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## COMPARISON OF ANGIOPLASTY WITH STENTING, WITH OR WITHOUT ABCIXIMAB, IN ACUTE MYOCARDIAL INFARCTION

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### ABSTRACT

**Background** As compared with thrombolytic therapy, primary percutaneous transluminal coronary angioplasty (PTCA) in acute myocardial infarction reduces the rates of death, reinfarction, and stroke, but recurrent ischemia, restenosis, and reocclusion of the infarct-related artery remain problematic. When used in combination with PTCA, coronary stenting and platelet glycoprotein IIb/IIIa inhibitors may further improve outcomes.

**Methods** Using a 2-by-2 factorial design, we randomly assigned 2082 patients with acute myocardial infarction to undergo PTCA alone (518 patients), PTCA plus abciximab therapy (528), stenting alone with the MultiLink stent (512), or stenting plus abciximab therapy (524).

**Results** Normal flow was restored in the target vessel in 94.5 to 96.9 percent of patients and did not vary according to the reperfusion strategy. At six months, the primary end point — a composite of death, reinfarction, disabling stroke, and ischemia-driven revascularization of the target vessel — had occurred in 20.0 percent of patients after PTCA, 16.5 percent after PTCA plus abciximab, 11.5 percent after stenting, and 10.2 percent after stenting plus abciximab ( $P < 0.001$ ). There were no significant differences among the groups in the rates of death, stroke, or reinfarction; the difference in the incidence of the primary end point was due entirely to differences in the rates of target-vessel revascularization (ranging from 15.7 percent after PTCA to 5.2 percent after stenting plus abciximab,  $P < 0.001$ ). The rate of angiographically established restenosis was 40.8 percent after PTCA and 22.2 percent after stenting ( $P < 0.001$ ), and the respective rates of reocclusion of the infarct-related artery were 11.3 percent and 5.7 percent ( $P = 0.01$ ), both independent of abciximab use.

**Conclusions** At experienced centers, stent implantation (with or without abciximab therapy) should be considered the routine reperfusion strategy. (N Engl J Med 2002;346:957-66.)

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As compared with thrombolytic reperfusion in acute myocardial infarction, primary percutaneous transluminal coronary angioplasty (PTCA) increases the rates of patency of the infarcted artery, improves survival rates, and reduces the rates of reinfarction and stroke.<sup>1-3</sup> However, ischemia and reinfarction recur within one month in 10 to 15 percent and 3 to 5 percent of patients, respectively, and late restenosis or reocclusion of the infarcted artery develops in as many as 50 percent and 10 percent, respectively — events that increase morbidity, mortality, and costs.<sup>3-6</sup> Outcomes may be further improved if coronary stents<sup>7-15</sup> and platelet glycoprotein IIb/IIIa inhibitors<sup>16-19</sup> are used in conjunction with PTCA. We therefore performed a large-scale multicenter, prospective, randomized trial to determine the optimal reperfusion strategy in patients with evolving acute myocardial infarction.

### METHODS

#### Study Population and Study Protocol

The study was conducted from November 1997 to September 1999. Inclusion criteria were an age of more than 18 years, the presence for at least 30 minutes but less than 12 hours of symptoms consistent with acute myocardial infarction, and the presence of ST-segment elevation in at least two contiguous leads or left bundle-branch block. Patients with other electrocardiographic patterns were enrolled if angiography demonstrated that they had a high-

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grade stenosis and associated abnormalities in regional wall motion. Patients were excluded if they were in cardiogenic shock (defined as systolic blood pressure of less than 80 mm Hg for more than 30 minutes or the need for intravenous pressors or intraaortic-balloon counterpulsation); had a history of bleeding diathesis or allergy to the study drug; had undergone major surgery within the preceding six weeks; had had gastrointestinal or genitourinary bleeding within the preceding six months; had had a cerebrovascular event within the preceding two years or had any permanent residual neurologic defect; had a history of leukopenia, thrombocytopenia, or hepatic or renal dysfunction; had recently received a thrombolytic agent; had a noncardiac illness associated with a life expectancy of less than one year; or were participating in another study. The study was approved by the institutional review board or ethics committee at each participating center, and consecutive, eligible patients provided written informed consent.

Before undergoing catheterization, patients received 324 mg of chewable aspirin (or 250 mg intravenously at European centers), 500 mg of ticlopidine or 300 mg of clopidogrel orally, a 5000-U bolus of heparin, and a beta-blocker intravenously in the absence of contraindications. Left ventriculography and arteriography were performed with the use of ioxaglate, and all patients who met the angiographic enrollment criteria underwent randomization. The angiographic inclusion criterion was the finding of a native coronary-artery vessel with a lesion that was no longer than 64 mm and that had a reference diameter of 2.5 to 4.0 mm. Patients were excluded if the angiographic findings indicated that noninterventional (medical or surgical) management was the proper approach, if multivessel angioplasty was required during the index procedure, or if pre-specified anatomical conditions were present that would reduce the likelihood of successful stenting. Patients who were excluded from randomization received clinically appropriate treatment.

