

COMPLEMENTARY CLINICAL BENEFITS OF CORONARY-ARTERY STENTING AND BLOCKADE OF PLATELET GLYCOPROTEIN IIb/IIIa RECEPTORS

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ABSTRACT

Background Inhibition of the platelet glycoprotein IIb/IIIa receptor with the monoclonal-antibody fragment abciximab reduces the acute ischemic complications associated with percutaneous coronary revascularization, whereas coronary-stent implantation reduces restenosis. We conducted a trial to determine the efficacy of abciximab and stent implantation in improving long-term outcome.

Methods A total of 2399 patients were randomly assigned to stent implantation and placebo, stent implantation and abciximab, or balloon angioplasty and abciximab. The patients were followed for six months.

Results At six months, the incidence of the composite end point of death or myocardial infarction was 11.4 percent in the group that received a stent and placebo, as compared with 5.6 percent in the group that received a stent and abciximab (hazard ratio, 0.47; 95 percent confidence interval, 0.33 to 0.68; $P < 0.001$) and 7.8 percent in the group assigned to balloon angioplasty and abciximab (hazard ratio, 0.67; 95 percent confidence interval, 0.49 to 0.92; $P = 0.01$). The hazard ratio for stenting plus abciximab as compared with angioplasty plus abciximab was 0.70 (95 percent confidence interval, 0.48 to 1.04; $P = 0.07$). The rate of repeated revascularization of the target vessel was 10.6 percent in the stent-plus-placebo group, as compared with 8.7 percent in the stent-plus-abciximab group (hazard ratio, 0.82; 95 percent confidence interval, 0.59 to 1.13; $P = 0.22$) and 15.4 percent in the angioplasty-plus-abciximab group (hazard ratio, 1.49; 95 percent confidence interval, 1.13 to 1.97; $P = 0.005$). The hazard ratio for stenting plus abciximab as compared with angioplasty plus abciximab was 0.55 (95 percent confidence interval, 0.41 to 0.74; $P < 0.001$). Among patients with diabetes, the combination of abciximab and stenting was associated with a lower rate of repeated target-vessel revascularization (8.1 percent) than was stenting and placebo (16.6 percent, $P = 0.02$) or angioplasty and abciximab (18.4 percent, $P = 0.008$).

Conclusions For coronary revascularization, abciximab and stent implantation confer complementary long-term clinical benefits. (N Engl J Med 1999;341:319-27.)

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SINCE the introduction of balloon angioplasty more than 20 years ago, two therapies have been demonstrated to improve outcomes after the procedure and have been widely adopted into clinical practice. Inhibition of platelet aggregation by blockade of the platelet surface glycoprotein IIb/IIIa receptor with abciximab, a monoclonal-antibody Fab fragment, was shown to reduce the incidence of periprocedural ischemic complications among patients undergoing balloon angioplasty or atherectomy.¹⁻³ The development of techniques for blocking the glycoprotein IIb/IIIa receptor was paralleled by the widespread acceptance of coronary-artery stent implantation as the predominant means of percutaneous coronary intervention, on the basis of the efficacy of the device in reducing rates of repeated revascularization.⁴⁻⁷

In the Evaluation of Platelet IIb/IIIa Inhibition in Stenting (EPISTENT) trial, a randomized, placebo-controlled study, the effect of abciximab therapy among patients undergoing stent implantation or balloon angioplasty was evaluated and compared with the effect of stent implantation alone. As compared with stenting plus placebo, administration of abciximab in addition to either stenting or angioplasty significantly reduced the risk of ischemic complications within 30 days of the procedure.⁸ The known efficacy of stenting, however, is largely due to reductions in the rates of long-term restenosis and repeated target-vessel revascularization, benefits that would not be manifest within the first 30 days. In this re-

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port, we present the results of clinical and angiographic follow-up of the patients in the EPISTENT study at six months, which provide evidence that stent implantation and platelet glycoprotein IIb/IIIa receptor blockade have complementary clinical effects on the long-term efficacy and safety of percutaneous coronary revascularization.

METHODS

Patients

The details of the trial design have been reported previously.⁸ In brief, 2399 patients undergoing elective or urgent percutaneous coronary revascularization were enrolled between July 22, 1996, and September 25, 1997, at 63 centers throughout the United States and Canada. Patients were eligible for enrollment if they had at least one target lesion suitable for treatment either by stenting or by balloon angioplasty and were not undergoing primary intervention for acute myocardial infarction. The protocol was approved by the institutional review board at each clinical site, and all the patients gave written informed consent.

Study Protocol

All the patients were treated with aspirin. Ticlopidine was to be given after stent implantation, and according to the protocol, one or more doses could be given before study-drug administration. Patients were randomly assigned (by means of telephone calls to the randomization center at the Duke Clinical Research Institute) to one of three groups: stenting and placebo, stenting and abciximab, or balloon angioplasty and abciximab. The stent manufactured by Johnson and Johnson (New Brunswick, N.J.) was to be used unless it could not be deployed. Criteria were specified for unplanned stent implantation to maintain patency after manifest or threatened abrupt closure in patients assigned to angioplasty, and cross-over to stenting occurred in 19 percent of these patients. Investigators were blinded to the drug assignment (abciximab or placebo) of the two groups that also underwent stenting, but they could not be blinded to the drug assignment of the angioplasty group, since only abciximab was given. Abciximab (ReoPro, Centocor, Malvern, Pa.) was administered as a bolus of 0.25 mg per kilogram of body weight 10 to 60 minutes before balloon inflation, followed by an infusion of 0.125 μ g per kilogram per minute (maximal dosage, 10 μ g per minute) for 12 hours. Patients assigned to abciximab received low-dose, weight-adjusted heparin, and those assigned to placebo received heparin at a standard, weight-adjusted dose.²

