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A Randomized Trial Comparing Primary Infarct Artery Stenting With or Without Abciximab in Acute Myocardial Infarction

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OBJECTIVES We sought to evaluate the efficacy of abciximab as adjunctive therapy to routine infarct-related artery (IRA) stenting.

BACKGROUND The impact of abciximab on the efficacy of myocardial reperfusion and the outcome of patients with acute myocardial infarction (AMI) undergoing IRA stenting have not yet been defined.

METHODS In a randomized trial, we assigned 400 patients with AMI to undergo IRA stenting alone or stenting plus abciximab. The primary end point was a composite of death, reinfarction, target vessel revascularization (TVR), and stroke at one month.

RESULTS The incidence of the primary end point was lower in the abciximab group than in the stent only group (4.5% and 10.5%, respectively; $p = 0.023$), and randomization to abciximab was independently related to the risk of the primary end point (odds ratio 0.41, 95% confidence interval 0.17 to 0.97; $p = 0.041$). Early ST-segment resolution was more frequent in the abciximab group (85% vs. 68%, $p < 0.001$). Infarct size, as assessed by one-month technetium-99m sestamibi scintigraphy, revealed smaller infarcts in the abciximab group. At six months, the cumulative difference in mortality between the groups increased (4.5% vs. 8%), and the incidence of the composite of six-month death and reinfarction was lower in the abciximab group than in the stent only group (5.5% and 13.5%, respectively; $p = 0.006$). Six-month repeat TVR and restenosis rates were similar in the two groups.

CONCLUSIONS Abciximab plus IRA stenting should be considered the routine reperfusion strategy in patients with AMI undergoing primary percutaneous mechanical revascularization, especially in high-risk patients. (J Am Coll Cardiol 2003;42:1879–85) © 2003 by the American College of Cardiology Foundation

Several studies comparing primary coronary angioplasty with primary stenting for acute myocardial infarction (AMI) have shown that primary stenting improves the procedural success rate and clinical outcome (1–6). The impact of

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abciximab as adjunctive therapy to stenting on the efficacy of myocardial reperfusion and the outcome of patients with AMI have not yet been defined, and three completed randomized trials comparing stenting alone with stenting plus abciximab have produced conflicting results (6–8). Differences in the criteria used for patient recruitment and in adjunctive pharmacologic treatments may partly explain these discrepancies and prevent the generalizability of the concluded trial results to all patients with AMI. We therefore conducted an international, multicenter randomized trial to determine the impact of abciximab on the clinical outcome of patients with ST-segment elevation AMI undergoing routine infarct-related artery (IRA) stenting. We used broad inclusion criteria, and patients were enrolled without any restriction based on age, the risk of clinical status on presentation, and the risk of coronary anatomy, in order to have an enrolled population representative of the "real world" of patients with AMI.

METHODS

Study population and protocol. The study was conducted from January 2001 to August 2002. Criteria for enrollment included: 1) chest pain persisting more than 30 min and associated with ST-segment elevation of at least 0.1 mV in two or more contiguous electrocardiographic (ECG) leads; and 2) admission either within 6 h of symptom onset or between 6 and 24 h if there was evidence of continuing

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Abbreviations and Acronyms

ADMIRAL = Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up trial
AMI = acute myocardial infarction
CADILLAC = Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications trial
CK = creatine kinase
CS = cardiogenic shock
ECG = electrocardiogram or electrocardiographic
IRA = infarct-related artery
ISAR = Intracoronary Stenting and Antithrombotic Regimen trial
^{99m}Tc = technetium-99m
TIMI = Thrombolysis In Myocardial Infarction
TVR = target vessel revascularization

ischemia. Patients with cardiogenic shock (CS) due to predominant ventricular failure were included. Cardiogenic shock due to predominant ventricular failure was defined as systolic blood pressure <90 mm Hg (without inotropic or intra-aortic balloon support) that was thought to be secondary to ventricular dysfunction and associated with signs of end-organ hypoperfusion such as: cold or diaphoretic extremities; altered mental status; or anuria. The exclusion criteria included previous administration of fibrinolytic or abciximab therapy, a history of bleeding diathesis or allergy to the study drug, major surgery within 15 days, active bleeding, participation in another study, and inability to obtain informed consent. All patients with a reference IRA diameter ≥2.5 mm were eligible for stenting and randomization. Unlike in previous studies, evidence of massive coronary thrombus, diffuse disease, a major branch involved in the culprit lesion, left main coronary disease, or severe vessel tortuosity were not considered contraindications to stenting. Angiographic criteria for exclusion from randomization included: 1) IRA reference diameter <2.5 mm on visual assessment at baseline angiography; 2) a previously stented IRA; 3) <70% stenosis of the IRA associated with Thrombolysis In Myocardial Infarction (TIMI) trial flow grade 3 (9); and 4) an inability to identify the IRA.