Patients were randomly assigned in a balanced fashion to one of four interventional strategies of reperfusion with the use of a 2-by-2 factorial design: PTCA alone, PTCA plus abciximab, stenting alone, or stenting plus abciximab. The stent used was the MultiLink<sup>20</sup> or MultiLink Duet<sup>21</sup> (Guidant, Santa Clara, Calif.), available in diameters ranging from 2.5 to 4.0 mm and in multiple lengths, up to 38 mm. Abciximab (ReoPro, Centocor, Malvern, Pa.), which binds to the glycoprotein IIb/IIIa receptor of human platelets and inhibits platelet aggregation, was administered as a bolus of 0.25 mg per kilogram of body weight, followed by a 12-hour infusion at a rate of 0.125  $\mu$ g per kilogram per minute (maximum, 10  $\mu$ g per minute). The dose of heparin was calculated with use of a nomogram to achieve an activated clotting time of at least 350 seconds (200 to 300 seconds among the patients assigned to receive abciximab). In the two PTCA groups, crossover to stenting was allowed if, after PTCA, there was residual stenosis of more than 50 percent despite prolonged balloon inflations or a dissection of at least type C. In the two groups of patients who were not assigned to receive abciximab, crossover to abciximab therapy was allowed after the intervention if flow could not be reestablished in the absence of a mechanical obstruction ("no reflow"), despite therapy with intracoronary calcium-channel blockers, or if there was persistent thrombus within or adjacent to the stent.

After the intervention, patients received 325 mg of aspirin daily, as well as beta-blockers and angiotensin-converting-enzyme inhibitors, if these agents were not contraindicated. Patients who received stents were given 250 mg of ticlopidine orally twice daily or 75 mg of clopidogrel orally per day for four weeks. Follow-up visits were scheduled at 1, 6, and 12 months. According to the study protocol, follow-up angiography was prespecified at seven months in a subgroup of 900 consecutive patients who had not had a stroke and were not scheduled to undergo early bypass surgery.

#### Data Collection and Management

Clinical data were prospectively collected by research nurses, and follow-up was performed during office visits to physicians. Inde-

pendent study monitors verified 100 percent of the data for the case-report form on site. The data for all patients with primary end-point events were reviewed by an independent adjudication committee whose members were unaware of patients' treatment assignments. A data safety and monitoring committee reviewed blinded data after 250, 500, and 1000 patients had undergone randomization, and each time it recommended that the study continue without modification. Independent analysis was performed at the core angiographic laboratory as previously described<sup>22</sup> by technicians who were unaware of patients' clinical outcomes. All films were reread for accuracy by one physician. The left ventricular ejection fraction was calculated with use of the area-length method,<sup>23</sup> and regional wall motion was determined with use of the centerline chord method.<sup>24</sup> The investigators had full access to the data and independently confirmed all analyses initially performed by the sponsor.

#### Statistical Analysis

The primary end point was a composite of death from any cause, reinfarction, repeated intervention or revascularization of the target vessel as a result of ischemia, or disabling stroke during the first six months after the index procedure. Reinfarction was defined by the presence of recurrent ischemic symptoms or electrocardiographic changes accompanied by a creatine kinase level that was more than twice the upper limit of the normal range (with an elevated MB isoform level) or more than 50 percent higher than the previous value obtained during hospitalization. Revascularization of the target vessel was considered to have been prompted by ischemia if there was evidence of ischemia during functional testing or of angina. Disabling stroke was defined as an acute neurologic deficit that lasted more than 24 hours and affected the ability to perform daily activities or resulted in death.

Two primary hypotheses were prespecified: stenting without abciximab is superior to PTCA without abciximab, and stenting without abciximab is not inferior to PTCA plus abciximab. With respect to the first hypothesis, we calculated that a total of 966 patients would be required, using a two-sided test for differences in independence binomial proportions at the 2.5 percent level of significance (with Bonferroni's correction) and given an expected rate of events of 30 percent after PTCA,<sup>2,3,6,10-16</sup> for the study to have more than 90 percent power to detect a reduction in the primary end point of 10 percentage points after stenting. With respect to the second hypothesis, we used the Blackwelder method<sup>25</sup> to estimate that a total of 898 randomized patients would be required for the study to have more than 80 percent power to detect the preservation of a difference of 7.5 percentage points between the event rate for PTCA plus abciximab and that for stenting without abciximab, using a significance level of 2.5 percent and an expected event rate of 20 percent for PTCA plus abciximab.

