PLATELET GLYCOPROTEIN IIb/IIIa INHIBITION WITH CORONARY STENTING FOR ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

Background When administered in conjunction with primary coronary stenting for the treatment of acute myocardial infarction, a platelet glycoprotein IIb/IIIa inhibitor may provide additional clinical benefit, but data on this combination therapy are limited.

Methods We randomly assigned 300 patients with acute myocardial infarction in a double-blind fashion either to abciximab plus stenting (149 patients) or placebo plus stenting (151 patients) before they underwent coronary angiography. Clinical outcomes were evaluated 30 days and 6 months after the procedure. The angiographic patency of the infarct-related vessel and the left ventricular ejection fraction were evaluated at 24 hours and 6 months.

Results At 30 days, the primary end point — a composite of death, reinfarction, or urgent revascularization of the target vessel — had occurred in 6.0 percent of the patients in the abciximab group, as compared with 14.6 percent of those in the placebo group (P=0.01); at 6 months, the corresponding figures were 7.4 percent and 15.9 percent (P=0.02). The better clinical outcomes in the abciximab group were related to the greater frequency of grade 3 coronary flow (according to the classification of the Thrombolysis in Myocardial Infarction trial) in this group than in the placebo group before the procedure (16.8 percent vs. 5.4 percent, P=0.01), immediately afterward (95.1 percent vs. 86.7 percent, P=0.04), and six months afterward (94.3 percent vs. 82.8 percent, P=0.04). One major bleeding event occurred in the abciximab group (0.7 percent); none occurred in the placebo group.

Conclusions As compared with placebo, early administration of abciximab in patients with acute myocardial infarction improves coronary patency before stenting, the success rate of the stenting procedure, the rate of coronary patency at six months, left ventricular function, and clinical outcomes. (N Engl J Med 2001;344:1895-903.)

CORONARY stenting and antiplatelet therapy both play an important part in interventional cardiology,[1-3] and the emergence and development of both therapies have been closely associated.[4-7] The combination of ticlopidine and aspirin enhances the benefit of coronary stenting by reducing acute stent thrombosis, and new agents such as platelet glycoprotein IIb/IIIa inhibitors[8] limit ischemic complications in patients undergoing balloon angioplasty[9-12] or stent implantation.[13,14] However, despite the potential link between fibrinogen and restenosis, blockade of glycoprotein IIb/IIIa has not been shown to alter the frequency of restenosis as determined by angiography or echocardiography.[15,16]

There are few data on the use of the combination of stenting and glycoprotein IIb/IIIa inhibition in patients with acute myocardial infarction.[17-20] A recent large, randomized trial of angioplasty with or without stent implantation showed that stenting was beneficial in reducing the need for revascularization but found no reduction in the rates of death or reinfarction.[20] In contrast, glycoprotein IIb/IIIa inhibition decreased the rate of ischemic events after balloon angioplasty but had no effect on the need for revascularization at six months.[21]

This study (conducted by the Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up [ADMIRAL] investigators) was a multicenter, double-blind, randomized trial with broad inclusion criteria, no angiographic selection criteria, and early randomization after presentation, to reflect the common practice of primary stenting in patients with acute myocardial infarction. We hypothesized that abciximab followed by stenting would be superior to stenting alone.

METHODS

Patients

Patients scheduled for primary percutaneous coronary revascularization were eligible for enrollment if they were more than 18 years old, had had the first symptoms of acute myocardial infarction within 12 hours before enrollment, and had ST-segment elevation of more than 1 mm in at least two contiguous leads of the electrocardiogram. Exclusion criteria were bleeding diathesis, administration of thrombolytic agents for the current episode, neoplasm, recent

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stroke, uncontrolled hypertension, recent surgery, oral anticoagulant therapy, a limited life expectancy, childbearing potential, and known contraindications to therapy with aspirin, ticlopidine, or heparin. There were no angiographic selection criteria. The ethics review board of the Pitié–Salpêtrière Hospital approved the protocol, and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patients.

Study Protocol

All the patients received aspirin and were randomly assigned, in the order in which they were enrolled, to receive either abciximab or placebo. The study drug was administered immediately after randomization, in the mobile intensive care unit before arrival at the hospital, in the emergency department, in the intensive cardiac care unit, or in the catheterization laboratory; in all cases it was administered before sheath insertion and coronary angiography. The patients, investigators, and sponsors of the study were blinded to the treatment assignments during the entire study. Patients received either abciximab (ReoPro, Centocor, Malvern, Pa.) as a bolus of 0.25 mg per kilogram of body weight, followed by a 12-hour infusion of 0.125 μg per kilogram per minute (maximum, 10 μg per minute), or placebo.