Angiographic Substudy

The first 899 consecutive patients in the trial gave their consent to be included in an angiographic substudy and underwent repeated angiography 184 to 275 days after randomization. Angiographic follow-up was to be carried out if the index revascularization procedure (performed at the time of randomization) was successful (residual stenosis, \leq 50 percent) in at least one target lesion, unless the patient subsequently died or underwent repeated revascularization of all target lesions within seven days of the index procedure. Angiograms that were obtained before repeated revascularization or three to six months after randomization or that demonstrated occlusion of all the target lesions were included in the angiographic analysis. Computerized quantitative analysis of procedural and follow-up cineangiograms was performed at a core laboratory with an AngioComm Review Station (Quinton Instruments, Bothell, Wash.). Quantitative coronary analysis was carried out with first- and second-derivative automated edge-detection software (CathView, version 2.6, Quinton Instruments).⁹

Study End Points

Two principal end points were defined for assessment 6 months (\geq 183 days) after randomization: death or myocardial infarction

as a composite measure and repeated revascularization of a target vessel. Classifications with respect to the end points were made by a clinical-events committee, which was blinded to the patients' study-group assignments. An in-hospital myocardial infarction was defined as the presence of new "significant" Q waves (according to the Minnesota code¹⁰) in two or more contiguous electrocardiographic leads or an elevation of creatine kinase or its MB isoenzyme to at least three times the upper limit of normal at each hospital's laboratory in two samples collected at different times. Myocardial infarction after hospital discharge was defined as the development of new Q waves or an elevation of creatine kinase or its MB isoenzyme to more than two times the upper limit of normal.

In the angiographic substudy, analysis was carried out on a per-lesion basis. Luminal dimensions were taken as the average of measured values in two orthogonal projections (or in one projection if only one was available). The principal end point for the angiographic substudy was the minimal luminal diameter at follow-up.

Data Collection and Statistical Analysis

For assessment of the outcome at 6 months, all patients were to be contacted by investigators at the individual study sites and electrocardiography was to be performed 183 days or more after randomization. Hospital records, death certificates, and autopsy reports were obtained when relevant. Investigators and study coordinators remained blinded to the study-group assignments of individual patients.

Differences among patients with regard to efficacy were examined in an intention-to-treat analysis. To be considered complete, the 6-month follow-up evaluation had to have been performed at least 165 days after randomization. Pairwise comparisons between each of the two abciximab groups (stenting and balloon angioplasty) and the stent-plus-placebo group were made with use of the log-rank test, and event rates were calculated by the Kaplan-Meier method. A secondary comparison was made between the two abciximab groups. Reported P values were two-sided. Analysis of outcomes among the subgroups of patients with and without diabetes mellitus was prospectively planned; patients with diabetes were identified by a documented medical history of hyperglycemia with dietary or pharmacologic therapy.

30-Day Outcome and Completeness of Follow-up

The results of the analysis of the primary efficacy end point at 30 days have been reported previously.⁸ This primary efficacy end point consisted of the composite of death, myocardial infarction, or urgent repeated revascularization and occurred in 10.8 percent of the patients in the stent-plus-placebo group, 5.3 percent of those in the stent-plus-abciximab group, and 6.9 percent of those in the angioplasty-plus-abciximab group ($P < 0.001$ and $P = 0.007$, respectively, for the comparison with stent plus placebo).

No additional entries were permitted in the six-month follow-up data base after July 27, 1998. Survival status at 165 days was unknown for 14 of the 2399 patients enrolled (0.6 percent); for these 14 patients, the median follow-up time was 34 days. For the assessment of events other than death, a total of 42 patients (1.8 percent) had fewer than 165 days of follow-up with no report of an end-point event. Rates of completeness of follow-up were similar among the three treatment groups.

RESULTS

Base-Line Characteristics

Base-line clinical characteristics of the study patients have been described previously.⁸ Of the 2399 patients, 491 (20 percent) had diabetes. At the time of randomization, 379 of these patients (77 percent) were receiving oral hypoglycemic agents, insulin, or both; of the others, 21 had previously been treated with oral hypoglycemic agents.

Angiographic characteristics were well matched among the three treatment groups. In 25 percent of patients multiple coronary lesions were treated. Coronary vessels that required treatment were the left anterior descending, circumflex, and right coronary arteries in 39 percent, 25 percent, and 42 percent of patients, respectively; a coronary-artery bypass graft was treated in 4 percent. Characteristics of complex lesions included a length of more than 10 mm in 50 percent of patients, eccentricity in 56 percent, moderate or extreme tortuosity in 24 percent, moderate or extreme angulation in 15 percent, calcification in 11 percent, thrombus in 13 percent, and total occlusion in 7 percent, with some patients having lesions with several of these features.

Before administration of the study drug, 53 percent of the patients received at least one dose of ticlopidine.