We used the likelihood-ratio chi-square test or Fisher's exact test to compare categorical variables. Continuous variables are presented as medians and interquartile ranges and were compared with use of one-way analysis of variance or the Kruskal-Wallis test and, in pairwise analyses, with use of the Wilcoxon two-sample test. Time-to-event data were analyzed with use of survival techniques and compared with use of the log-rank test. All cross-group pairwise statistical comparisons are reported if the results of the log-rank test for the four treatment groups were statistically significant ( $\alpha = 0.05$ )<sup>26</sup>; otherwise, the two-way significance level was set at 0.01 to correct for multiple comparisons. The influence of base-line demographic and angiographic variables on the primary end point at six months was evaluated with use of logistic regression with Wald's chi-square test, and the results are expressed as odds ratios with 95 percent confidence intervals. All analyses were conducted according to the intention-to-treat principle unless otherwise stated, and all P values are two-sided. Statistical tests were performed with SAS for Windows, version 8.02 (SAS Institute, Cary, N.C.).

## RESULTS

## Patient Population and Base-Line Characteristics

A total of 2681 patients with acute myocardial infarction were enrolled at 76 centers in nine countries, of whom 2082 (77.7 percent) met the angiographic criteria for stent implantation and underwent randomization. The base-line characteristics of the patients were similar in the four randomized groups (Table 1). Patients were excluded for the following reasons (some met more than one exclusion criterion): the lesion was longer than 64 mm (in 56 patients); the reference diameter was less than 2.5 mm or more than 4.0 mm (in 118); stenosis was present within a stent (in 36); the culprit lesion was in a vein graft (in 52); there was excessive tortuosity (in 90), calcification (in 64), involvement of major side branches (in 31), or disease of

the left main coronary artery or ostia (in 67); or multivessel angioplasty (in 36), surgical management (in 221), or medical management (in 139) was indicated.

Among the 599 patients who did not undergo randomization, 190 (31.7 percent) were treated medically, 140 (23.4 percent) underwent bypass surgery, and 269 (44.9 percent) underwent PTCA before being discharged from the hospital, of whom 142 received stents. Thus, 88.6 percent of all patients who underwent primary angioplasty and 94.6 percent of those who received or were eligible to receive a stent underwent randomization.

## Procedural Results

Approximately 16 percent of patients who were randomly assigned to undergo PTCA received stents because the results of balloon angioplasty were sub-

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

CHARACTERISTIC	PTCA (N=518)	PTCA PLUS ABCIXIMAB (N=528)	STENTING (N=512)	STENTING PLUS ABCIXIMAB (N=524)	P VALUE
Age (yr)					
Median	59	60	60	59	0.58
Interquartile range	50-68	51-69	51-68	51-69	—
Range	21-90	29-91	28-95	24-94	—
Male sex (% of patients)	71.4	74.1	72.5	74.0	0.73
Diabetes mellitus (% of patients)	15.3	15.7	16.2	19.3	0.30
Hypertension (% of patients)	44.8	51.7	50.2	45.6	0.07
Hyperlipidemia (% of patients)	35.7	40.7	37.5	37.6	0.41
Current cigarette use (% of patients)	41.9	43.6	45.1	42.0	0.69
Prior myocardial infarction (% of patients)	13.9	15.9	11.9	13.0	0.28
Prior PTCA (% of patients)	11.8	12.3	8.8	11.8	0.24
Prior coronary bypass surgery (% of patients)	2.3	2.3	1.2	1.9	0.48
Prior stroke or transient ischemic attack (% of patients)	4.1	2.7	2.3	2.9	0.41
Killip class $\geq$ II (% of patients)	9.9	11.1	11.4	11.2	0.53
ST-segment elevation or left bundle-branch block (% of patients)	87.9	88.2	87.3	87.8	0.98
Myocardial infarction without ST-segment elevation (% of patients)	12.1	11.8	12.7	12.2	0.98
Time from onset of symptoms to hospital presentation (hr)					0.12
Median	1.8	1.6	1.9	1.8	
Interquartile range	1.0-3.9	1.0-3.0	1.1-3.8	1.0-3.3	
Time from hospital presentation to angioplasty (hr)					0.99
Median	2.1	2.0	2.0	2.0	
Interquartile range	1.5-2.8	1.5-2.7	1.5-2.7	1.5-2.7	
Angiographic features					
Single-vessel disease (% of patients)	54.2	49.8	48.8	51.9	0.31
Double-vessel disease (% of patients)	31.3	32.8	35.7	33.2	0.49
Triple-vessel disease (% of patients)	14.5	17.4	15.4	14.9	0.55
Left ventricular ejection fraction					0.33
Median	0.48	0.50	0.50	0.50	
Interquartile range	0.40-0.55	0.40-0.56	0.40-0.56	0.40-0.60	
Infarct-related vessel (% of patients)					
Left anterior descending coronary artery	39.4	35.4	38.5	33.8	0.20
Left circumflex artery	16.0	17.8	17.4	19.3	0.59
Right coronary artery	44.6	46.6	44.1	46.9	0.74
Left main coronary artery (protected)	0	0.2	0	0	0.99