Before catheterization, patients received 325 mg aspirin orally or 250 mg intravenously.

After coronary angiography, patients were randomly assigned to stenting alone or stenting plus abciximab. Randomization was carried out by means of a computer-generated sequence, and assignments were made using a centralized telephone system. Data on nonrandomized patients were collected in a parallel registry.

Coronary stenting had to be attempted with a carbofilm-coated tubular stent (Carbostent, SORIN, Saluggia, Italy). Crossover to other types of stent was allowed only after failure of a Carbostent implantation attempt. Coronary stenting was accomplished using a standard technique or directly, without predilation, at the discretion of the operator. Patients randomized to abciximab (ReoPro, Centocor, Malvern, Pennsylvania) received the drug immediately before the procedure as a bolus of 0.25 mg/kg body weight, followed by a 12-h infusion at a rate of 0.125 μg/kg/min. Heparin was given as an initial bolus of 70 U/kg, and additional boluses were administered during the procedure to achieve an activated clotting time of 200 to 300 s among the patients assigned to receive abciximab and at least 300 s in patients assigned to stenting alone. In the group of patients who were assigned to stenting alone, crossover to abciximab was strongly discouraged. In patients receiving abciximab, heparin was continued for 12 h, whereas in the remaining patients, intravenous heparin was continued for two days after the procedure. Immediately after the procedure, patients received 500 mg ticlopidine or 300 mg clopidogrel. Patients were routinely treated with aspirin (325 mg/day indefinitely), and either ticlopidine (500 mg/day for 1 month) or clopidogrel (75 mg/day for 1 month).

Coronary angiography was required for all eligible patients six months after the procedure. Quantitative coronary angiography included the assessment of TIMI flow grade, corrected TIMI frame count, IRA reference diameter, minimum lumen diameter, and reference and minimum lumen diameters at six months. These quantitative angiographic parameters were assessed as previously described (9–11).

A 12-lead ECG was recorded continuously 30 min after IRA recanalization. The ST-segment changes were evaluated in the single lead with the most prominent ST-segment elevation before mechanical intervention. ST-segment elevation was measured to the nearest 0.5 mm at 60 ms after the J point, with the aid of hand-held calipers. According to a previous report (12), a reduction in ST-segment elevation was defined as a decrease of ≥50% in ST-segment elevation at 30 min after IRA recanalization.

Creatine kinase (CK) measurements were systematically performed on hospital admission, every 3 h for the subsequent 24 h, and then every 12 h for two days. The peak CK value and the time to peak CK were estimated for each patient.

A technetium-99m (^{99m}Tc)-sestamibi scintigram for determination of infarct size at one month, as previously described (13), was pre-specified in a subgroup of 250 consecutive patients.

Independent analyses of the ECGs, scintigrams, and coronary angiograms were performed at ECG, nuclear medicine, and angiographic core laboratories whose members were unaware of patient treatment assignment and clinical outcome.

End points. The primary end point was a composite of death from any cause, reinfarction, target vessel revascularization (TVR), and stroke within one month of the index procedure. Patients with more than one event were assigned the highest ranked event, according to the previous list. The secondary end points were ST-segment reduction, postprocedural corrected TIMI frame count, infarct size at one month, death from any cause at six months, reinfarction at

