp IIb/IIIa inhibition, especially if there is a heightened likelihood of bleeding. In particular, the validation of bivalirudin therapy leaves little justification for the continued practice of treating some patients with heparin alone during contemporary percutaneous coronary revascularization. What remains to be investigated is whether outcome during PCI may be further optimized in a cost-effective manner by routine combination of bivalirudin and Gp IIb/IIIa blockade in high-risk patients.

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Canada (450 Patients): Royal Alexandra Hospital, Edmonton, Alberta: W. Hui, L. Kville; University of Alberta Hospital, Edmonton: J. Burton, L. Lindholm; Vancouver General Hospital, Vancouver, British Columbia: C. Buller; University of Ottawa, Ottawa, Ontario: M. Labinaz, J. Steele; Sunnybrook & Womens College Health Sciences Center, Toronto, Ontario: E. Cohen, L. Balleza; Foothills Hospital, New Calgary, Alberta: F. Spence, C. Ellis; Trillium Health Center, Mississauga, Ontario: C. Lazzam, M. Bassila; Montreal Heart Institute, Montreal, Quebec: J. Tanguay, M. Caron; Hospital Maisonneuve Rosemont, Montreal, Quebec: C. Constance, F. Prince; Hamilton General Hospital, Hamilton, Ontario: M. Natarajan, J. Joval; St Paul's Hospital, Vancouver, British Columbia: J. Webb, L. Milosavljevic; St Boniface General Hospital, Winnipeg, Manitoba: T. Kashaour, M. Wilson; Sudbury Regional Hospital, Sudbury, Ontario: Z. Juma, R. Dhaliwal; Toronto General Hospital, Toronto, Ontario: J. Ross, A. Patel; Health Sciences Center, Winnipeg, Manitoba: H. Kozman, A. Munoz; St Michael's Hospital, Toronto, Ontario: W. Cantor, K. Young; Hospital Notre-Dame, Montreal, Quebec: F. Reeves, M. C. Pashko; and Queen Elizabeth II Health Sciences Center, Halifax, Nova Scotia: B. O'Neill, N. Fitzgerald.

Israel (267 Patients): Tel Aviv Sourasky Medical Center, Tel Aviv: G. Keren, R. Dayan; Lady Davis Carmel Medical Center, Haifa: B. Lewis, R. Yuval; Rabin Medical Center, Petach-Tikva: R. Kornowski, N. Shor; Chaim Sheba Medical Center, Ramat-Gan: Y. Har-Zahav, N. Eizenberg; Kaplan Hospital, Rehovot: O. Eizenberg; and Sharei-Zedek Medical Center, Jerusalem: Y. Almagor, A. Rojansky.

Germany (230 Patients): University Clinic Charite Berlin, Berlin: W. Rutsch, S. Schroeckh; Vivantis Krankenhaus Friedrichshain, Berlin: S. Hoffmann, S. Boremski; Medizinische Klinik II-Kardiologie, Mainz: H. Rupprecht, J. Dopheide; Allgemeines Krankenhaus Celle, Celle: W. Terres, P. Werner; Krankenhaus Dresden-Friedrichstadt, Dresden: E. Altmann, Graf; Robert Bosch Krankenhaus, Stuttgart: U. Sechtem, A. Athanasiadis; Christian-Albrechts-Universität zu Kiel, Kiel: R. Simon; Städtisches Klinikum Brandenburg

GmbH, Brandenburg An Der Havel: M. Oeff, G. Janssen; Humboldt-University, Berlin: R. Dietz, W. Bocksch; and Krankenhaus Neukoelien, Berlin: F. Forycki, R. Henzgen.

Belgium (207 Patients): Academisch Ziekenhuis Middelheim, Antwerpen: F. Van Den Branden, N. Aertes; A. Z. St-Jan, Brugge: P. Coussement, A. Rotsaert; Ziekenhuis Oost-Limburg, Genk: M. Vrolix, M. Schaefer; University Hospital Gasthuisberg, Leuven: W. Desmet, G. Oosterwijk; Imelda Ziekenhuis, Bonheiden: L. Janssens, C. Muller; Virga Jesse Ziekenhuis, Hasselt: E. Benit, L. Vandebeek; and Onze Lieve Vrouwe Ziekenhuis, Aalst: G. Heyndrickx, H. De Pril.