\*PTCA denotes percutaneous transluminal coronary angioplasty.

optimal, and less than 10 percent of patients who were assigned to undergo PTCA or stenting alone received abciximab. The minimal luminal diameter was significantly greater ( $P<0.001$ ) and the degree of residual stenosis significantly lower ( $P<0.001$ ) after stenting than after PTCA (Table 2). Flow rates of grade 3 according to the classification of the Thrombolysis in

Myocardial Infarction (TIMI) trial were achieved in 94.5 to 96.9 percent of patients, whatever their randomization assignment.

**Major Adverse Cardiac Events**

At 30 days, the incidence of the primary end point — a composite of death, reinfarction, revasculariza-

**TABLE 2. PROCEDURAL RESULTS.\***

VARIABLE	PTCA (N=518)	PTCA PLUS ABCIXIMAB (N=528)	STENTING (N=512)	STENTING PLUS ABCIXIMAB (N=524)	P VALUE
One or more stents implanted (% of patients)	18.1	14.0	98.0	97.7	—
No. of stents implanted†					—
Median	1	1	1	1	
Interquartile range	1–2	1–2	1–2	1–1	
Length of stent (mm)†					0.94
Median	—	—	25	25	
Interquartile range	—	—	18–35	15–35	
Maximal size of balloon or stent (mm)					0.69
Median	3.5	3.5	3.5	3.5	
Interquartile range	3.0–3.5	3.0–3.5	3.0–3.5	3.0–3.5	
Maximal pressure (atm)					<0.001
Median	10	10	14‡	14‡	
Interquartile range	8–12	8–12	12–16	12–16	
Abciximab therapy (% of patients)	7.3	99.1	4.7	99.4	—
TIMI flow (% of patients)					
Before procedure					
Grade 0 or 1	71.0	66.7	68.0	66.0	0.33
Grade 2	9.7	9.7	10.7	10.0	0.95
Grade 3	19.3	23.6	21.3	24.0	0.24
After procedure					
Grade 0 or 1	1.0	1.6	1.8	1.2	0.69
Grade 2	4.3	2.3	3.7	1.9	0.08
Grade 3	94.7	96.1	94.5	96.9	0.16
Reference diameter (mm)					0.06
Before procedure					
Median	2.95	2.96	2.89	3.01	
Interquartile range	2.61–3.31	2.56–3.31	2.61–3.31	2.65–3.37	
Final					0.02
Median	2.96	2.95	2.96	3.03‡	
Interquartile range	2.60–3.34	2.60–3.35	2.64–3.35	2.69–3.42	
Minimal luminal diameter (mm)					0.49
Before procedure					
Median	0	0	0	0	
Interquartile range	0–0.64	0–0.75	0–0.70	0–0.74	
Final§					<0.001
Median	2.20	2.15	2.64‡	2.70‡	
Interquartile range	1.92–2.55	1.88–2.55	2.37–2.90	2.47–2.99	
Extent of stenosis (%)					0.48
Before procedure					
Median	100	100	100	100	
Interquartile range	77.0–100	73.4–100	75.1–100	75.4–100	
Final§					<0.001
Median	25.2	25.2	11.7‡	10.8‡	
Interquartile range	16.7–34.3	18.2–33.2	3.8–18.9	3.8–17.6	

\*PTCA denotes percutaneous transluminal coronary angioplasty, and TIMI Thrombolysis in Myocardial Infarction.

†Only patients who received one or more stents are included.

‡ $P<0.001$  for the two-way comparison with PTCA and with PTCA plus abciximab.

§Measurements were made within a lesion or within a stent if a stent was implanted.

tion, or disabling stroke — was highest in the group assigned to receive PTCA alone, and the lower rates in the other three groups were not significantly different from one another (Table 3). Subacute thrombosis of the target vessel was less common after intervention with abciximab use than without its use (0.4 percent vs. 1.4 percent,  $P<0.001$ ), though there were no significant differences in the rates of clinical reinfarction. Analyses according to the treatment received showed that thrombocytopenia and the need for blood-product transfusions were more common in patients who received abciximab than in those who did not (4.2 percent vs. 1.9 percent,  $P=0.002$ ; and 5.4 percent vs. 3.4 percent,  $P=0.02$ , respectively).