Table 1. Baseline Characteristics of the Patients

	Stenting Alone Group (n = 200)	Stenting Plus Abciximab Group (n = 200)	p Value
Age (yrs)			
Median	63	64	0.473
Interquartile range	53–74	55–74	
Range	32–90	36–90	
Male	157 (79%)	152 (76%)	0.551
Hypertension	94 (47%)	92 (46%)	0.841
Hypercholesterolemia	78 (39%)	80 (40%)	0.838
History of smoking	82 (41%)	78 (39%)	0.683
Diabetes mellitus	37 (19%)	33 (17%)	0.699
Previous myocardial infarction	25 (12%)	20 (10%)	0.279
Previous coronary angioplasty	11 (6%)	7 (4%)	0.335
Previous coronary surgery	6 (3%)	4 (2%)	0.522
Anterior AMI	92 (46%)	81 (40%)	0.267
Cardiogenic shock	21 (10%)	16 (8%)	0.388
Not-low-risk patients	134 (67%)	129 (65%)	0.588
Symptom onset to reperfusion (h)			
Median	4.17	3.73	0.080
Interquartile range	3.1–5.5	2.9–5.5	
Infarct-related artery (%)			0.453
LAD	91 (45%)	79 (40%)	
RCA	74 (37%)	89 (44%)	
LCx	33 (17%)	31 (15%)	
LMCA	2 (1%)	1 (0.5%)	
TIMI flow grade 0–1	149 (75%)	156 (78%)	0.411
Multivessel disease	115 (57%)	108 (54%)	0.481
Collateral flow grade ≥2	17 (8%)	12 (6%)	0.335
Reference infarct artery diameter (mm)			
Median	3.13	3.18	0.624
Interquartile range	2.88–3.53	2.91–3.49	
Minimal lumen diameter (mm)			
Median	0	0	0.974
Interquartile range	0–0.48	0–0.46	

Data are presented as the number (%) of patients, unless otherwise specified.
AMI = acute myocardial infarction; LAD = left anterior descending coronary artery; LCx = left circumflex artery; LMCA = left main coronary artery; RCA = right coronary artery; TIMI = Thrombolysis in Myocardial Infarction trial.

six months, six-month composite of death and reinfarction, TVR at six months, and angiographic restenosis of the IRA at six months. "Reinfarction" was defined as recurrent chest pain with ST-segment or T-wave changes and recurrent elevation of cardiac enzymes. "Repeat TVR" was defined as coronary angioplasty or coronary surgery performed due to restenosis or reocclusion of the IRA. "Stroke" was defined as an acute neurologic defect that lasted more than 24 h and resulted in death or an inability to perform normal activities.

Statistical analysis. The sample size was calculated on the assumption that the primary end point would occur in 13% of patients randomized to stenting alone and in 5% of patients randomized to stenting plus abciximab. To detect a difference with 80% power and a type I error (alpha) of 0.05, 198 patients per group were required. Discrete data are summarized as frequencies, whereas continuous data are expressed as median values and interquartile ranges. The chi-squared test was used for comparison of categorical variables. The Mann-Whitney *U* test was used to test differences among continuous variables. Survival curves were generated using the Kaplan-Meier method, and the difference between curves was assessed by the log-rank test. Forward stepwise multivariate logistic regression analysis was performed to identify independent correlates of the primary end point, six-month mortality, and cumulative six-month mortality and reinfarction. The factors analyzed included age (years), gender, diabetes mellitus, hypertension, anterior AMI, previous myocardial infarction, history of angina, CS, multivessel disease, preprocedural TIMI flow grade ≤1, Rentrop collateral flow grade >1 (14), primary failure, time from symptom onset to recanalization (hours), randomization to abciximab, and stent length ≥20 mm. All analyses were conducted according to the intention-to-treat principle. A p value <0.05 was considered significant. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Analyses were performed using the package software SPSS version 8.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Patient population. A total of 485 patients with ST-segment elevation AMI were admitted to four centers in three countries, 400 (82%) of whom underwent randomization. The reasons for exclusion of 85 patients from random-

Table 2. Procedural Characteristics and Results

	Stenting Alone Group (n = 200)	Stenting Plus Abciximab Group (n = 200)	p Value
Primary failure	2 (1%)	1 (0.5%)	0.511
Infarct artery stenting	197 (99%)	198 (99%)	0.653
Stent type			
Carbostent	197	198	
Others	0	0	
Multiple stents	55 (27%)	47 (23%)	0.359
Stent length (mm)			
Median	19	15	0.266
Interquartile range	12–24	12–25	
Abciximab administration	22 (11%)	200 (100%)	<0.001
Intra-aortic balloon counterpulsation	21 (10%)	15 (7.5%)	0.295
Final TIMI flow grade 3	192 (96%)	194 (97%)	0.719
Final minimal lumen diameter (mm)			
Median	2.86	2.87	0.974
Interquartile range	2.54–3.15	2.45–3.20	
Final stenosis (%)			
Median	10	10	0.117
Interquartile range	3–12	5–17	
Peak CK ≥median value	111 (57%)	89 (45%)	0.018
Time to peak CK (h)			
Median	14.12	10.08	<0.001
Interquartile range	11.0–16.0	8.5–12.5	
≤6 h	60 (31%)	139 (70%)	<0.001

