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PLATELET GLYCOPROTEIN IIb/IIIa RECEPTOR BLOCKADE AND LOW-DOSE HEPARIN DURING PERCUTANEOUS CORONARY REVASCULARIZATION

THE EPILOG INVESTIGATORS*

ABSTRACT

Background Blockade of the platelet glycoprotein IIb/IIIa receptor with abciximab (a monoclonal-antibody Fab fragment directed against the receptor) has been shown to diminish ischemic complications among patients undergoing high-risk coronary angioplasty or atherectomy but increases bleeding complications. The widespread applicability of this treatment is unknown, particularly in view of the observed risk of hemorrhage.

Methods In a prospective, double-blind trial, we randomly assigned patients undergoing urgent or elective percutaneous coronary revascularization at 69 centers to receive abciximab with standard-dose, weight-adjusted heparin (initial bolus of 100 U per kilogram of body weight); abciximab with low-dose, weight-adjusted heparin (initial bolus of 70 U per kilogram); or placebo with standard-dose, weight-adjusted heparin. The primary efficacy end point was death from any cause, myocardial infarction, or urgent revascularization within 30 days of randomization.

Results The trial was terminated at the first interim analysis, with 2792 of the planned 4800 patients enrolled. At 30 days, the composite event rate was 11.7 percent in the group assigned to placebo with standard-dose heparin; 5.2 percent in the group assigned to abciximab with low-dose heparin (hazard ratio, 0.43; 95 percent confidence interval, 0.30 to 0.60; $P < 0.001$); and 5.4 percent in the group assigned to abciximab with standard-dose heparin (hazard ratio, 0.45; 95 percent confidence interval, 0.32 to 0.63; $P < 0.001$). There were no significant differences among the groups in the risk of major bleeding, although minor bleeding was more frequent among patients receiving abciximab with standard-dose heparin.

Conclusions Inhibition of the platelet glycoprotein IIb/IIIa receptor with abciximab, together with low-dose, weight-adjusted heparin, markedly reduces the risk of acute ischemic complications in patients undergoing percutaneous coronary revascularization, without increasing the risk of hemorrhage. (N Engl J Med 1997;336:1689-96.)

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NEW strategies for preventing ischemic complications during percutaneous coronary revascularization have focused on the platelet surface-membrane glycoprotein IIb/IIIa receptor.¹ In a previous large-scale trial (Evaluation of 7E3 for the Prevention of Ischemic Complications, or EPIC), blockade of this receptor by abciximab (c7E3 Fab, ReoPro, Centocor, Malvern, Pa.), a human-murine chimeric antibody Fab fragment, was shown to reduce the incidence of acute ischemic events by 35 percent among patients undergoing "high-risk" percutaneous coronary revascularization² but was accompanied by a doubling of the incidence of major bleeding complications. Important questions were thus raised regarding the balance between risk and benefit with glycoprotein IIb/IIIa receptor blockade during coronary intervention, particularly among patients not considered to be at high risk for ischemic complications. The concurrent administration of high doses of heparin, however, may have potentiated the hemorrhagic toxicity of abciximab observed in the EPIC trial.^{2,3} A pilot study suggested that the blood loss associated with abciximab might be attenuated by using lower doses of heparin, as well as by early removal of the vascular sheath to eliminate the need for the post-procedural infusion of heparin.⁴

The objectives of the present trial were first, to determine whether the clinical benefits of abciximab therapy could be extended to all patients undergoing coronary intervention, regardless of their risk of ischemic complications, and second, to evaluate

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whether the incidence of hemorrhagic complications associated with this agent could be reduced without loss of efficacy by adjusting the heparin dose for body weight or reducing it.