At six months, the primary end point had occurred in 20.0 percent of patients in the PTCA group, 16.5 percent of those in the group assigned to receive PTCA plus abciximab, 11.5 percent of those in the

stenting group, and 10.2 percent of those in the group assigned to receive a stent plus abciximab ( $P<0.001$ ). The two primary hypotheses were met: stenting alone was superior to PTCA alone (incidence of the primary end point, 11.5 percent vs. 20.0 percent;  $P<0.001$ ), and stenting alone was not inferior to PTCA plus abciximab (incidence of the primary end point, 11.5 percent vs. 16.5 percent;  $P<0.001$  according to the Blackwelder  $z$  statistic for noninferiority). There were no significant differences among the four groups in the rates of death, disabling stroke, or reinfarction; the difference in the rates of the primary end point was driven by the lower rates of revascularization of ischemic target vessels in the stenting groups than in the PTCA groups (Table 3). The higher rate of event-free survival with stenting than with PTCA was consistent across the prespecified clinical subgroups evaluated (Fig. 1).

TABLE 3. KAPLAN-MEIER ESTIMATES OF THE CLINICAL OUTCOMES AT 30 DAYS AND 6 MONTHS.\*

OUTCOME	PTCA (N=518)	PTCA PLUS ABCIXIMAB (N=528)	STENTING (N=512)	STENTING PLUS ABCIXIMAB (N=524)	P VALUE
	percent				
<b>At 30 days</b>					
Death	2.5	1.1	2.2	2.7	0.31
Reinfarction	0.8	0.8	1.0	0.8	0.97
Disabling stroke	0.2	0.0	0.2	0.2	0.79
Revascularization of ischemic target vessel	5.6	3.4	3.2	1.6†	0.004
Composite end point	8.3‡	4.8	5.7	4.4	0.02
Other adverse events					
Target-vessel revascularization for any reason	6.0	3.6	3.4§	1.6†	0.002
Subacute thrombosis	1.9	0.8	1.0	0.0	0.01
Hemorrhagic complication					
Severe	0.6	0.4	0.2	0.8	0.58
Moderate	2.5	2.3	4.3	2.5	0.18
Intracranial hemorrhage	0.0	0.0	0.0	0.2	0.99
Thrombocytopenia (<100,000 cells/mm <sup>3</sup> )	1.4¶	4.0	2.6	4.0	0.02
Blood-product transfusion	3.7	5.1	4.1	5.0	0.62
<b>At 6 months (cumulative)</b>					
Death	4.5	2.5	3.0	4.2	0.23
Reinfarction	1.8	2.7	1.6	2.2	0.64
Disabling stroke	0.2	0.2	0.4	0.4	0.88
Revascularization of ischemic target vessel	15.7	13.8	8.3	5.2**	<0.001
Composite end point	20.0	16.5	11.5††	10.2‡‡	<0.001
Target-vessel revascularization for any reason	16.9	14.8	8.9‡‡	5.7**	<0.001

\*PTCA denotes percutaneous transluminal coronary angioplasty.

† $P<0.001$  for the two-way comparison with PTCA, and  $P<0.05$  for the two-way comparison with PTCA plus abciximab.

‡ $P<0.02$  for the two-way comparison with PTCA plus abciximab, and  $P=0.08$  for the two-way comparison with stenting plus abciximab.

§ $P<0.05$  for the two-way comparison with PTCA.

¶ $P<0.01$  for the two-way comparison with PTCA plus abciximab and with stenting plus abciximab.

|| $P<0.001$  for the two-way comparison with PTCA, and  $P=0.006$  for the two-way comparison with PTCA plus abciximab.

\*\* $P<0.001$  for the two-way comparison with PTCA and with PTCA plus abciximab.