Data are presented as the number (%) of patients, unless otherwise specified.
CK = creatine kinase; TIMI = Thrombolysis In Myocardial Infarction.

ization were IRA diameter <2.5 mm (n = 15), contraindication to abciximab treatment (n = 25), moribund state on admission (n = 8), previous IRA stenting (n = 8), abciximab treatment before admission (n = 8), and an inability to obtain informed consent (n = 21).

Table 1 summarizes the baseline characteristics of randomized patients. The two groups were well matched in terms of all baseline characteristics, and the majority of the patients were "not low risk," according to the TIMI criteria (15).

In-hospital therapy. Table 2 summarizes the procedural characteristics and results. All patients randomized to abciximab had abciximab treatment, and crossover to abciximab occurred in 22 patients (11%) of the stent only group. Overall, there were three primary angioplasty failures. Stenting of the IRA was accomplished in 99% of patients using the study stent, and no crossover to other types of stent occurred in patients with an unsuccessful Carbostent implantation attempt.

Primary end point. The incidence of the primary end point was lower in the abciximab group than in the stent only group (4.5% and 10.5%, respectively; p = 0.023) (Table 3, Fig. 1). Each of the components of the primary end point was lower in the abciximab group, and the difference in the incidence of the primary end point was mostly due to the lower incidence of reinfarction. Early target vessel failure occurred in 14 patients and resulted in reinfarction in 10, despite repeat successful emergency revascularization. Coronary angiography revealed stent thrombosis in 11 patients and post-stent dissection in three. Stent thrombosis was detected in all but one patient who developed reinfarction. All patients with stent thrombosis had one or more of the following unfavorable clinical and procedural characteristics: multiple stents (n = 5), diabetes (n = 5), CS (n = 3), crossover to bailout abciximab (n = 3), and final inflation pressure >18 atm (n = 6). By multivariate analysis, the independent predictors of the primary end point were age (OR 1.03, 95% CI 1.00 to 1.07; p = 0.031), multivessel disease (OR 3.02, 95% CI 1.15 to 7.93; p = 0.025), CS (OR 7.53, 95% CI 3.12 to 18.14; p < 0.001), and randomization to abciximab (OR 0.41, 95% CI 0.17 to 0.97; p = 0.041).

Secondary end points. ST-segment reduction was more frequent in the abciximab group (Table 3). There were no differences in the postprocedural corrected TIMI frame count between the groups (Table 3).

Infarct size, as assessed by one-month ^{99m}Tc-sestamibi scintigraphy, revealed smaller infarcts in the abciximab group (Table 3). This difference was more evident in the subset of patient with ST-segment reduction. Moreover, patients with no detectable scintigraphic defect at one month were more frequently included in the abciximab group.

At six months, the cumulative difference in mortality between groups increased, with a 44% reduction in the abciximab groups (4.5% vs. 8.0%, p = 0.148), whereas the difference in the incidence of reinfarction was maintained. The incidence of the composite of six-month death or reinfarction was lower in the abciximab group than in the stent only group (5.5% and 13.5%, respectively; p = 0.006) (Fig. 2A). By multivariate analysis, the independent predictors of six-month mortality or reinfarction were age (OR 1.04, 95% CI 1.01 to 1.08; p = 0.014), CS (OR 7.85, 95% CI 3.21 to 19.16; p < 0.001), ST-segment reduction (OR 0.34, 95% CI 0.15 to 0.76; p = 0.009), and randomization to abciximab (OR 0.40, 95% CI 0.17 to 0.93; p = 0.033). The six-month mortality rate was 3.4% in the subset of patients with ST-segment reduction (10 of 294 patients) and 16% in the subset of patients without ST-segment reduction (14 of 88 patients) (Fig. 2B). The ST-segment reduction was independently related to six-month mortality (OR 0.31, 95% CI 0.12 to 0.81; p = 0.016).

Rates of repeat TVR and restenosis were similar in the two groups.