Heparin was given as an initial bolus of 70 U per kilogram (maximum, 7000 U). If necessary, additional boluses were administered to achieve an activated clotting time of 200 seconds. After percutaneous coronary revascularization, a continuous infusion of 7 U of heparin per kilogram per hour was initiated and maintained until a coronary angiogram had been obtained, 24 hours after the procedure. The target activated partial-thromboplastin time was between 1.5 and 2.0 times the control value. It was recommended in the protocol that the investigators stop the administration of heparin on completion of the 24-hour angiography study and that they remove the sheaths 4 to 6 hours later. Ticlopidine (250 mg twice daily, without a loading dose) was given for the 30 days immediately after stent implantation in both groups. Previously validated treatment algorithms for the management of bleeding, emergency coronary-artery bypass surgery, and thrombocytopenia were recommended in the protocol to decrease the likelihood of hemorrhagic complications.[12,13]

Catheterization Procedures and Angiographic Analysis

A stent was implanted if the diameter of the infarct-related artery was greater than 2.5 mm, without extensive calcification or unsuitable anatomical features. The first choice was the Saint-Côme stent (Saint-Côme-Chirurgie, Marseilles, France), a balloon-expandable, slotted tube stent, but the investigators were permitted to use an alternative stent if necessary.

All the patients who were randomly assigned to one of the two study groups were part of the angiographic analysis, which involved four coronary angiograms (obtained on admission, at the end of the percutaneous coronary revascularization procedure, and 24 hours and 6 months after the procedure). Complete angiographic follow-up at 6 months was carried out to evaluate the patency of the target vessel unless the patient had died, had undergone repeated revascularization, had had an occluded vessel at the end of the procedure or at 24 hours, had not undergone a revascularization procedure after the initial coronary angiography (e.g., because the rate of flow in the target vessel was classified as grade 3 according to the classification of the Thrombolysis in Myocardial Infarction [TIMI] trial and the stenosis was judged to be less than 50 percent), or refused angiography at 6 months.

Cineangiograms were obtained according to standard acquisition guidelines and submitted to an independent core angiography laboratory, which was not one of the study centers. Analyses were carried out on a per-lesion basis. Perfusion was graded according to the TIMI classification system. Occlusion and reocclusion were defined as a TIMI grade 0 or 1 flow in the occluded artery. Left ventricular volumes and ejection fractions were computed according to Simpson's rule from two orthogonal right anterior oblique and left anterior oblique views. Computerized quantitative and qualitative analyses of angiograms were performed (Tagarno 35AX Viewing Station, General Electric Medical Systems, Waukesha, Wis., and VIEW NT system with Quantitative Coronary Analysis and Ventricular Analysis software, Electromed International Society, Quebec, Que., Canada).[22-26]

End Points

The primary end point was the composite of death, reinfarction, or urgent revascularization of the target vessel at 30 days after randomization. The key secondary end point was the composite of death, reinfarction, or any revascularization (percutaneous coronary revascularization or coronary-artery bypass grafting on an urgent or elective basis) at 30 days and at 6 months. Other secondary end points were death or reinfarction at 30 days and at 6 months; death, reinfarction, or urgent revascularization of the target vessel at 6 months; the TIMI flow grade before, immediately after, 24 hours after, and 6 months after the revascularization procedure; and the left ventricular ejection fraction within 24 hours and at 6 months after the revascularization procedure.

Reinfarction was defined according to clinical symptoms and new electrocardiographic changes with a new elevation of the creatine kinase or creatine kinase MB isoenzyme levels.[12,21] Creatine kinase and creatine kinase MB were measured before the administration of abciximab or placebo; 8, 16, 24, and 48 hours afterward; and whenever reinfarction was suspected. Urgent target-vessel revascularization was defined as a repeated coronary revascularization procedure or coronary-artery bypass grafting performed within 24 hours after a new ischemic episode. Episodes of bleeding were defined as major or minor according to the TIMI classification,[27] and severe thrombocytopenia was defined by a platelet count of less than 50,000 per cubic millimeter.

Data were collected on case-report forms at the clinical study centers and checked against medical records. A blinded clinical-events adjudication committee evaluated each event related to the primary end point or the secondary end point. A clinical end-points and safety monitoring committee continuously checked and monitored all adverse events in a blinded manner.

Statistical Analysis

When the study was planned, the incidence of the primary end point in the group of patients who were assigned to placebo was expected, according to the findings of observational studies, to be between 13 percent and 20 percent. The minimal sample size was determined to be 150 patients per group to ensure 80 percent power to detect a difference between a placebo group in which the incidence of events was 15 percent and a treatment group in which the incidence of events was 5 percent, with use of the chi-square test and at a two-sided significance level of 5 percent. The data were retained by Eli Lilly, where the analyses were performed. Independent statistical advice was provided by E. Vicant (Paris VII University). All analyses were performed on an intention-to-treat basis. The rates (percentages) reported for demographic, procedural, efficacy, and safety data are based on observations in patients with no missing data. The percentages in the two groups were compared with use of Pearson's chi-square test or Fisher's exact test. Kaplan–Meier curves were constructed for the primary end point at 30 days and at 6 months. Continuous variables are presented as means ±SD and were analyzed with a linear model that included fixed effects of treatment, the investigator, and their interaction. Analyses among subgroups of the patients were planned in advance.