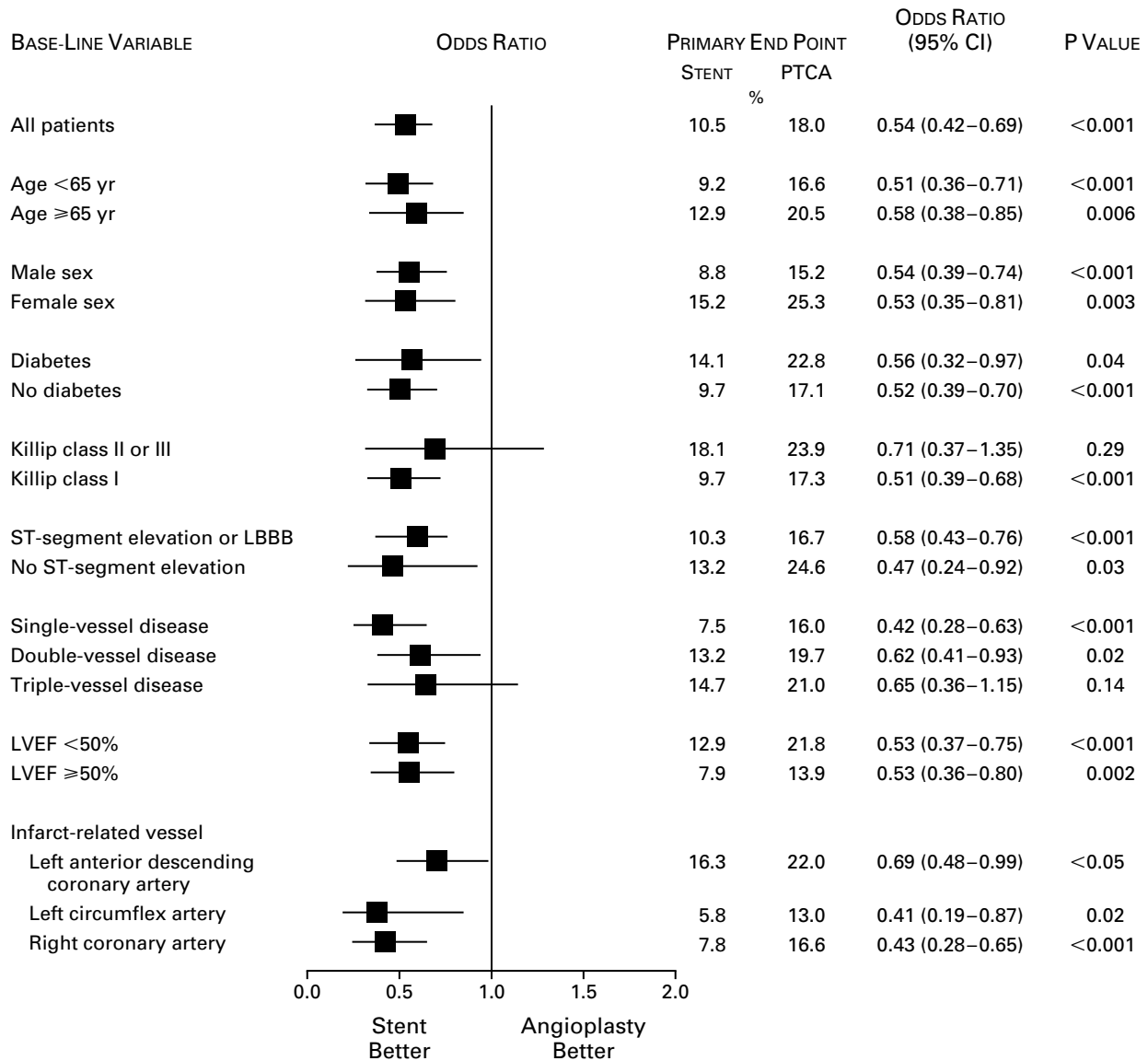
†† $P<0.001$  for the two-way comparison with PTCA, and  $P=0.03$  for the two-way comparison with PTCA plus abciximab.

‡‡ $P<0.001$  for the two-way comparison with PTCA, and  $P=0.004$  for the two-way comparison with PTCA plus abciximab.

**Angiographic Results**

Of the 900 prespecified eligible patients, 656 (72.9 percent) completed the angiographic follow-up at seven months, and the results could be evaluated at the core angiographic laboratory in 636 patients. The base-line characteristics of patients with angiographic follow-up data and those without such data were similar, except for a slightly greater prevalence of men among those with follow-up data (76.9 percent vs.

68.5 percent,  $P=0.009$ ). The overall rate of restenosis was 40.8 percent after PTCA and 22.2 percent after stenting ( $P<0.001$ ), and the respective rates of reocclusion of the infarct-related artery were 11.3 percent and 5.7 percent ( $P=0.01$ ), both independent of abciximab use (Table 4). The left ventricular ejection fraction and regional wall motion in the infarcted zone improved to a similar degree from base line to follow-up in all four groups (Table 4).



**Figure 1.** Odds Ratio of the Primary Composite End Point of Death, Reinfarction, Revascularization of the Target Vessel, and Disabling Stroke at Six Months among All 1046 Patients Randomly Assigned to Undergo Percutaneous Transluminal Coronary Angioplasty (PTCA), as Compared with All 1036 Patients Randomly Assigned to Undergo Stenting, According to Base-Line Characteristics. CI denotes confidence interval, LBBB left bundle-branch block, and LVEF left ventricular ejection fraction.

DISCUSSION

The principal finding of our study is that routine stent implantation results in higher rates of event-free survival and better angiographic outcomes than does PTCA (with stenting performed only in the event of suboptimal results). The clinical benefits of stenting were consistent in all clinical subgroups, independent of abciximab use, and attributable primarily to lower rates of early and late restenosis and reocclusion of the infarct-related artery.

The survival benefit of PTCA over thrombolytic therapy derives from the higher rates of antegrade epicardial TIMI grade 3 blood flow, as well as from lower rates of reinfarction and stroke.<sup>1-3</sup> However, dissection and residual luminal narrowing after PTCA may

result in early or late reocclusion or restenosis.<sup>4</sup> In this regard, the mechanical scaffolding properties of coronary stents<sup>27,28</sup> may be expected further to enhance outcomes.