METHODS

Study Population

The Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade (EPILOG) study was a randomized, double-blind, placebo-controlled trial conducted at 69 clinical sites in the United States and Canada. Patients undergoing elective or urgent percutaneous coronary revascularization with a device approved by the Food and Drug Administration were eligible for inclusion if they were over 21 years old and had a target lesion in which there was stenosis of at least 60 percent of the diameter of the vessel. Because the previous trial had suggested that abciximab provided substantial clinical benefit among patients with acute ischemic syndromes,² patients who had either acute myocardial infarction or unstable angina with associated electrocardiographic changes during the previous 24 hours were excluded. Other exclusion criteria were planned stent implantation or rotational atherectomy; percutaneous coronary intervention performed within the previous three months; a left-main-coronary-artery stenosis of more than 50 percent not protected by collateral vessels; concurrent warfarin therapy or a base-line prothrombin time more than 1.2 times the control value; cerebrovascular accident within the previous two years or a residual neurologic deficit; intracranial neoplasm, aneurysm, or arteriovenous malformation; history of vasculitis, known hemorrhagic diathesis, or active internal bleeding; hypertension, with a systolic blood pressure of more than 180 mm Hg or a diastolic blood pressure of more than 100 mm Hg; and major surgery, gastrointestinal bleeding, or genitourinary bleeding within the previous six weeks. The protocol was approved by the institutional review board at each clinical site, and all patients gave informed consent.

Study Protocol

Patients were given 325 mg of aspirin orally two hours before the percutaneous revascularization procedure and daily thereafter. Patients were randomly assigned in a double-blind fashion by means of a central telephone hot line to one of three treatment groups: placebo with standard-dose, weight-adjusted heparin; abciximab with standard-dose, weight-adjusted heparin; or abciximab with low-dose, weight-adjusted heparin. For those receiving abciximab, a bolus of 0.25 mg per kilogram of body weight was administered 10 to 60 minutes before inflation of the balloon or activation of the device, followed by an infusion of 0.125 μ g per kilogram per minute (maximum, 10 μ g per minute) for 12 hours. The standard-dose, weight-adjusted heparin regimen consisted of an initial bolus of 100 U of heparin per kilogram (maximum, 10,000 U) before the interventional procedure, with additional weight-adjusted boluses calculated according to an algorithm intended to achieve and maintain an activated clotting time of at least 300 seconds. The group assigned to low-dose, weight-adjusted heparin received an initial bolus of 70 U of heparin per kilogram (maximum, 7000 U), with additional boluses as necessary to achieve and maintain an activated clotting time of at least 200 seconds. To preserve the blinding of all investigators and personnel involved in patient care, a heparin coordinator at each clinical site performed all measurements of activated clotting time and directed the administration of heparin. The protocol recommended that heparin be discontinued immediately after the interventional procedure and that vascular sheaths be removed when the activated clotting time was 175 seconds or less (usually 2 to 6 hours later).

Implantation of stents was discouraged and was reserved as a means of maintaining patency after manifest or threatened abrupt

closure. Specific guidelines for sites of vascular access stressed the early removal of sheaths, avoidance of routine placement of venous sheaths, selective anterior-arterial-wall puncture, compression of the femoral access site for 30 minutes to achieve hemostasis after removal of the vascular sheath, and strict bed rest and immobilization of limbs for 6 to 8 hours after the cessation of abciximab treatment and removal of sheaths. Algorithms were provided for the management of uncontrolled bleeding, urgent coronary-artery bypass surgery, and thrombocytopenia, and it was recommended that red-cell transfusions be administered according to the clinical guidelines of the American College of Physicians.⁵

Study End Points

The primary efficacy end point was a composite of death from any cause, myocardial infarction or reinfarction, or severe myocardial ischemia requiring urgent coronary bypass surgery or repeated percutaneous coronary revascularization within 30 days after randomization. A second efficacy end point was a composite of death, myocardial infarction, or coronary bypass surgery or repeated percutaneous revascularization (urgent or nonurgent) within six months after randomization. End-point classifications of a clinical-events committee, blinded to study-group assignment, were used for the final analyses.

An end-point in-hospital myocardial infarction was defined by one of two criteria: new, clinically significant Q waves in two or more contiguous electrocardiographic leads; or elevation in creatine kinase or its MB isoenzyme to at least three times the upper limit of normal, representing an increase of at least 50 percent over the previous trough level, in two samples collected at different times (enzyme analysis was conducted on blood obtained before and 2 hours after the initiation of treatment with the study agent, every 6 hours up to 24 hours, and then every 8 hours up to 48 hours or discharge). After discharge from the hospital, myocardial infarction was defined by the occurrence of Q waves or the elevation of creatine kinase or its MB isoenzyme to more than twice the upper limit of normal. The MB isoenzyme value was used if it was available; if not, the total creatine kinase value was used.