In a complementary analysis based on multiple logistic-regression models, none of the base-line characteristics (including the diameter of the target coronary artery, the dose of heparin, and the type of stent) were found to have a significant effect on the incidence of the primary end point or the incidence of death, and there was no significant interaction between these variables and the treatment effect. Consequently, unadjusted estimates of the relative risk were used in the current analyses. All the tests were two-sided, with significance levels of 5 percent and two-sided 95 percent confidence

intervals. All the calculations were performed with SAS statistical software (version 6.12, SAS Institute, Cary, N.C.).

RESULTS

Base-Line Characteristics of the Patients

From July 12, 1997, to December 22, 1998, 300 patients with acute myocardial infarction were enrolled at 26 centers. The two study groups were well matched with respect to base-line characteristics and key angiographic features (Table 1). Seventy-eight patients (26 percent) were randomly assigned to one of the two study groups early (in the mobile intensive care unit or emergency department), with either abciximab or placebo administered before and during transportation to the catheterization laboratory. The other 222 patients were randomly assigned to one of the study groups on admission to the intensive cardiac care unit or in the catheterization laboratory. The length of time between the onset of chest pain and coronary angiography did not differ among these sites. The length of time between the onset of chest pain and administration of the bolus of the study drug was shorter among the patients who received it in the mobile intensive care unit (178±94 minutes) than among those who received it in the emergency department (266±139 minutes, P=0.02) or in the intensive cardiac care unit or catheterization laboratory (238±142 minutes, P=0.002).

The prevalence of congestive heart failure was similar in the two groups, as was the incidence of cardiogenic shock during the first 24 hours after randomization. Initial angiography showed that the infarct-related vessel was small (reference diameter, <2.5 mm) in 12.5 percent of the patients; small vessels were more frequently found in the abciximab group than in the placebo group (18.3 percent vs. 5.9 percent, P=0.006).

After the initial angiogram, percutaneous coronary revascularization was attempted in 92 percent of the patients in the abciximab group and 95 percent of those in the placebo group; this small difference may reflect the more frequent presence of fully open arteries in those who received abciximab. Of the patients who underwent balloon angioplasty, 92 percent received at least one stent and 32 percent received more than one stent. The Saint-Côme stent was implanted in 66 percent of the patients who received a stent; the others received other stents (XT, Bard, Murray Hill,

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

VARIABLE	ABCIXIMAB (N=149)	PLACEBO (N=151)	P VALUE
Age (yr)	59.6±13.0	62.1±12.8	0.09
Male sex (%)	85.2	78.2	0.14
Weight (kg)	75.9±12.5	76.4±13.8	0.81
Clinical characteristics (%)			
Diabetes	15.4	19.9	0.31
Current smoker	45.0	39.7	0.33
Hyperlipidemia	39.6	37.1	0.65
History of hypertension	34.2	41.1	0.22
History of myocardial infarction	14.1	7.3	0.06
History of unstable angina	8.7	7.3	0.67
History of stable angina	12.1	14.6	0.53
History of heart failure	2.0	0	0.08
Congestive heart failure	0.7	2.0	0.33
Cardiogenic shock during first 24 hr after randomization	7.4	9.3	0.55
Previous intervention (%)			
Percutaneous transluminal coronary angioplasty	18.1	10.0	0.04
Coronary-artery bypass grafting	10.0	13.3	0.28
Administration of study drug (%)			
Bolus	100	98.7	0.50
Bolus and infusion	99.3	96.0	0.12
Infarct territory (%)			0.43†
Anterior	35.8	41.1	
Inferior	50.7	46.4	
Other	13.5	12.5	
Infarct-related vessel (%)			0.99†
Left anterior descending	46.2	46.2	
Right coronary	42.1	41.5	
Circumflex	10.3	10.9	
Graft	1.4	1.4	

*Plus–minus values are means ±SD.

†The P value is for the overall comparison between the abciximab group and the placebo group.

N.J.; Tenax, Biotronik, Bulak, Germany; NIR and NIR Primo, Boston Scientific, Natick, Mass.; Crossflex, Cordis, Miami; ACS Multi-Link and Duet Guidant, Indianapolis; Jostent, Jomed, Helsingborg, Sweden; and Bestent, GFX, and Wiktor, Medtronic, Minneapolis). Among the patients who received a stent, the incidence of the primary end point was similar among those in whom a Saint-Côme stent was used and those in whom other stents were used (10.1 percent vs. 9.9 percent, respectively; P=0.96). Ticlopidine was given to 99 percent of the patients who received a stent. Doses of heparin and measurements of anticoagulation were similar in the study groups (activated clotting time, 316 seconds in the abciximab group vs. 348 seconds in the placebo group; and activated partial-thromboplastin time, 2.2 vs. 2.4 times the control value, respectively, during revascularization).