The Netherlands (90 Patients): Amphia Ziekenhuis, Breda: J. A. M. te Riele, P. Schelfhout; University Hospital Dijkzigt, Rotterdam: P. de Feyter, P. Cummins; Onze Lieve Vrouwe Gasthuis, Amsterdam: G. Laarman, R. Riezebos; Catharina Ziekenhuis, Eindhoven: J. J. R. M. Bonnier, A. Spierings; and Hospital de Weezenlanden, Zwolle: H. Suryapranata, K. Nijbrinks.

Spain (50 Patients): Hosp Clinic I Provincial, Barcelona: A. Betriu, T. Martorell; Hospital Marques de Valdecilla, Santander: T. Colman; and Hospital de Bellvitge, Barcelona: A. Cequier.

United Kingdom (36 Patients): Wythenshawe Hospital, Manchester: R. Levy, J. Hornsey; Royal Victoria Hospital, Belfast: M. Khan, B. Smith; Nottingham City Hospital, Nottingham: R. Henderson, M. Marriott; and University of Leicester, Leicester Warwick Medical School, Leicester: A. Gershlick, A. Stephenson Lloyd.

France (22 Patients): University Hospital Jean-Minjoz, Besancon Cedex: J. Bassand, A. Daval; CHU de Bordeaux-Hopital Haut Leveque, Pessac: P. Coste, S. Beylot; and Hopital Bichat, Paris Cedex 18: J. M. Juliard, R. Farnoud.

REFERENCES

- Weitz JI, Hudoba M, Massel D, Maraganore J, Hirsh J. Clot-bound thrombin is protected from inhibition by heparin-antithrombin III but is susceptible to inactivation by antithrombin III independent inhibitors. *J Clin Invest*. 1990;86:385-391.
- Eitzman DT, Chi L, Saggin L, Schwartz RS, Lucchesi BR, Fay WP. Heparin neutralization by platelet-rich thrombi: role of platelet factor 4. *Circulation*. 1994;89:1523-1529.
- Xiao Z, Theroux P. Platelet activation with unfractionated heparin at therapeutic concentrations and comparisons with a low-molecular-weight heparin and with a direct thrombin inhibitor. *Circulation*. 1998;97:251-256.
- Sobel M, Fish WR, Toma N, et al. Heparin modulates integrin function in human platelets. *J Vasc Surg*. 2001;33:587-594.
- Lincoff AM, Califf RM, Topol EJ. Platelet glycoprotein IIb/IIIa blockade in coronary artery disease. *J Am Coll Cardiol*. 2000;35:1103-1115.
- Bittl JA, Strony J, Brinker JA, et al. Treatment with bivalirudin (Hirulog) as compared with heparin during coronary angioplasty for unstable or postinfarction angina. *N Engl J Med*. 1995;333:764-769.
- Bittl JA, Chaitman BR, Feit F, Kimball W, Topol EJ, for the Bivalirudin Angioplasty Study Investigators. Bivalirudin vs heparin during coronary angioplasty for unstable or post-infarction angina: final report reanalysis of the Bivalirudin Angioplasty Study. *Am Heart J*. 2001;142:952-959.
- Lincoff AM, Kleiman NS, Kottke-Marchant K, et al. Bivalirudin with planned or provisional abciximab versus low-dose heparin and abciximab during percutaneous coronary revascularization: results of the Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial (CACHET). *Am Heart J*. 2002;143:847-853.
- Lincoff AM, Bittl JA, Kleiman NS, et al. The REPLACE 1 Trial: a pilot study of bivalirudin vs heparin during