Clinical Efficacy at Six Months

Six months after treatment, the incidence of the composite end point of death or myocardial infarction was 11.4 percent in the group randomly assigned to stent implantation and placebo, as compared with 5.6 percent in the group assigned to stent implantation and abciximab (hazard ratio, 0.47; 95 percent confidence interval, 0.33 to 0.68; $P < 0.001$) and 7.8 percent in the group assigned to balloon angioplasty and abciximab (hazard ratio, 0.67; 95 percent confidence interval, 0.49 to 0.92; $P = 0.01$); the hazard ratio for stent implantation and abciximab as compared with angioplasty and abciximab was 0.70 (95 percent confidence interval, 0.48 to 1.04; $P = 0.07$) (Fig. 1A). The effect of abciximab treatment was achieved early and was maintained throughout the 6-month follow-up period; the absolute reduction in the number of events that met the definition of the composite end point (number of events prevented per 100 patients treated) as compared with the number in the group that underwent stent implantation with placebo was 5.5 at 30 days and 5.8 at 6 months in the stent-plus-abciximab group and 4.4 at 30 days and 3.6 at 6 months in the angioplasty-plus-abciximab group.

Results with respect to individual components of the composite end point (death or myocardial infarction), as well as revascularization procedures performed on an urgent basis, are shown in Table 1. As compared with stenting accompanied by placebo, stenting and abciximab resulted in reductions of a similar magnitude with respect to each of these end-point events. As compared with stenting accompanied by placebo, balloon angioplasty accompanied by abciximab was associated with a lower risk of myocardial infarction but similar rates of death or urgent revascularization procedures. Among patients who received abciximab, mortality was significantly lower among those who underwent stent implanta-

tion than among those who underwent balloon angioplasty (0.5 percent vs. 1.8 percent, $P = 0.02$).

At six months, the incidence of repeated revascularization of the target vessel was 10.6 percent in the stent-plus-placebo group, as compared with 8.7 percent in the stent-plus-abciximab group (hazard ratio, 0.82; 95 percent confidence interval, 0.59 to 1.13; $P = 0.22$) and 15.4 percent in the angioplasty-plus-abciximab group (hazard ratio, 1.49; 95 percent confidence interval, 1.13 to 1.97; $P = 0.005$) (Table 2 and Fig. 1B). Rates of target-vessel revascularization and overall revascularization were significantly lower among patients who underwent stenting with or without abciximab than among those who underwent balloon angioplasty with abciximab; this beneficial effect was confined to eliminating the need for nonurgent percutaneous revascularization (Table 2). Event curves for repeated target-vessel revascularization procedures began to diverge after approximately 60 days (Fig. 1B). Among the patients in the two abciximab groups, random assignment to stent implantation rather than angioplasty resulted in a 44 percent lower incidence of target-vessel revascularization (hazard ratio, 0.55; 95 percent confidence interval, 0.41 to 0.74; $P < 0.001$).

Among patients with diabetes mellitus, rates of repeated revascularization of the target vessel after stent implantation were significantly lower among patients given abciximab than among those given placebo (Fig. 2A). Among these patients, stenting accompanied only by placebo was not associated with a significantly lower rate of subsequent target-vessel revascularization than was balloon angioplasty accompanied by abciximab, whereas the rate of this end point was roughly half as high among patients assigned to stenting and abciximab. Abciximab had no effect on the need for repeated revascularization among patients without diabetes (Fig. 2B). The effect of abciximab on the end point of death or myocardial infarction at six months was similar among patients with diabetes and those without diabetes.

Angiographic Substudy

Of the 899 patients enrolled in the angiographic substudy, 816 were eligible for analysis; the others were excluded because of an unsuccessful index revascularization procedure, revascularization performed within seven days of the index procedure or without a previous angiogram, or death. Of the 816 eligible patients, follow-up angiography was not performed in 105, and angiograms were technically inadequate or unavailable or were obtained more than 275 days after the index procedure in an additional 65 patients. Thus, follow-up angiograms from a total of 646 of the 816 eligible patients (79 percent) were analyzed in the angiographic substudy.

Patients included in the substudy were representative of the overall population in the trial, and there