Bleeding events were classified as major or minor according to the criteria used by the Thrombolysis in Myocardial Infarction Study Group.⁶ Hemoglobin was measured before and 12 and 36 hours after initiation of the study agent (or at discharge). To account for the influence of red-cell transfusions on measured hemoglobin values, the estimated decreases in hemoglobin were adjusted according to the technique suggested by Landefeld et al.⁷ Platelet counts were obtained before and ½, 2, 12, 24, 48, and 72 hours after administration of the study agent (or at discharge). All suspected occurrences of stroke or intracranial hemorrhage were adjudicated by an independent neurologist.

Data Management and Statistical Analysis

Data were collected on case-report forms by study coordinators at the clinical sites and verified with medical records by study monitors. The investigators, study coordinators, and trial sponsor (Centocor) remained blinded to the treatment assignments until after the data were entered and reviewed by the clinical-events committee and the analysis plan was made final.

The differences among patients with regard to efficacy and bleeding variables were examined according to an intention-to-treat analysis. Hazard ratios were based on time-to-event analyses using the Cox proportional-hazards model. The P values for efficacy end points were derived from the log-rank statistic, and the P values for dichotomous safety end points were calculated with the Pearson chi-square statistic or Fisher's exact test.

An interim analysis was performed to review efficacy and safety data for the first 1500 patients, in order to ensure that the low-dose heparin regimen did not result in a higher rate of ischemic complications than placebo. The primary end point of this interim analysis was the occurrence of death or myocardial infarction within 30 days after randomization. An unbalanced stopping rule

was applied that favored termination of the trial for reasons of safety rather than efficacy, requiring a one-sided P value of ≤ 0.025 if an abciximab group had a higher event rate than the placebo group, but a one-sided P value of ≤ 0.0005 if an abciximab group had a lower event rate than the placebo group.

The goal of the prespecified final analyses was to test whether either abciximab group had a lower rate of the 30-day or 6-month composite end point than the placebo group. Simulations were performed for the computation of the type I error. We controlled for type I error for each end point by requiring consistent effects for the combined abciximab groups as compared with the placebo group; a screening test was required to show significance at a level of $P = 0.0287$ for a given end point before pairwise testing could be performed. Both screening and pairwise tests were one-sided. With this strategy, the total probability of concluding that either abciximab group fared better than the placebo group with respect to any one or more of the 30-day, 6-month, or interim-analysis end points was less than 5 percent if, in fact, no difference existed. A sample of 4800 patients was chosen to provide an 80 percent power to detect a 35 percent reduction in the rate of the 30-day primary end point, assuming a base-line (placebo-group) event rate of 7 percent.

RESULTS

Enrollment began on February 27, 1995. End-point and safety data for the first 1500 patients were reviewed by the Data and Safety Monitoring Com-

mittee on December 11, 1995. This interim analysis revealed that the incidence of death or myocardial infarction at 30 days was 8.2 percent for patients in the placebo group, as compared with 2.6 percent for patients treated with abciximab and low-dose heparin, and 3.6 percent for patients treated with abciximab and standard-dose heparin ($P < 0.001$). Since the prespecified stopping rule was met, the trial was terminated on December 14, 1995, with a total of 2792 of the planned 4800 patients enrolled.

There were no significant differences in base-line characteristics among patients in the three treatment groups (Table 1). Notably, despite the exclusion of patients with unstable angina accompanied by reversible electrocardiographic changes within the previous 24 hours, 48 percent of the patients enrolled met other clinical criteria for unstable angina.