Coronary Flow and Left Ventricular Function

The initial proportion of patients with TIMI grade 3 flow was significantly higher in the abciximab group than in the placebo group (Table 2), and the difference between these two groups was greater when TIMI grades 2 and 3 were considered together (rate in the abciximab group, 25.8 percent, vs. 10.8 percent in the placebo group; P=0.006). After the revascularization procedure, the proportion with TIMI grade 3 flow greatly increased in both study groups and remained higher in the abciximab group than in the placebo group. The rate of procedural success (defined as stenosis of <50 percent and TIMI grade 3 flow) was higher with abciximab than with placebo (95.1 percent vs. 84.3 percent, P=0.01). At six months, the frequency of both TIMI grade 3 flow and of TIMI grade 2 or 3 flow remained higher in the abciximab group than in the placebo group (rate of TIMI grade 2 or 3 flow, 97.1 percent vs. 87.9 percent; P=0.04), with fewer angiographically detected reocclusions with abciximab than with placebo (2.9 percent vs. 12.1 percent, P=0.04). At six months, abciximab was also associated with a higher rate of patency in the subgroup of patients with small arteries (≤2.5 mm) than was placebo (TIMI grade 2 or 3 flow, 100 percent vs. 60.0 percent; P=0.02). Abciximab was associated with a more rapid and persistent improvement in left ventricular ejection fraction (improvement occurring within 24 hours and lasting at least 6 months) than placebo (Table 2).

TIMI grade 3 flow at the end of the procedure was strongly related to the risk of both the 30-day and the 6-month clinical end points. The primary end point at 30 days had occurred in 7.4 percent of the patients with TIMI grade 3 flow, as compared with 35.3 percent of the patients with TIMI grade 0, 1, or 2 flow (P<0.001). This difference persisted at 6 months (P<0.001). Similarly, the incidence of the key secondary end point at 30 days and 6 months was significantly lower in the patients with TIMI grade 3 flow than in those with a lower TIMI grade of flow. Moreover, the presence of TIMI grade 3 flow at the end of the procedure was significantly related to the risk of death within the following 30 days or 6 months (6-month mortality, 2.3 percent among patients with TIMI grade 3 flow, vs. 17.6 percent among patients with lower TIMI grades of flow; P=0.001), and abciximab had a significant effect on this relation (P=0.03). The lowest mortality was seen among the patients who were assigned to abciximab and had TIMI grade 3 flow at the end of the revascularization procedure.

TABLE 2. TIMI FLOW GRADES AND LEFT VENTRICULAR EJECTION FRACTION.*

FLOW GRADE	ABCIXIMAB	PLACEBO	P VALUE
Before revascularization procedure			
TIMI grade 3 (% of patients)	16.8	5.4	0.01
TIMI grade 2 (% of patients)	9.1	5.4	0.34
TIMI grade 1 (% of patients)	7.1	7.7	0.87
TIMI grade 0 (% of patients)	67.0	81.5	0.02
Immediately after revascularization procedure			
TIMI grade 3 (% of patients)	95.1	86.7	0.04
TIMI grade 2 (% of patients)	2.9	4.5	0.58
TIMI grade 1 (% of patients)	1.0	4.4	0.13
TIMI grade 0 (% of patients)	1.0	4.4	0.13
24 Hr after revascularization procedure			
TIMI grade 3 (% of patients)	95.9	92.6	0.33
TIMI grade 2 (% of patients)	0	4.9	0.02
TIMI grade 1 (% of patients)	0	0	1.00
TIMI grade 0 (% of patients)	4.1	2.5	0.56
Left ventricular ejection fraction (%)	57.0±10.4	53.9±10.4	<0.05
6 Mo after revascularization procedure			
TIMI grade 3 (% of patients)	94.3	82.8	0.04
TIMI grade 2 (% of patients)	2.9	5.2	0.50
TIMI grade 1 (% of patients)	1.4	1.7	0.89
TIMI grade 0 (% of patients)	1.4	10.3	0.03
Left ventricular ejection fraction (%)	61.1±10.6	57.0±11.1	0.05

*Analyses at the core angiography laboratory were performed in the 193 patients (101 in the abciximab group and 92 in the placebo group) who had complete angiographic data at all time points during the six-month follow-up. Plus–minus values are means ±SD. TIMI denotes Thrombolysis in Myocardial Infarction.

Clinical Outcomes

As compared with placebo, abciximab significantly reduced the incidence of the primary end point at 30 days, with a substantial reduction in each of the components of the end point (Table 3); the benefit was mainly observed during the first week after stent implantation (Fig. 1). When analyzed in subgroups according to clinical characteristics, most of the subgroups had similar benefit with abciximab as compared with placebo (Fig. 2). The incidence of the key

secondary end point was also significantly lower in the abciximab group than in the placebo group at 30 days. Episodes of minor bleeding occurred more frequently in the abciximab group than in the placebo group, mainly in association with groin hematomas (Table 3).