After the promising results of early pilot studies<sup>7-9</sup> and small randomized trials<sup>10-14</sup> of primary stenting in patients with acute myocardial infarction, we randomly assigned 900 patients to undergo either PTCA or stenting with use of the sheathed, heparin-coated Palmaz-Schatz stent as part of the Stent Primary Angioplasty in Myocardial Infarction (PAMI) trial.<sup>15</sup> Though stenting did reduce the rates of recurrent ischemia and restenosis, the percentage of patients with TIMI grade 3 flow rates was unexpectedly lower after stenting than after PTCA, resulting in a strong trend

TABLE 4. ANGIOGRAPHIC MEASUREMENTS OBTAINED AT THE TIME OF THE INDEX PROCEDURE AND AT MONTH 7 OF FOLLOW-UP.

VARIABLE	PTCA	PTCA PLUS ABCIXIMAB	STENTING	STENTING PLUS ABCIXIMAB	P VALUE
<b>Infarct-related lesion at follow-up</b>					
No. of patients	148	163	152	173	
Reference diameter (mm)					0.58
Median	2.85	2.85	2.80	2.88	
Interquartile range	2.45 to 3.29	2.49 to 3.22	2.46 to 3.23	2.58 to 3.26	
Minimal luminal diameter (mm)*					<0.001
Median	1.60	1.55	1.75†	1.88‡	
Interquartile range	1.12 to 2.07	0.99 to 1.94	1.36 to 2.19	1.42 to 2.30	
Extent of stenosis (%)*					<0.001
Median	41.6§	45.1¶	34.7	34.2	
Interquartile range	27.8 to 57.1	30.5 to 65.3	26.7 to 48.7	25.3 to 46.1	
Restenosis (% of patients)					
Stenosis ≥50%	36.5	44.8¶	23.7	20.8	<0.001
Stenosis ≥70%	18.9	18.4	9.2**	6.4‡	<0.001
Total occlusion	12.2	10.4	6.5	5.2	0.08
<b>Myocardial function</b>					
No. of patients	105	106	109	116	
Left ventricular ejection fraction (%)					
At index procedure					0.48
Median	56.8	58.1	56.4	58.6	
Interquartile range	44.7 to 63.7	51.6 to 63.7	49.4 to 62.8	46.8 to 65.9	
At follow-up					0.84
Median	59.3	59.8	60.5	61.6	
Interquartile range	49.8 to 67.3	52.6 to 68.4	53.5 to 68.3	50.7 to 69.6	
Regional wall motion in infarcted zone (SD/chord)††					
At index procedure					0.99
Median	-1.25	-1.21	-1.26	-1.25	
Interquartile range	-1.64 to -0.91	-1.53 to -0.80	-1.64 to -0.67	-1.61 to -0.88	
At follow-up					0.97
Median	-0.79	-0.77	-0.86	-0.76	
Interquartile range	-1.33 to -0.13	-1.14 to -0.40	-1.30 to -0.20	-1.25 to -0.28	

\*Measurements were made within the lesion.

†P=0.04 for the two-way comparison with PTCA, and P=0.002 for the two-way comparison with PTCA plus abciximab.

‡P<0.001 for the two-way comparison with PTCA and with PTCA plus abciximab.

§P=0.03 for the two-way comparison with stenting, and P=0.004 for the two-way comparison with stenting plus abciximab.

¶P<0.001 for the two-way comparison with stenting and with stenting plus abciximab.

||P<0.02 for the two-way comparison with stenting, and P<0.002 for the two-way comparison with stenting plus abciximab.

\*\*P<0.02 for the two-way comparison with PTCA and with PTCA plus abciximab.

††Regional wall motion was determined with use of the centerline chord method.

toward increased intermediate-term<sup>15</sup> and late mortality rates (one-year survival, 97.0 percent after PTCA, as compared with 94.6 percent after stenting;  $P=0.054$ ) (unpublished data). This finding of slower antegrade flow after stenting than after balloon angioplasty, which was subsequently reported by other groups,<sup>29,30</sup> is at least partly attributable to the extrusion of thrombus through the stent struts, followed by distal embolization.<sup>31</sup> Because of concern about the possibility of reduced epicardial flow and increased mortality rates, routine stenting in patients with acute myocardial infarction has been recommended only for those with suboptimal PTCA results.<sup>15</sup> However, abciximab was used in only 5 percent of patients in the Stent PAMI trial.<sup>15</sup> Since the thromboemboli that occur after mechanical intervention are rich in platelets,<sup>31</sup> blockade of glycoprotein IIb/IIIa receptors may have a particularly synergistic effect when paired with stent implantation. This contention is supported by the findings of an earlier study, in which abciximab therapy during stenting resulted in improved distal microcirculatory flow capacity with a corresponding improvement in the early recovery of myocardial function.<sup>18</sup> Moreover, whether newer stents with a lower profile could decrease the tendency toward distal embolization was unknown.