The incidence of the composite end point of death, myocardial infarction, or urgent revascularization for severe myocardial ischemia at 30 days (Fig. 1) was 11.7 percent in the placebo group, 5.2 percent in the group assigned to abciximab with low-dose heparin (hazard ratio, 0.43; 95 percent confidence

TABLE 1. BASE-LINE DEMOGRAPHIC, CLINICAL, AND PROCEDURAL CHARACTERISTICS OF THE STUDY PATIENTS.*

CHARACTERISTIC	PLACEBO + STANDARD-DOSE HEPARIN (N=939)	ABCIXIMAB + LOW-DOSE HEPARIN (N=935)	ABCIXIMAB + STANDARD-DOSE HEPARIN (N=918)
Age — yr			
Median	60	60	60
Interquartile range	51–68	52–68	51–69
Weight — kg			
Median	84	84	84
Interquartile range	73–95	75–95	75–95
Male sex — no. (%)	674 (72)	668 (71)	670 (73)
Diabetes — no. (%)	224 (24)	212 (23)	202 (22)
Previous bypass surgery — no. (%)	119 (13)	121 (13)	109 (12)
Indication for procedure — no. (%)			
Recent infarction	189 (20)	200 (21)	190 (21)
Unstable angina	474 (50)	434 (46)	420 (46)
Stable ischemia	276 (29)	301 (32)	308 (34)
Interventional procedure — no. (%)*			
None	16 (1.7)	12 (1.3)	12 (1.3)
Balloon angioplasty	889 (95)	886 (95)	873 (95)
Directional atherectomy	50 (5)	46 (5)	48 (5)
Rotational atherectomy	5 (0.5)	5 (0.5)	5 (0.5)
Extraction atherectomy	2 (0.2)	4 (0.4)	2 (0.2)
Excimer laser treatment	7 (0.7)	4 (0.4)	3 (0.3)
Elective stenting	20 (2)	19 (2)	17 (2)
Unplanned stenting	124 (13)	81 (9)	121 (13)
Preintervention heparin dose — U			
Median	9400	5500	8600
Interquartile range	7800–11,700	4700–6600	7000–10,000
Preintervention heparin dose — U/kg			
Median	104.4	69.2	100.3
Interquartile range	97.4–145.8	59.3–72.0	83.0–115.8
Preintervention activated clotting time — sec			
Median	329	283	361
Interquartile range	311–358	247–324	326–402

*The categories are not mutually exclusive.

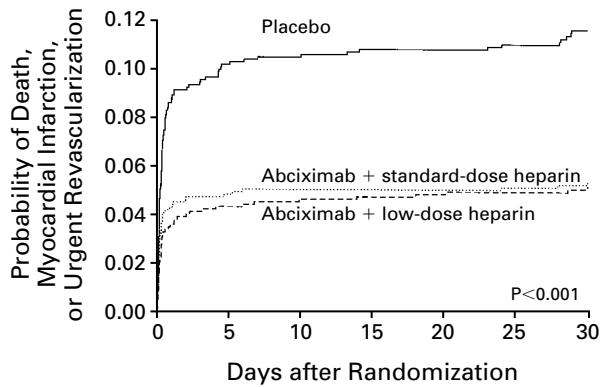


Figure 1. Kaplan–Meier Estimate of the Probability of the Primary Efficacy End-Point Events (Death, Myocardial Infarction, or Urgent Revascularization) within 30 Days after Randomization, According to Treatment Assignment.

interval, 0.30 to 0.60; $P < 0.001$), and 5.4 percent in the group assigned to abciximab with standard-dose heparin (hazard ratio, 0.45; 95 percent confidence interval, 0.32 to 0.63; $P < 0.001$). Each of the components of the composite end point was similarly reduced (Table 2). The treatment effect of abciximab with either heparin regimen was homogeneous among all patient groups (Fig. 2). Proportional-hazards regression using the base-line variables in Table 1 identified no significant interactions between the

characteristics of the patients and the effect of abciximab treatment.