The incidence of the primary end point at six months was significantly lower in the abciximab group than in the placebo group, with an absolute reduction of 8.5 percent (relative reduction, 53 percent) and preservation of the early benefit (Fig. 1). A nonsignificant, 55 percent reduction in mortality with abciximab as compared with placebo also persisted at six months. A consistent benefit with abciximab was seen in all the subgroups of patients; the patients who received their randomly assigned treatment with abciximab early had a greater benefit with respect to the primary end point at both 30 days and 6 months than did those treated with abciximab in the intensive cardiac care unit or catheterization laboratory (Fig. 2). At six months, the incidence of the key secondary end point and the rates of target-vessel revascularization were lower with abciximab than with placebo, suggesting that the drug had an effect on clinical restenosis (Table 3). Patients with diabetes who received abciximab had a significant reduction in the six-month mortality rate as compared with patients with diabetes who received placebo (0 percent vs. 16.7 percent, $P=0.02$), as well as a reduction in the incidence of death, reinfarction, or any revascularization (20.7 percent vs. 50.0 percent, $P=0.02$), a reduction in the need for urgent target-vessel revascularization (0 percent vs. 12.5 percent, $P=0.049$), and a reduction in the need for any target-vessel revascularization (13.8 percent vs. 37.5 percent, $P=0.046$).

DISCUSSION

The complementary effects of platelet glycoprotein IIb/IIIa inhibition and stenting have been previously shown in scheduled (i.e., elective) percutaneous coronary revascularization, but not in primary revascularization for acute myocardial infarction. The results of this trial show that, as compared with placebo, abciximab therapy initiated before catheterization improves outcomes in patients with acute myocardial infarction who are treated with primary stenting. Abciximab in combination with stent placement reduces

TABLE 3. CLINICAL EVENTS AT 30 DAYS AND 6 MONTHS AND BLEEDING COMPLICATIONS.*

OUTCOME	ABCIXIMAB (N=149)	PLACEBO (N=151)	P VALUE	RELATIVE RISK (95% CI)
	no. (%)			
30 Days				
Death	5 (3.4)	10 (6.6)	0.19	0.51 (0.17–1.52)
Reinfarction	2 (1.3)	4 (2.6)	0.42	0.51 (0.09–2.81)
Death or reinfarction	7 (4.7)	12 (7.9)	0.25	0.59 (0.23–1.54)
Urgent target-vessel revascularization	2 (1.3)	10 (6.6)	0.02	0.20 (0.04–0.94)
Death, reinfarction, or urgent target-vessel revascularization	9 (6.0)	22 (14.6)	0.01	0.41 (0.18–0.93)
Elective target-vessel revascularization	5 (3.4)	7 (4.6)	0.57	0.72 (0.22–2.33)
Urgent or elective target-vessel revascularization	7 (4.7)	17 (11.3)	0.04	0.42 (0.17–0.99)
Elective revascularization	10 (6.7)	12 (7.9)	0.69	0.84 (0.35–2.01)
Any revascularization	11 (7.4)	19 (12.6)	0.20	0.59 (0.27–1.28)
Death, reinfarction, or any revascularization	18 (12.1)	31 (20.5)	0.047	0.59 (0.32–0.99)
6 Months				
Death	5 (3.4)	11 (7.3)	0.13	0.46 (0.16–1.36)
Reinfarction	3 (2.0)	6 (4.0)	0.32	0.51 (0.12–2.06)
Death or reinfarction	8 (5.4)	15 (9.9)	0.14	0.54 (0.22–1.31)
Urgent target-vessel revascularization	3 (2.0)	10 (6.6)	0.049	0.30 (0.08–0.99)
Death, reinfarction, or urgent target-vessel revascularization	11 (7.4)	24 (15.9)	0.02	0.46 (0.22–0.93)
Elective target-vessel revascularization	14 (9.4)	26 (17.2)	0.046	0.55 (0.27–0.99)
Urgent or elective target-vessel revascularization	17 (11.4)	36 (23.8)	0.005	0.48 (0.26–0.87)
Elective revascularization	24 (16.1)	28 (18.5)	0.58	0.87 (0.48–1.57)
Any revascularization	26 (17.4)	36 (23.8)	0.17	0.73 (0.42–1.27)
Death, reinfarction, or any revascularization	34 (22.8)	51 (33.8)	0.03	0.68 (0.41–0.97)
Bleeding complications at 30 days				
Major bleeding	1 (0.7)	0	0.31	1.01 (0.73–1.37)
Minor bleeding	18 (12.1)	5 (3.3)	0.004	3.65 (1.32–10.08)
Groin hematomas with minor bleeding	9 (6.0)	1 (0.7)	0.009	9.12 (1.14–72.89)
Thrombocytopenia (<100,000 platelets/mm^3)	7 (4.7)	2 (1.3)	0.08	3.55 (0.72–17.35)
Severe thrombocytopenia (<50,000 platelets/mm^3)	2 (1.3)	2 (1.3)	1.00	1.01 (0.14–7.29)

*Some patients had more than one event. Any "revascularization" refers to the revascularization of any vessel, including the target vessel, performed on either an urgent or an elective basis. CI denotes confidence interval.