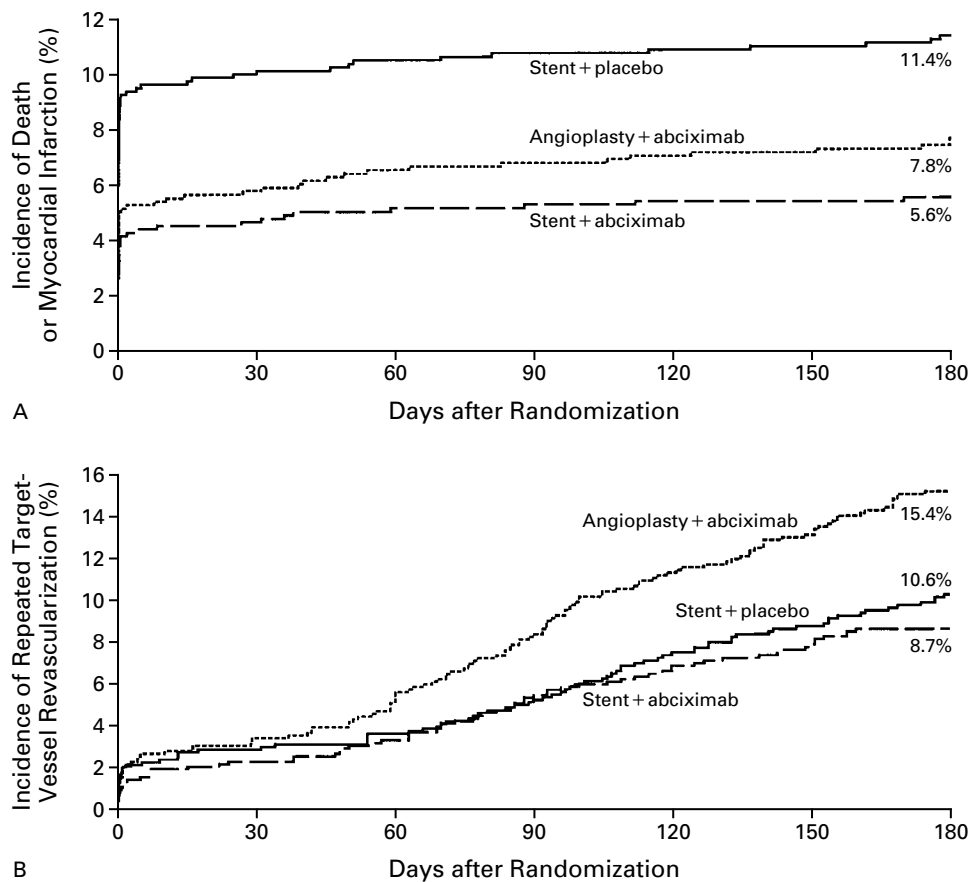


Figure 1. Kaplan-Meier Estimates of the Incidence of the Efficacy End Points.

Panel A shows the incidence of the composite end point of death or myocardial infarction, and Panel B the incidence of repeated target-vessel revascularization within six months after randomization, according to treatment assignment. For the composite end point of death or myocardial infarction, $P < 0.001$ for the comparison between the stent-plus-abciximab group and the stent-plus-placebo group, $P = 0.01$ for the comparison between the angioplasty-plus-abciximab group and the stent-plus-placebo group, and $P = 0.07$ for the comparison between the stent-plus-abciximab group and the angioplasty-plus-abciximab group. For the end point of repeated target-vessel revascularization, $P = 0.22$ for the comparison between the stent-plus-abciximab group and the stent-plus-placebo group, $P = 0.005$ for the comparison between the angioplasty-plus-abciximab group and the stent-plus-placebo group, and $P < 0.001$ for the comparison between the stent-plus-abciximab group and the angioplasty-plus-abciximab group.

were no significant differences in base-line characteristics or clinical outcomes between those who were included in the substudy and those who were not. Angiographic outcomes among the patients in the substudy are summarized in Table 3. Minimal luminal diameters after the intervention and early gains in diameter were significantly greater among patients who underwent stent implantation than among those who underwent angioplasty. Among patients who received a stent, the net gain in diameter was significantly greater among those who received abciximab than among those assigned to placebo, with a trend toward greater minimal luminal diameters at six months and a lower loss index (late loss divided by early gain) (Table 3). Key angiographic variables among patients

with diabetes and those without it are illustrated in Figure 3. At follow-up, minimal luminal diameters and net gain were substantially lower among patients with diabetes than among those without this condition in the angioplasty-plus-abciximab and stent-plus-placebo groups. In contrast, among those who underwent stenting and received abciximab, there were virtually no differences between patients with diabetes and those without it with regard to these angiographic variables.

DISCUSSION

The design of our trial allowed the roles of platelet glycoprotein IIb/IIIa receptor blockade and coronary-artery stenting to be defined in patients re-

TABLE 1. INCIDENCE OF THE EFFICACY END-POINT EVENTS AT SIX MONTHS.*

EFFICACY END POINT	STENT PLUS PLACEBO (N=809)	STENT PLUS ABCIXIMAB (N=794)	P VALUE†	ANGIOPLASTY PLUS ABCIXIMAB (N=796)	P VALUE‡	P VALUE§
	no. of patients (%)			no. of patients (%)		
Composite end points						
Death or myocardial infarction	92 (11.4)	44 (5.6)	<0.001	62 (7.8)	0.01	0.07
Death, myocardial infarction, or urgent repeated revascularization	98 (12.1)	51 (6.4)	<0.001	73 (9.2)	0.05	0.04
Death or large myocardial infarction¶	75 (9.4)	32 (4.1)	<0.001	54 (6.9)	0.06	0.02
Death	10 (1.2)	4 (0.5)	0.12	14 (1.8)	0.39	0.02
Myocardial infarction	83 (10.3)	41 (5.2)	<0.001	52 (6.6)	0.007	0.24
Q-wave	12 (1.5)	10 (1.3)	0.83	17 (2.1)	0.35	0.17
Large non-Q-wave	47 (5.8)	16 (2.0)	<0.001	21 (2.6)	0.002	0.51
Small non-Q-wave	17 (2.1)	12 (1.5)	0.46	9 (1.1)	0.17	0.52
Non-Q-wave after index hospitalization	7 (0.9)	3 (0.4)	0.34	5 (0.6)	0.77	0.73
Urgent revascularization	21 (2.6)	13 (1.6)	0.18	17 (2.1)	0.54	0.46
Repeated percutaneous intervention	12 (1.5)	8 (1.0)	0.39	12 (1.5)	0.97	0.37
Coronary-artery bypass grafting	11 (1.4)	6 (0.8)	0.24	5 (0.6)	0.14	0.76

*Percentages were derived by Kaplan–Meier analysis.