The rates of hemorrhagic complications during hospitalization are summarized in Table 3. There were no significant differences among the treatment groups in the risk of major bleeding. Patients receiving abciximab with standard-dose heparin, but not those receiving abciximab with low-dose heparin, had significantly more minor bleeding events than patients receiving placebo. The rate of red-cell transfusions was significantly lower among patients receiving abciximab with low-dose heparin than among those receiving placebo. One patient in each abciximab group, but none in the placebo group, had a hemorrhagic stroke; two patients receiving abciximab with standard-dose heparin had other intracranial bleeding or a nonhemorrhagic stroke. Severe thrombocytopenia (platelet count, $< 50,000$ per cubic millimeter) occurred in four patients in the placebo group (0.4 percent), four patients assigned to abciximab and low-dose heparin (0.4 percent), and eight patients in the group assigned to abciximab and standard-dose heparin (0.9 percent, $P = 0.260$).

At six months, the cumulative incidence of death, myocardial infarction, or repeated revascularization was 25.8 percent in the placebo group, 22.8 percent in the group assigned to abciximab with low-dose heparin (11.7 percent risk reduction, $P = 0.07$), and 22.3 percent in the group assigned to abciximab with standard-dose heparin (13.7 percent risk reduc-

TABLE 2. COMPONENTS OF THE 30-DAY PRIMARY COMPOSITE EFFICACY END POINT.*

EFFICACY END POINT	PLACEBO + STANDARD-DOSE HEPARIN (N = 939)	ABCIXIMAB + LOW-DOSE HEPARIN (N = 935)	P VALUE†	ABCIXIMAB + STANDARD-DOSE HEPARIN (N = 918)	P VALUE†
	no. of patients (%)			no. of patients (%)	
Composite	109 (11.7)	48 (5.2)	<0.001	49 (5.4)	<0.001
Death	7 (0.8)	3 (0.3)	0.21	4 (0.4)	0.39
Myocardial infarction	81 (8.7)	34 (3.7)	<0.001	35 (3.8)	<0.001
Q-wave	7 (0.8)	4 (0.4)	0.36	4 (0.5)	0.38
Non-Q-wave	74 (7.9)	30 (3.2)	<0.001	31 (3.4)	<0.001
Large non-Q-wave (CK MB $\geq 5 \times$ control)‡	53 (5.6)	19 (2.0)	<0.001	23 (2.5)	<0.001
Small non-Q-wave (CK MB 3–5 \times control)‡	18 (1.9)	11 (1.2)	0.26	8 (0.9)	0.07
Non-Q-wave after hospitali- zation	3 (0.3)	0	0.25	0	0.25
Urgent revascularization	48 (5.2)	15 (1.6)	<0.001	21 (2.3)	0.001
Repeated percutaneous inter- vention	35 (3.8)	11 (1.2)	<0.001	14 (1.5)	0.003
Coronary-artery bypass grafting	16 (1.7)	4 (0.4)	0.007	8 (0.9)	0.11
Death or myocardial infarction	85 (9.1)	35 (3.8)	<0.001	38 (4.2)	<0.001

*Data were incomplete for 3 percent of the study patients — 30 patients in the placebo group, 30 in the group given abciximab and low-dose heparin, and 24 in the group given abciximab and standard-dose heparin.

†P values are for the comparison between the abciximab group and the placebo group.

‡CK denotes creatine kinase.