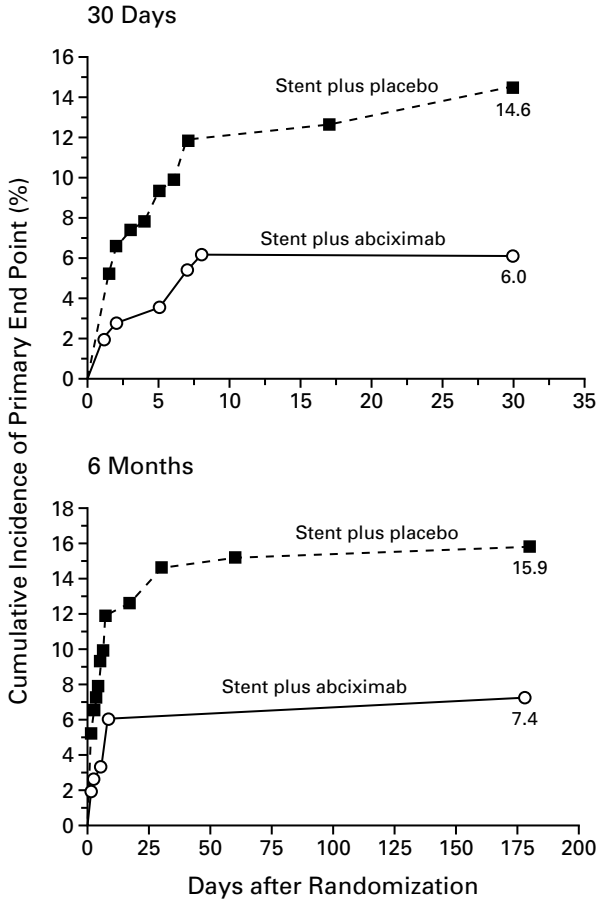

Figure 1. Kaplan–Meier Curves Showing the Cumulative Incidence of the Primary End Point at 30 Days and at 6 Months.

The primary end point was the composite of death, reinfarction, and urgent target-vessel revascularization within 30 days after random assignment to treatment with abciximab or placebo. In the abciximab group, there was a 59 percent relative reduction in the risk of the primary end point at 30 days (P=0.01 for the comparison between the two groups) (top panel). At six months, there was a 53 percent reduction in the risk of the primary end point in the abciximab group (P=0.02 for the comparison between the two groups) (bottom panel).

both the incidence of acute ischemic events and the incidence of end points related to clinical restenosis. This study also shows that in comparison with stenting alone, the addition of abciximab (along with aspirin) as a first-line treatment for acute myocardial infarction more frequently opens the occluded artery, improves the success of stenting, reduces the rate of reocclusion, and more frequently restores an optimal flow for up to six months, with concomitant improvements in both left ventricular ejection fraction and prognosis.

To reflect as closely as possible the real practice of primary percutaneous coronary revascularization, patients were selected for the study only on the basis of typical chest pain with ST-segment elevation on the electrocardiogram; there were few clinical exclusion criteria and no angiographic criteria for the selection of patients. In this high-risk population, the benefits seen with abciximab are consistent with those in a recent open-label trial of stenting that included patients with Q-wave or non–Q-wave myocardial infarction within 48 hours after the onset of pain.[17]

The benefit of abciximab, as compared with placebo, was observed even in specific subgroups of patients with acute myocardial infarction who are usually excluded from trials of stenting — namely, those with small arteries or with cardiogenic shock. In patients with diabetes, abciximab reduced the six-month rates of death and clinical restenosis, confirming previous results in patients undergoing elective stenting.[28] Although they constituted a prespecified subgroup, the patients with diabetes were few in number, and there was no specific stratification for diabetes. Therefore, caution is required in the interpretation of these results; whether abciximab has specific effects in diabetic patients remains to be fully explored. In addition, the number of women in the trial was small, and there was inadequate power to allow us to draw meaningful conclusions about this therapeutic approach in women.

As with thrombolytic agents,[29] the administration of abciximab early after presentation resulted in a higher initial frequency of TIMI grade 3 flow than that achieved with placebo. As compared with placebo, it led to a better rate of procedural success with stenting, which translated into a better 24-hour left ventricular ejection fraction (a change that may have involved other mechanisms, such as less distal emboli, less side-branch closure,[13] or improvements in microcirculation).[17] Treatment during the first few hours after acute myocardial infarction is critical to the long-term prognosis,[30-33] and early TIMI grade 3 flow is important in reducing the risk of death, as shown in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial.[29] The relation found in the current study between the presence of TIMI grade 3 flow and risk of death at both 30 days and 6 months is consistent with the idea that platelet glycoprotein IIb/IIIa inhibition helps both to achieve coronary-artery patency and to improve the prognosis (and thus supports the "open-artery" hypothesis).