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

‡P values are for the comparison between the stent-plus-placebo group and the angioplasty-plus-abciximab group.

§P values are for the comparison between the stent-plus-abciximab group and the angioplasty-plus-abciximab group.

¶A large myocardial infarction was a Q-wave myocardial infarction, a large non-Q-wave myocardial infarction, or a non-Q-wave myocardial infarction after the index hospitalization.

||A large non-Q-wave myocardial infarction was defined as one associated with a creatine kinase MB isoenzyme level greater than five times the control level, and a small non-Q-wave myocardial infarction as one associated with a creatine kinase MB isoenzyme level three to five times the control level.

TABLE 2. REPEATED REVASCULARIZATION PROCEDURES WITHIN SIX MONTHS AFTER RANDOMIZATION.*

TYPE OF PROCEDURE OR END POINT	STENT PLUS PLACEBO (N=809)	STENT PLUS ABCIXIMAB (N=794)	P VALUE†	ANGIOPLASTY PLUS ABCIXIMAB (N=796)	P VALUE‡	P VALUE§
	no. of patients (%)			no. of patients (%)		
Repeated target-vessel revascularization	84 (10.6)	68 (8.7)	0.22	120 (15.4)	0.005	<0.001
Any repeated revascularization	104 (13.1)	88 (11.2)	0.26	135 (17.3)	0.02	<0.001
Any percutaneous revascularization	74 (9.3)	59 (7.5)	0.21	110 (14.1)	0.003	<0.001
Any coronary-artery bypass grafting	37 (4.6)	34 (4.3)	0.76	31 (4.0)	0.50	0.71
Urgent revascularization	21 (2.6)	13 (1.6)	0.18	17 (2.1)	0.54	0.46
Nonurgent revascularization	85 (10.7)	77 (9.9)	0.60	121 (15.5)	0.005	<0.001
Death, myocardial infarction, or repeated target-vessel revascularization	147 (18.3)	102 (13.0)	0.003	162 (20.5)	0.37	<0.001

*Percentages were derived by Kaplan–Meier analysis.

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

‡P values are for the comparison between the stent-plus-placebo group and the angioplasty-plus-abciximab group.

§P values are for the comparison between the stent-plus-abciximab group and the angioplasty-plus-abciximab group.

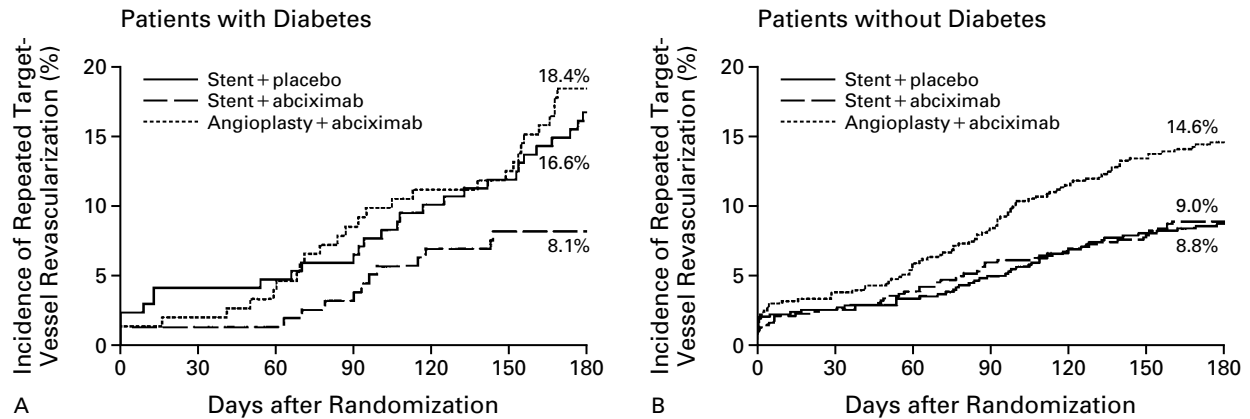


Figure 2. Kaplan–Meier Estimates of the Incidence of Repeated Target-Vessel Revascularization within Six Months after Randomization, According to Treatment Assignment, among Patients with Diabetes (Panel A) and Patients without Diabetes (Panel B).

Among patients with diabetes, P=0.02 for the comparison between the stent-plus-abciximab group and the stent-plus-placebo group, P=0.70 for the comparison between the angioplasty-plus-abciximab group and the stent-plus-placebo group, and P=0.008 for the comparison between the stent-plus-abciximab group and the angioplasty-plus-abciximab group (Panel A). Among patients without diabetes, P=0.95 for the comparison between the stent-plus-abciximab group and the stent-plus-placebo group, P=0.002 for the comparison between the angioplasty-plus-abciximab group and the stent-plus-placebo group, and P=0.002 for the comparison between the stent-plus-abciximab group and the angioplasty-plus-abciximab group (Panel B).