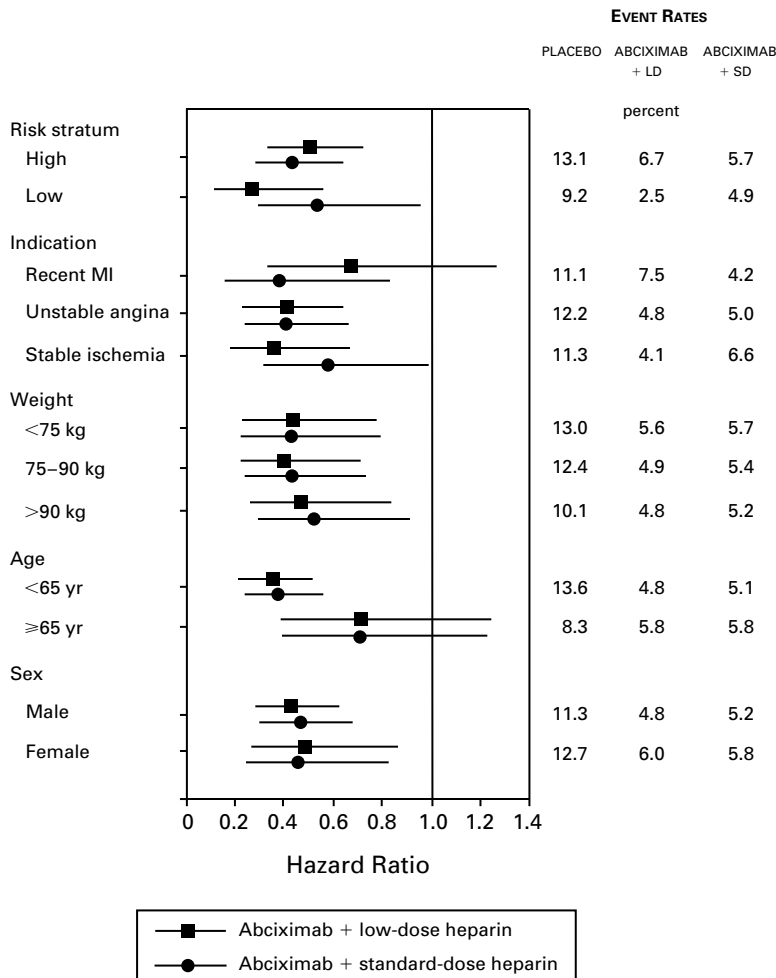


Figure 2. Hazard Ratios and 95 Percent Confidence Intervals for the 30-Day Primary Efficacy End Point in Prespecified Subgroups Defined According to Risk Stratum, Indication for Revascularization, Weight, Age, and Sex.

LD denotes low-dose, weight-adjusted heparin; SD standard-dose, weight-adjusted heparin; and MI myocardial infarction. The high-risk stratum was defined at the time of randomization as the patients with myocardial infarction within the previous seven days or adverse lesion morphology on angiography²; all other patients were considered to be at low risk. Hazard ratios are for the abciximab groups as compared with the placebo group.

tion, $P=0.04$). The treatment effect observed at 30 days for the reduction in acute ischemic complications (death, myocardial infarction, or urgent revascularization) was maintained throughout the 6-month follow-up period; thus, the attenuation of risk reduction observed for the 6-month composite end point was due to the lack of effect of abciximab on the incidence of nonurgent repeated revascularization procedures (Table 4). There were no significant differences in the incidence of target-vessel revascularization among the three treatment groups.

DISCUSSION

The EPIC study demonstrated the efficacy of abciximab in reducing complications among patients

at high risk during coronary intervention because of unstable ischemic syndromes or unfavorable lesion morphology on angiography.² However, important questions were raised regarding whether such a strategy should be used for all patients undergoing percutaneous coronary revascularization, particularly in view of the increased risk of hemorrhage associated with the use of abciximab. In the current trial, abciximab administered with a reduced-dose, weight-adjusted heparin regimen decreased the rate of the composite 30-day end point by 56 percent across a broad spectrum of patients without an attendant increase in the risk of major bleeding complications.

A noteworthy consistency of treatment effect was observed for each of the components of the com-

TABLE 3. BLEEDING END POINTS.*

BLEEDING END POINT†	PLACEBO + STANDARD-DOSE HEPARIN (N=939)	ABCIXIMAB + LOW-DOSE HEPARIN (N=935)	P VALUE‡	ABCIXIMAB + STANDARD-DOSE HEPARIN (N=918)	P VALUE‡
	no. of patients (%)			no. of patients (%)	
Major bleeding	29 (3.1)	19 (2.0)	0.19	32 (3.5)	0.7
Minor bleeding	35 (3.7)	37 (4.0)	0.81	68 (7.4)	<0.001
Transfusion					
Red cells	37 (3.9)	18 (1.9)	0.013	30 (3.3)	0.46
Platelets	10 (1.1)	8 (0.9)	0.81	15 (1.6)	0.32
Major bleeding unrelated to CABG	10 (1.1)	10 (1.1)	1.000	17 (1.9)	0.18
Minor bleeding unrelated to CABG	32 (3.4)	37 (4.0)	0.54	70 (7.6)	<0.001
Transfusion unrelated to CABG					
Red cells	18 (2.0)	11 (1.2)	0.20	16 (1.8)	0.86
Platelets	1 (0.1)	4 (0.4)	0.37	5 (0.6)	0.12
Stroke or intracranial bleeding	0	2 (0.2)	0.25	3 (0.3)	0.12
Hemorrhagic stroke	0	1 (0.1)	0.5	1 (0.1)	0.494
Nonhemorrhagic stroke with hemorrhagic transformation	0	0	1.000	0	1.000
Other intracranial bleeding	0	0	1.000	2 (0.2)§	0.24
Nonhemorrhagic stroke	0	1 (0.1)	0.5	1 (0.1)§	0.49