Although low doses of heparin were recommended,[12,13] the investigators may have given higher doses in the context of the double-blind study design. The activated clotting time or activated partial-thromboplastin time measured during the procedure in the placebo group was in agreement with a consensus statement[34] and recent studies of stenting.[20,35] However, in the abciximab group, these doses of heparin resulted in excessively high activated clotting times, leading to an increase in the incidence of groin hematomas (which may also be related to the use of a sheath that is left in place for 24 hours). To limit the risk of he-

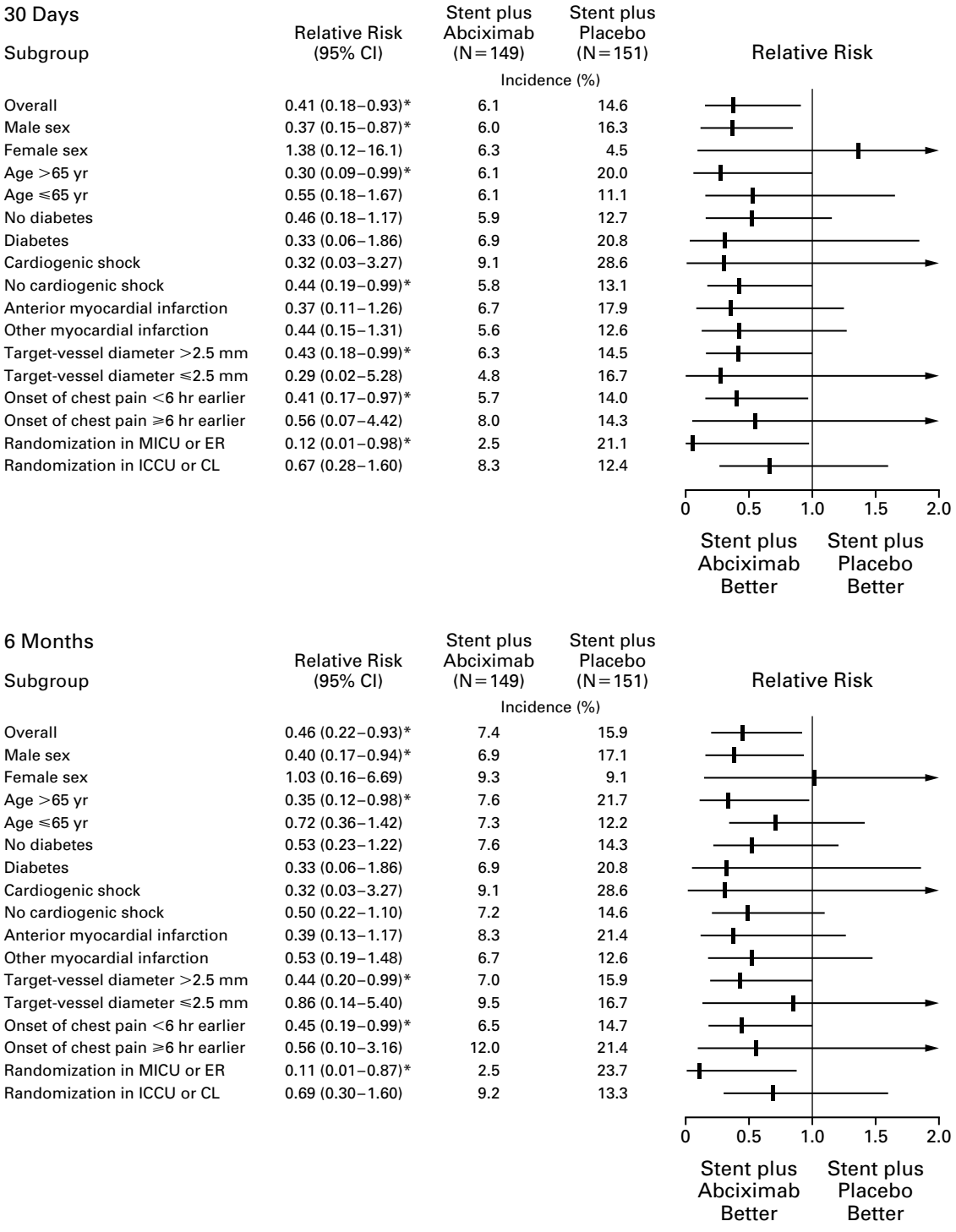

Figure 2. Relative Risks of the Primary End Point at 30 Days and 6 Months, According to Subgroup.

The primary end point was death, reinfarction, or urgent target-vessel revascularization. Asterisks denote a significant difference between the two treatment groups ($P<0.05$). CI denotes confidence interval, MICU mobile intensive care unit, ER emergency room, ICCU intensive cardiac care unit, and CL catheterization laboratory.

matomas with powerful antiplatelet agents, leaving the sheath in for prolonged periods must be strongly discouraged, whereas low doses of heparin and careful management of the femoral access site are advisable.[12] Oral antiplatelet therapy in the current study was based on the ticlopidine regimen that has been tested and approved for stent implantation.[5-7] Although most intervention centers have recently switched from ticlopidine to clopidogrel with or without a loading dose, recent data showed no difference between these two drugs in the prevention of major cardiac events,[36] and the results presented here probably apply equally to patients receiving clopidogrel.