- percutaneous coronary intervention with stenting and Gp IIb/IIIa blockade [abstract]. *J Am Coll Cardiol*. 2002;39:16A.
10. Rao AK, Pratt C, Berke A, et al. Thrombolysis in myocardial infarction (TIMI) trial, Phase I: Hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol*. 1988;11:1-11.
 11. Landefeld LS, Cook EF, Hatley M, Weisberg M, Goldman L. Identification and preliminary validation of predictors of major bleeding in hospitalized patients starting anticoagulant therapy. *Am J Med*. 1987;82:703-713.
 12. EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein IIb/IIIa blockade. *Lancet*. 1998;352:87-92.
 13. ESPRIT Investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. *Lancet*. 2000;356:2037-2044.
 14. Hasselblad V, Kong DF. Statistical methods for comparison to placebo in active-control trials. *Drug Inf J*. 2001;35:435-449.
 15. Topol EJ, Moliterno DJ, Herrmann HC, et al. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med*. 2001;344:1888-1894.
 16. Temple R, Ellenberg SS. Placebo-controlled trials and active-control trials in the evaluation of new treatments, I: ethical and scientific issues. *Ann Intern Med*. 2000;133:455-475.
 17. Chew DP, Bhatt DL, Lincoff AM, Moliterno DJ, Brener SJ, Wolski KE, et al. Defining the optimal activated clotting time during percutaneous coronary intervention. *Circulation*. 2001;103:961-966.
 18. Topol EJ, Mark DB, Lincoff AM, et al. Enhanced survival with platelet glycoprotein IIb/IIIa blockade in patients undergoing coronary stenting: one year outcomes and health care economic implications from a multicenter, randomized trial. *Lancet*. 1999;354:2019-2024.
 19. Topol EJ, Lincoff AM, Kereiakes DJ, et al. Multi-year follow-up of abciximab therapy in three randomized, placebo-controlled trials of percutaneous coronary revascularization. *Am J Med*. 2002;113:1-6.
 20. Anderson KM, Califf RM, Stone GW, et al. Long-term mortality benefit with abciximab in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol*. 2001;37:2059-2065.
 21. EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med*. 1994;330:956-961.
 22. EPILOG Investigators. Platelet glycoprotein IIb/IIIa blockade with abciximab with low-dose heparin during percutaneous coronary revascularization. *N Engl J Med*. 1997;336:1689-1696.
 23. Berkowitz S, Sane D, Sigmon K, et al. Occurrence and clinical significance of thrombocytopenia in a population undergoing high-risk percutaneous coronary revascularization. *J Am Coll Cardiol*. 1998;32:311-319.
 24. Kereiakes DJ, Berkowitz SD, Lincoff AM, et al. Clinical correlates and course of thrombocytopenia during percutaneous coronary intervention in the era of abciximab glycoprotein IIb/IIIa blockade. *Am Heart J*. 2000;140:74-80.
 25. Cohen H, ed. *Redbook Drug Topics 2002*. Montvale, NJ: Thomson Medical Economics; 2002.
 26. Lefkowitz J, Topol EJ. Direct thrombin inhibitors in cardiovascular medicine. *Circulation*. 1994;90:1522-1536.
 27. Weitz JI, Bates SM. Acute coronary syndromes: a focus on thrombin. *J Invasive Cardiol*. 2002;14:2B-7B.
 28. Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: the importance of rigorous methods. *BMJ*. 1996;313:36-39.
 29. US Food and Drug Administration. Medical-statistical review for xeloda [NDA No. 20-896]; 2001. Available at: http://www.fda.gov/cder/foi/nda/2001/20-896S010_Xeloda_medr_P1.pdf. Accessed January 15, 2003.
 30. INJECT Investigators. Randomised, double-blind comparison of reteplase double-bolus administration with streptokinase in acute myocardial infarction (INJECT): trial to investigate equivalence. *Lancet*. 1995;346:329-336.
 31. Rothmann M, Li N, Chen G, Chi GYH, Temple R, Tsou H-H. Design and analysis of non-inferiority mortality trials in oncology. *Stat Med*. In press.
 32. Siegel JP. Equivalence and noninferiority trials. *Am Heart J*. 2000;139:S166-S170.
 33. Koerber JM, Mattson JC, Smythe MA, Gauss IA, Wright JA. A comparison of the Hemochron 401 and the Hemochron Jr Signature in cardiac catheterization and interventional patients [online only abstract]. *J Thrombosis Haemostasis*. 2001;86(suppl). Available at: <http://www.cartesian-secure.com/isth2001/iAbstract/html/absP1589.html>. Accessed January 15, 2003.
 34. Topol EJ, Ferguson JJ, Weisman HF, et al, for the EPIC Investigator Group. Long-term protection from myocardial ischemic events in a randomized trial of brief integrin β 3 blockade with percutaneous coronary intervention. *JAMA*. 1997;278:479-484.
 35. Lincoff AM, Tcheng JE, Califf RM, et al. Sustained suppression of ischemic complications of coronary intervention by platelet GP IIb/IIIa blockade with abciximab: one year outcome in the EPILOG trial. *Circulation*. 1999;99:1951-1958.
 36. Lincoff AM, Califf RM, Van de Werf F, et al. Mortality at 1 year with combination platelet glycoprotein IIb/IIIa inhibition and reduced-dose fibrinolytic therapy vs conventional fibrinolytic therapy for acute myocardial infarction: GUSTO V randomized trial. *JAMA*. 2002;288:2130-2135.
 37. Kereiakes DJ, Lincoff AM, Anderson KM, et al. Abciximab survival advantage following percutaneous coronary intervention is predicted by clinical risk profile. *Am J Cardiol*. 2002;90:628-630.