*The categories are not mutually exclusive.

†CABG denotes coronary-artery bypass grafting.

‡P values are for the comparison between the abciximab group and the placebo group.

§One patient had both nonhemorrhagic stroke and other intracranial bleeding.

TABLE 4. COMPONENTS OF THE SIX-MONTH COMPOSITE EFFICACY END POINT.*

EFFICACY END POINT	PLACEBO + STANDARD-DOSE HEPARIN (N=939)	ABCIXIMAB + LOW-DOSE HEPARIN (N=935)	P VALUE†	ABCIXIMAB + STANDARD-DOSE HEPARIN (N=918)	P VALUE†
	no. of patients (%)			no. of patients (%)	
Composite — death, myocardial infarction, or any revascularization‡	241 (25.8)	212 (22.8)	0.07	203 (22.3)	0.04
Composite — death, myocardial infarction, or urgent revascularization§	138 (14.7)	78 (8.4)	<0.001	76 (8.3)	<0.001
Death	16 (1.7)	10 (1.1)	0.24	13 (1.4)	0.62
Myocardial infarction	93 (9.9)	47 (5.0)	<0.001	48 (5.3)	<0.001
Q-wave	15 (1.6)	12 (1.3)	0.56	13 (1.4)	0.74
Non-Q-wave	79 (8.4)	36 (3.9)	<0.001	36 (3.9)	<0.001
Repeated revascularization	180 (19.4)	176 (19.0)	0.71	167 (18.4)	0.52
Urgent revascularization	63 (6.7)	29 (3.1)	<0.001	32 (3.5)	0.002
Nonurgent revascularization	127 (13.8)	155 (16.7)	0.07	139 (15.4)	0.33
Target-vessel revascularization	168 (18.1)	157 (17.0)	0.41	147 (16.2)	0.23

*Data were incomplete for 0.4 percent of the study patients — three patients in the placebo group, three in the group given abciximab and low-dose heparin, and six in the group given abciximab and standard-dose heparin.

†P values are for the comparison between the abciximab group and the placebo group.

‡This was the prespecified six-month composite end point.

§This was the composite end point used for the 30-day analysis.

posite end point, as well as for the magnitude of benefit among the various subgroups of patients. The reduction in acute ischemic complications after abciximab treatment was durable over six months of follow-up, although incremental efficacy in reducing the need for nonurgent revascularization procedures was not observed. This study not only establishes the central role of platelet aggregation in the pathogenesis of acute ischemic complications associated with routine percutaneous revascularization, regardless of the patient's risk profile, but also provides proof that the clinical benefit derived from the inhibition of platelet thrombus formation by blockade of glycoprotein IIb/IIIa receptor may be uncoupled from the risk of hemorrhage.

Although it is correlated with the risk of hemorrhage during catheterization or interventional procedures,⁸⁻¹¹ adjunctive heparin therapy is universally employed in patients undergoing percutaneous revascularization. On the basis of observational data indicating that the probability of abrupt vessel closure or ischemic complications may be related to lower levels of anticoagulation,¹²⁻¹⁴ the standard of care in many catheterization laboratories has been the routine administration of a bolus of 10,000 to 15,000 U of heparin to achieve an activated clotting time of at least 300 to 350 seconds before coronary angioplasty is begun.^{15,16}