In acute myocardial infarction, the administration of both aspirin and a glycoprotein platelet IIb/IIIa inhibitor at presentation facilitates acute reperfusion. In addition, we found that a rapid and aggressive antiplatelet strategy, in generally unselected patients with acute myocardial infarction who were treated with primary stenting, led to improved outcomes. This strategy is feasible, effective, and safe. The results thus add support to the "open-artery" hypothesis with IIb/IIIa inhibition in primary coronary stenting.

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APPENDIX

The following persons participated in the trial: **Trial Organization:** *Steering Committee:* G. Montalescot (chairperson) (Groupe Hospitalier Pitié–Salpêtrière, Paris), P. Barragan (Clinique Beauregard, Marseilles), and P. Pinton (Eli Lilly, Saint-Cloud); *Clinical End Points and Safety Monitoring Committee:* A. Leizorovicz (chairperson) (Hôpital Louis Pradel, Lyons), A. Cribier (Hôpital Charles Nicolle, Rouen), and M. Meyer Samama (Hôpital Hôtel Dieu, Paris); *Clinical Events Adjudication Committee:* J.L. Dubois Randé (chairperson) (Hôpital Henri Mondor, Créteil), M. Slama (Hôpital Antoine Béclère, Clamart), and K. Boughalem (Hôpital Broussais, Paris); *Angiographic Core Laboratory:* I. Azancot (chairperson) and V. Stratiev (Hôpital Lariboisière, Paris); **Trial Investigators:** *Pitié–Salpêtrière Hospital, Paris:* G. Montalescot, Cardiology Division (42 patients enrolled), and P. Ecollan, mobile intensive care unit (26); *Des Franciscaines Clinic, Nîmes:* O. Wittenberg, Cardiology Division (44), and J.E. De La Coussaye, University Hospital and mobile intensive care unit (4); *Lagny-Marne-la-Vallée Hospital, Lagny-sur-Marne:* S. Elhadad (28); *Les Fleurs Clinic, Ollioules:* P. Villain (24); *Saint-Joseph Clinic, Colmar:* J.M. Boulenc (20); *Institut Cardiovasculaire Paris Sud, Antony:* M.-C. Morice (18); *Trousseau Hospital, Tours:* L. Maillard (12); *Henri Duffaut Hospital, Avignon:* M. Pansieri, Cardiology Division (8), and J. Vaque, mobile intensive care unit (3); *Les Alpilles Clinic, Marseilles:* P. Barragan (10); *La Valette Clinic, Montpellier:* X. De Boisgelin (10); *Centre Hospitalier Intercommunal, Eaubonne-Montmorency, Montmorency:* A. Akesbi (8); *Pays d'Aix Hospital, Aix-en-Provence:* C. Barnay (7); *Essey-Les-Nancy Clinic, Essey-Les-Nancy:* M. Amor (6) and P.E. Bollaert, Hôpital Central, Nancy, and mobile intensive care unit (1); *René Dubos Hospital, Pontoise:* F. Funck (5); *Boucicaut Hospital, Paris:* A. Lafont (4); *Centre Medico Chirurgical Obstetrical, Schiltigheim:* M. Zupan (4); *Hôpital Nord, Marseilles:* F. Paganelli (4); *Saint-Joseph Hospital, Marseilles:* F. Dhoudain (3); *Necker Hospital, Paris:* J.P. Metzger (3); *Rhône-Durance Clinic, Avignon:* J. Sainsous (3); *Haut Lévesque Hospital, Pessac:* P. Coste (2); and *La Cavale Blanche Hospital, Brest:* J.P. Boschat (1) — all in France.

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EDITORIAL BOARD MEETING

A meeting of the editorial board of the *Journal* was held on April 26 and 27, 2001. The board considered the new Clinical Practice series and the challenge of providing practical reviews of clinical topics in articles of more limited length and complexity than the traditional in-depth review articles in the *Journal*. In their editorial the series editors, Drs. Thomas H. Lee and Caren Solomon, solicited comments from readers on this issue. The board encourages readers to provide feedback to clinicalpractice@nejm.org. The board also discussed the goal of publishing more articles about international health in the *Journal*. The editorial accompanying the first of the six-part series *Health Policy 2001* included a general call for both opinion pieces and empirical reports about health policy. The board wishes to let readers of the *Journal* know that this call for manuscripts pertains to both U.S. and international health issues. The redesigned *Journal* Web site became public on May 30, 2001. The board had an extensive discussion of policies about the content that will be available to nonsubscribers. As detailed in the editorial announcing the redesigned Web site, the *Journal* is now providing the full text of its Original Articles and Special Articles free to all users beginning six months after publication. Access to the articles will require registration, but the registration information will remain confidential and will not be made available to any outsider. (The *Journal*'s privacy policy is available at http://www.nejm.org.) The purpose of this free-access policy is to give the international research and practice communities easier, direct access to the research published in the *Journal*. We are negotiating with several institutions to include *Journal* content in a number of comprehensive data bases and to allow electronic searching of the full text of these articles. As always, readers' comments on these issues are encouraged. Please respond to comments@nejm.org or to the Editor, *New England Journal of Medicine*, 10 Shattuck St., Boston, MA 02115.