TABLE 3. OUTCOMES IN THE ANGIOGRAPHIC SUBSTUDY.*

LUMINAL DIAMETER†	STENT PLUS PLACEBO (N=217)	STENT PLUS ABCIXIMAB (N=237)	P VALUE‡	ANGIOPLASTY PLUS ABCIXIMAB (N=192)	P VALUE§	P VALUE¶
Reference vessel (mm)	2.84±0.52	2.84±0.46	0.99	2.81±0.44	0.64	0.63
Before intervention (mm)	0.86±0.39	0.80±0.38	0.05	0.85±0.34	0.73	0.13
After intervention (mm)	2.39±0.49	2.39±0.43	0.93	1.93±0.44	<0.001	<0.001
At 6-mo follow up (mm)	1.60±0.70	1.66±0.62	0.26	1.47±0.56	0.04	<0.001
Early gain (mm)	1.53±0.55	1.60±0.52	0.11	1.09±0.48	<0.001	<0.001
Late loss (mm)	0.79±0.62	0.73±0.60	0.30	0.46±0.54	<0.001	<0.001
Net gain (mm)	0.73±0.71	0.86±0.66	0.03	0.62±0.58	0.09	<0.001
Loss index	0.60±1.14	0.41±0.81	0.07	0.48±1.27	0.37	0.39

*Values are expressed as means ±SD on a per-lesion basis.

†Early gain is the difference between the minimal luminal diameter after intervention and the diameter before intervention; late loss is the difference between the minimal luminal diameter after intervention and the diameter at the six-month follow-up; net gain is the difference between the early gain and the late loss; and loss index is the late loss divided by the early gain.

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

§P values are for the comparison between the stent-plus-placebo group and the angioplasty-plus-abciximab group.

¶P values are for the comparison between the stent-plus-abciximab group and the angioplasty-plus-abciximab group.

quiring coronary revascularization. We were able to compare stenting with balloon angioplasty among patients receiving abciximab and to compare the effectiveness of abciximab with that of placebo among patients who received a stent. The results at six months indicate that stent implantation and potent inhibition of platelet aggregation with abciximab provide

important and complementary long-term clinical benefits after coronary intervention. Specifically, the results validated the effectiveness of stenting in reducing restenosis in a diverse group of patients, showed that late mortality is lower with stenting than with angioplasty when treatment is accompanied by abciximab therapy, demonstrated that abciximab has a

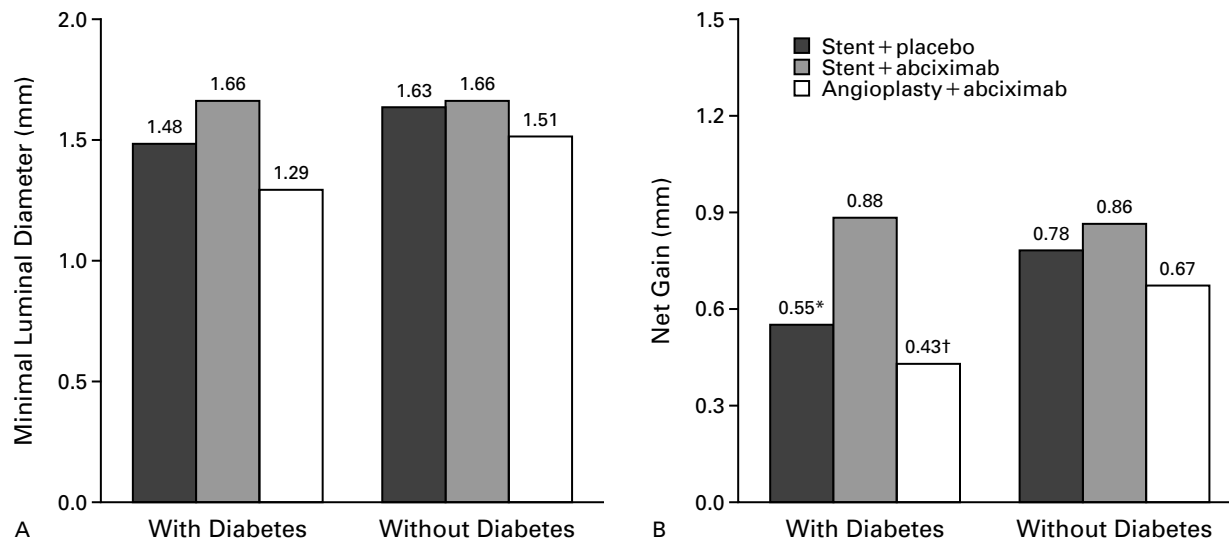


Figure 3. Angiographic Measurements of Restenosis in 127 Patients with Diabetes and 519 Patients without Diabetes at the Six-Month Follow-up.

Panel A shows measurements of minimal luminal diameter, and Panel B shows net gain (the difference between minimal luminal diameters at the six-month follow-up and before intervention). All measurements are expressed as mean values. The asterisk indicates $P=0.01$ and the dagger indicates $P=0.001$ for the comparison with the stent-plus-abciximab group.

long-lasting effect in reducing acute ischemic complications, and provided evidence that abciximab is associated with a reduction in the risk of restenosis among patients with diabetes mellitus who have received a stent.