Previous studies demonstrating benefit from aggressive anticoagulant therapy with heparin during percutaneous coronary revascularization may not, however, be relevant when more potent platelet inhibition is achieved. Moreover, heparin appears to potentiate the bleeding risk of glycoprotein IIb/IIIa receptor blockade. In the EPIC study,² the rate of major bleeding was increased from 6.6 percent among patients receiving placebo to 14 percent among those receiving abciximab, with the greatest risk of bleeding in the patients of lowest body weight, for whom the fixed heparin doses were highest on a weight-adjusted basis.^{2,3}

Because the heparin doses in the current trial were adjusted for body weight (Table 1), even the patients on the standard-dose heparin regimen received less heparin than the boluses of 10,000 to 15,000 U that are frequently used empirically in clinical practice. Moreover, other interventions included early removal of the sheath (with elimination of postprocedural heparin infusion), meticulous care of the vascular access site, and transfusion guidelines. With this integrated strategy, major hemorrhage and the need for transfusions occurred infrequently in all three treatment groups, although the lowest rates of hemorrhagic complications, particularly minor bleeding, were observed when abciximab was administered with low-dose heparin.

Despite the reduction in the dosage of heparin, the treatment effect of abciximab in limiting ische-

mic complications of coronary revascularization was marked: for every 1000 patients treated, 65 fewer had acute adverse events. No other therapy has been reported to produce this degree of reduction in important myocardial ischemic events in a broad population of patients undergoing coronary intervention. The rates of myocardial infarction, most frequently non-Q-wave infarction, and of urgent revascularization were reduced by a similar magnitude (relative risk reductions of 58 and 68 percent, respectively). Although the clinical significance of periprocedural non-Q-wave myocardial infarction after percutaneous coronary revascularization remains somewhat controversial, several recent reports have clearly demonstrated that patients who have elevated levels of creatine kinase after coronary intervention are at significantly greater risk for late death from cardiac causes than those who do not.¹⁷⁻²¹ An increased risk of late events has been observed in these studies even among patients with small elevations of creatine kinase MB (from more than 1 to 1.5 times the control value),^{19,21} but the risk of death appears to be proportional to the degree of enzyme elevation. The reduction in the rate of periprocedural myocardial infarction by abciximab in this trial occurred mainly for large, non-Q-wave infarctions (creatin kinase MB, >5 times the control value). This observation confirms that the ischemic events that were prevented would have been clinically relevant and not merely laboratory abnormalities.

Notably, the six-month outcome in the EPILOG trial differed from that in the EPIC trial with regard to the incidence of repeated revascularization events. In the EPIC trial, abciximab therapy was associated with a 26 percent reduction in the need for revascularization of the target vessel (defined as further revascularization in a vessel treated during the index procedure),²² leading to the hypothesis that this agent may inhibit the process of restenosis. In the EPILOG trial, in contrast, no differences in long-term revascularization rates were observed. Acute ischemic events (death, myocardial infarction, and urgent revascularization), however, were suppressed by abciximab throughout the six-month follow-up period. The reasons for the disparate effects of abciximab on nonurgent-revascularization rates in these two large-scale trials are unknown, but they may relate in part to changes in coronary interventional practice (including the unplanned use of stents in 12 percent of the patients in the EPILOG trial), or to differences in patient populations or the dosage of heparin.

The clinical applicability of glycoprotein IIb/IIIa receptor blockade during percutaneous coronary revascularization is potentially broad. However, the cost of abciximab (\$1,407 per dose, on average)²³ is an obstacle to the widespread use of this therapy. A formal economic analysis of the EPILOG trial will ex-

plore the key issue of the cost effectiveness of this treatment. Other important considerations include the associated risk of thrombocytopenia and the currently unknown consequences of readministration of this chimeric antibody fragment (IgG antibody response develops in approximately 6 percent of patients on first administration).

In summary, this trial establishes that blockade of platelet glycoprotein IIb/IIIa receptor with abciximab has potentially broad clinical use in reducing ischemic complications associated with percutaneous coronary revascularization. Optimal use of this treatment in clinical practice will require minimizing bleeding complications by using low-dose heparin therapy in conjunction with abciximab.

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APPENDIX

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