In contrast to the findings of the Stent PAMI trial,<sup>15</sup> in the present study the percentage of patients with TIMI grade 3 flow rates was not significantly smaller after stenting with the MultiLink stent than after PTCA, nor was survival adversely affected with stenting. Indeed, despite the fact that the patients in this study had entry criteria and base-line characteristics that were similar to those of patients in prior PAMI trials,<sup>1,8,15,32,33</sup> the percentages of patients with TIMI grade 3 flow rates (measured at the same core laboratory) and rates of infarct-free survival have continued to increase. Whether this progress can be ascribed to improvements in stent design, increasing operator experience, or more appropriate use of adjunct pharmacotherapy is uncertain. Regardless of the reason, because of the markedly lower rate of clinical and angiographic restenosis, routine stenting resulted in a higher rate of event-free survival at six months than did PTCA, with no increase in early or late complications.

The use of abciximab reduced the rates of subacute thrombosis and recurrent ischemia leading to repeated revascularization of the target vessel during the first several weeks after primary PTCA or stenting. Abciximab did not, however, significantly improve TIMI flow rates or reduce the rates of angiographic restenosis, late reocclusion of the infarcted artery, or late cardiac events after PTCA or stenting — a finding consistent with the results of two prior randomized trials.<sup>17-19</sup> In contrast, abciximab therapy increased

the event-free survival rates at one and six months in a French multicenter, randomized trial, in which about 86 percent of the patients received stents.<sup>34</sup> Notably, however, the statistically significant improvement in late outcomes in that study was confined to the 26 percent of patients who received abciximab well in advance of catheterization, which resulted in a higher incidence of TIMI grade 3 flow rates at base line.<sup>34</sup> Moreover, the favorable effect of abciximab on left ventricular function two weeks after primary or rescue stenting reported by Neumann and colleagues<sup>18</sup> in a single-center study was not duplicated in our larger, multicenter trial at seven months, suggesting that the initiation of therapy with glycoprotein IIb/IIIa inhibitors just before angioplasty may enhance the speed but not the ultimate extent of myocardial recovery. Finally, whether routine administration of a thienopyridine (ticlopidine or clopidogrel) in the emergency room, which has been associated with increased rates of TIMI grade 3 flow before PTCA<sup>35</sup> and improved outcomes in patients with acute coronary syndromes,<sup>35,36</sup> diminished the relative efficacy of abciximab in this study is unknown.

The results of any randomized trial apply only to the patient cohort studied, and thus, the extent to which our study population is representative of all patients with acute myocardial infarction is a valid consideration. Our trial was large and broad in geographic scope; we used liberal entry criteria in the hope that the results might be applicable to most patients who are candidates for primary stenting. Moreover, we used a stent with a low-profile, sheathless delivery system similar to that of stents in current use. As a result, approximately 90 percent of the patients who met the clinical enrollment criteria and who were eligible to receive a stent underwent randomization. We therefore believe our results are applicable to the majority of patients who present with acute myocardial infarction. However, no conclusions can be drawn from this study regarding optimal treatment strategies for patients in cardiogenic shock,<sup>37</sup> patients with vein-graft occlusion,<sup>38</sup> or patients who present more than 12 hours after the onset of symptoms. Cost-effectiveness considerations and further lesion-specific analysis of subgroups may also affect the selection process for the use of stents and abciximab. Finally, we administered abciximab only in the catheterization laboratory. Future studies are warranted to investigate the value of the early use of glycoprotein IIb/IIIa inhibitors, either alone or in combination with reduced doses of thrombolytic agents, to facilitate vessel patency before definitive mechanical revascularization is attempted.<sup>35,39,40</sup>

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APPENDIX

The following investigators, research coordinators, and institutions participated in the study: *Executive Committee* — G.W. Stone (principal investigator), C.L. Grines (co-principal investigator), E. Garcia (European chairman), J.E. Tcheng, G. Johnson, M. Effron; *Data Monitoring* — Medical Device Division, Bior Research, Santa Clara, Calif.; D. McHugh (director); *Data Management and Biostatistical Analysis* — Guidant, Santa Clara, Calif.; S. Gedney, P. Hormel, R. White, D. Deyette, K. Anderberg, M. Saunders, N. Nishimura, S. Marucco, J. Kennedy, B. Madison, D. Taylor, D. Jones; *Clinical Events Adjudication Committee* — Duke Clinical Research Institute, Durham, N.C.; K. Mahaffey (director); *Data Safety and Monitoring Committee* — B. Gersh (chairman), A. Yeung, A. Guerci, D. DeMets; *Angiographic Core Laboratory* — Cardiovascular Research Foundation, New York; A.J. Lansky (director), K. 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