In this trial, the entry criteria were broad and were intended to reflect the practice of percutaneous coronary revascularization in the real world, rather than revascularization in a narrow or idealized subgroup of patients with stenoses, as has been evaluated in previous trials that have compared stenting with balloon angioplasty. The six-month results confirm the efficacy of stenting in reducing angiographic restenosis and its clinical manifestation, the need for repeated revascularization of the target vessel, in this diverse group of patients with a variety of coronary lesions. As compared with angioplasty accompanied by abciximab, stent implantation, both by itself and with abciximab therapy, reduced the need for repeated target-vessel revascularization (by 31 percent and 44 percent, respectively). In the angiographic substudy, stent implantation was associated with a significantly greater average minimal luminal diameter of the target vessel after six months. Moreover, with abciximab therapy, stenting conferred a benefit as compared with angioplasty with respect to mortality: mortality was more than 70 percent lower with stenting than with angioplasty. This finding confirms that the combination of stenting and abciximab sets a new standard of safety and efficacy during coronary intervention.

The early reduction in the risk of ischemic complications produced by abciximab among patients who underwent stenting was maintained without attenuation over the long term. This durability of treatment effect is concordant with the long-term follow-up results of previous randomized trials of this agent among patients undergoing balloon angioplasty and atherectomy.^{2,11-13} Ischemic events tended to take place early after the interventional procedure, at a time when the abciximab infusion exerts its protective effect through potent inhibition of platelet thrombus formation in the coronary vessels. The durability of this early clinical benefit suggests that the stimulus for new thrombus formation is largely attenuated within a few days after treatment of the coronary plaque.

In a previous trial of platelet glycoprotein IIb/IIIa receptor blockade during coronary intervention, therapy with abciximab was associated, by six months, with a 26 percent reduction in the rate of repeated target-vessel revascularization procedures, a finding that suggested that this agent might inhibit the restenotic process after balloon angioplasty or atherectomy.¹¹ In subsequent trials of angioplasty, however, significant differences in the rates of late revascularization of the target vessel were not observed between the placebo and abciximab groups.^{2,3} The six-month results of the current trial, however, again suggest that abciximab may inhibit one or more of the mechanisms of restenosis, at least in some subgroups of patients. Among patients randomly assigned to undergo stenting, therapy with abciximab,

as compared with placebo, was associated with a non-significant trend toward a reduction in the incidence of target-vessel revascularization, a benefit that was confined to patients with diabetes mellitus. The time-to-event curves for this end point in the stent-plus-abciximab group and the stent-plus-placebo group began to diverge approximately 90 days after stent implantation, during the period when restenosis at the site of the stent can become clinically manifest. This finding indicates that any salutary effect of abciximab was not due simply to a reduction in the need for early urgent revascularization procedures.

An influence of abciximab on in-stent restenosis among patients with diabetes is not inconsistent with the absence of a reproducible effect of abciximab on the rates of restenosis after balloon angioplasty. Stent implantation essentially eliminates the processes of elastic recoil and adverse remodeling, thereby isolating neointimal hyperplasia as the predominant mechanism of in-stent restenosis.¹⁴ Increased rates of restenosis due to neointimal hyperplasia after stenting have been consistently observed among patients with diabetes.¹⁵⁻¹⁸ In the current study, patients with diabetes who were randomly assigned to stenting and placebo had a substantially higher incidence of late target-vessel revascularization than did their nondiabetic counterparts (16.6 percent vs. 9.0 percent, respectively), and in contrast to the outcome among nondiabetic patients, stent implantation without abciximab did not significantly reduce the rate of late revascularization as compared with the rate with angioplasty. Treatment with abciximab in addition to stenting, however, diminished the incidence of target-vessel revascularization among patients with diabetes by 51 percent, neutralizing the excess risk of this end point among patients with diabetes (as compared with those without it). Angiographic results among patients with diabetes were concordant with clinical outcomes: minimal luminal diameters and net gains in diameter at follow-up were markedly improved by stenting accompanied by abciximab, but not by stenting alone, as compared with angioplasty. By reducing thrombus formation as well as by providing nonspecific blockade of the $\alpha_v\beta_3$ receptor on endothelial and smooth-muscle cells, treatment with abciximab may inhibit the neointimal hyperplastic response to arterial injury in these patients.¹⁹

Percutaneous coronary revascularization is performed in more than 1 million patients worldwide each year. Protection against the ischemic complications of death and myocardial infarction and the need for repeated revascularization remains the principal objective in the development of new devices and adjunct therapies for this procedure. In the combination of an improved mechanical technique for revascularization with potent pharmacologic therapy to suppress platelet thrombosis, substantial progress has been made in achieving this goal. Stent implan-

tation and blockade of the platelet glycoprotein IIb/IIIa receptor with abciximab provide potent complementary benefits, such that percutaneous revascularization can be performed at a new standard of safety and efficacy.

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APPENDIX

The principal investigators and study coordinators of the EPISTENT Study Group were as follows: *Operations Committee* — E.J. Topol (study chairman), R.M. Califf, A.M. Lincoff, J.E. Tchong. *Principal investigators and study coordinators* (numbers of patients enrolled are given in parentheses) — University of Manitoba, Winnipeg, Man., Canada (153): J. Ducas, P.K. Cheung, U. Schick; Our Lady of Lourdes Medical Center, Cherry Hill, N.J. (147): J.H. Kramer, P. Koren, R. Wilson; University of Arkansas, Little Rock (142): J.D. Talley, J. McClellan, M. Dearen; Toronto Hospital, Toronto (138): A.G. Adelman, P. Caramori, S. Webber; Baylor College of Medicine, Houston (135): N.S. Kleiman, J. Taylor, T. Ferrando; Sunnybrook Health Science Centre, Toronto (132): E. Cohen, L. Balleza; Cleveland Clinic Foundation, Cleveland (118): A.M. Lincoff, C. Rouse; University of Alberta Hospital, Edmonton, Alta., Canada (108): J. Burton, E. Anderson, N. Hogg; Moses Cone Memorial Hospital, Greensboro, N.C. (97): T. Kelly, S. Alston; St. Paul's Hospital, Vancouver, B.C., Canada (81): J. Webb, S. VanWeinen; Vancouver Hospital and Health Sciences Centre, Vancouver, B.C., Canada (76): D.R. Ricci, S. Mockman; Institut de Cardiologie de Montréal, Montreal (68): J.E. Tanguay, A.M. Poitras; William Beaumont Hospital, Royal Oak, Mich. (65): G. Timis, D. Davey; Northern Californian Medical Association, Santa Rosa, Calif. (57): P. Coleman, P. Herrold-Runge; Victoria General Hospital, Halifax, N.S., Canada (57): B.J. O'Neill, K. Foshey, N. Fitzgerald; London Health Sciences Centre, London, Ont., Canada (52): D. Almond, W. Kostuk, J. White; Graduate Hospital, Philadelphia (52): R. Gottlieb, H. Snyder, P. Koren, J. Lavoie; University of Connecticut Health Center, Farmington (48): M. Azrin, D. Murphy; Geisinger Medical Center, Danville, Pa. (47): J. Blankenship, L. Demko; Henry Ford Heart and Vascular Institute, Detroit (47): P. Kraft, L. Dvorak; Royal Columbian Hospital, New Westminster, B.C., Canada (45): R. Brown, M. Colclough, K. Stevens; University of Virginia, Charlottesville (45): I. Sarembock, L. Snyder, S. Sayre; Watson Clinic, Lakeland, Fla. (44): K. Browne, M. Roy; Presbyterian Hospital, Charlotte, N.C. (43): B. Reen, R. Short; Rochester General Hospital, Rochester, N.Y. (37): M. Thompson, V. Chiodo, D. Hoffman; University Medical Center, Jacksonville, Fla. (35): T.A. Bass, M. Zenni, G. Rohman; Ottawa Civic Hospital, Ottawa, Ont., Canada (35): J.F. Marquis, F. Reid, J. Jelley; Harbor—University of California at Los Angeles Medical Center, Torrance (30): W. French, S. Goldberg, S. Wang; Western Pennsylvania Hospital, Pittsburgh (27): A. Gradman, L. Botley, J. Collins; Lancaster Heart Foundation, Lancaster, Pa. (20): S. Worley, L. Hollywood; Midwest Cardiology Research Foundation, Columbus, Ohio (20): S. Yakibov, C. Gilliland; Florida Hospital, Orlando (19): R. Ivanhoe, K. Potter; Deborah Heart and Lung Center, Brown Mills, N.J. (19): M. Taylor, E. Cleary; Iowa Heart Center, Des Moines (18): M. Tannenbaum, A. Hartz; St. Luke's—Roosevelt Hospital, New York (13): J. Hochman, J. Slater; University of Michigan Medical Center, Ann Arbor (12): E. Bates, P. Fox-Bruenger; Orlando Regional Medical Center—Columbia, Orlando, Fla. (12): M. Gonzalez, L. Jopperri; University of Cincinnati Medical Center, Cincinnati (12): J.P. Runyon, N. Higby; Durham Veterans Affairs Medical Center, Durham, N.C. (11): J. Tchong, M. Rund; St. Louis University Hospital, St. Louis (8): R. Bach, C. Mechem; Hartford Hospital, Farmington, Conn. (8): M. Azrin, D. Murphy; Milwaukee Heart and Vascular Clinic, Milwaukee (5): E.E. Cummins, J. Nonweiler; Christ Hospital, Cincinnati (4): J.P. Runyon, N. Higby; Western Montana Clinic, Missoula (4): M. Sanz, C. Cole; Tampa General Hospital, Tampa, Fla. (4): M.W. Weston; University of Texas Medical School, Houston (3): H.V. Anderson, L. Weigelt; Evanston Hospital, Evanston, Ill. (3): T. Larkin, B.J. Jackson; Lutheran General Hospital, Park Ridge, Ill. (3): M.J. Rosenberg, S. Tully; Sentra Norfolk General Hospital, Norfolk, Va. (2): C. Hartman, S. Lunow; Prairie Cardiovascular Consult, Springfield, Ill. (2): C. Lucore, G. Miskel, K. McShane; LDS Hospital, Salt Lake City (2): B. Muhlestein, J. Jerman; Louisiana State University Medical Center, New Orleans (2): G. Sander, A. Stevens; St. Michael's Hospital, Toronto (2): R. Chisholm, S. Webber; Creighton Cardiac Center, Omaha, Nebr. (1): M. Del Core, L. Stengel; *Coordinating Center* — J. Booth (study coordinator), R. Cannata, V. Castle, H. Cohen, S. DeLuca, M. Kutner, T. Knuth, A. Lincoff, T. McCollough, J. McPhearson, J. Mellon, D. Miller, M. Pulliam, S. Sapp, K.N. Sigmon; *Clinical Events Committee* — M. Templin, E. Montague, J. Carlson, L. Heil, V. Zovkic, K. Malone,

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