Bleeding and vascular complications. There were no differences in hemorrhagic complications requiring blood transfusion or vascular repair between the groups (3.5% vs. 3.0%, p = 0.778). There were no hemorrhagic strokes (a computed tomographic scan showed that the only disabling stroke was nonhemorrhagic).

Table 3. End Points

	Stenting Alone Group (n = 200)	Stenting Plus Abciximab Group (n = 200)	p Value
Primary end point			
Death at 30 days	8 (4%)	7 (3.5%)	0.792
Reinfarction at 30 days	9 (4.5%)	1 (0.5%)	0.010
Target vessel revascularization at 30 days	3 (1.5%)	1 (0.5%)	0.315
Stroke	1 (0.5%)	0	0.317
Composite	21 (10.5%)	9 (4.5%)	0.023
Secondary end points			
ST-segment reduction ≥50% at 30 min	(n = 188)	(n = 194)	
	129 (68%)	165 (85%)	<0.001
Corrected TIMI frame count (frames)	(n = 193)	(n = 194)	
Median	25.00	27.17	0.697
Interquartile range	19.18–31.75	18.78–32.80	
Infarct size	(n = 107)	(n = 121)	
Median	16.60	12.50	0.067
Interquartile range	6.5–26.1	3.0–24.9	
No detectable defect	9 (8.4%)	22 (18%)	0.032
ST-segment reduction ≥50%	(n = 58)	(n = 95)	
Median	18.25	11.1	0.007
Interquartile range	11.7–24.4	1.6–22.6	
Death at 6 months (cumulative)	16 (8.0%)	9 (4.5%)	0.148
Causes of death			
Free wall rupture	3	3	
Heart failure	10	5	
Reinfarction	1	0	
Arrhythmia	1	1	
Stroke	1	0	
Reinfarction at 6 months (cumulative)	11 (5.5%)	2 (1%)	0.011
Composite of death and reinfarction at 6 months	27 (13.5%)	11 (5.5%)	0.006
Target vessel revascularization at 6 months (cumulative)	34 (17%)	32 (16%)	0.789
Six-month angiography	138 (83%)	157 (86%)	0.338
Stenosis at 6 months			
Median	30.77	23.87	0.065
Interquartile range	15.30–54.22	11.23–42.46	
Stenosis ≥50%	39 (28%)	33 (21%)	0.149

Data are presented as the number (%) of patients, unless otherwise specified.
TIMI = Thrombolysis In Myocardial Infarction.

DISCUSSION

The results of this trial show that abciximab provides a better clinical outcome than stenting alone in patients with ST-segment elevation AMI. The use of abciximab reduced the rate of the one-month composite of death, reinfarction, TVR, and stroke. At six months, the reduction in mortality increased, resulting in a significant reduction in the composite of death and reinfarction. These effects are likely related to the reduction in the subacute stent thrombosis rate and to more effective reperfusion at the tissue level, as shown by the more frequent ST-segment resolution in the abciximab-treated patients and the smaller infarcts at one-month scintigraphy. There were no differences in the corrected TIMI frame count between the groups. This lack of difference may be explained by the fact that assessment of this marker of reperfusion was done immediately after the procedure, when microvascular function might be not completely restored (16). Consistent with the results of previous studies (6,7), there was no evidence of an abciximab effect on six-month angiographic restenosis and TVR rates.

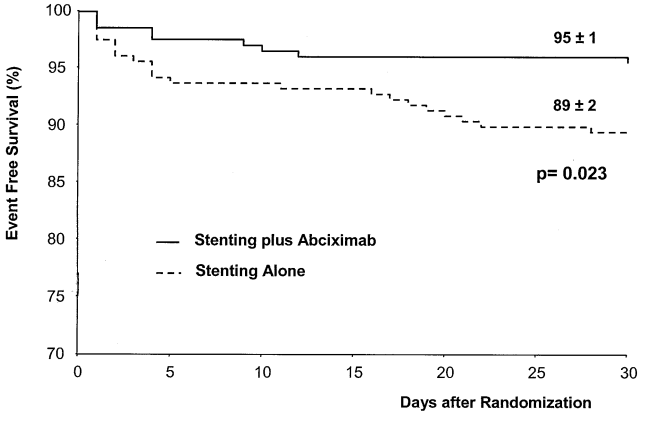

Figure 1. Kaplan-Meier curves for the primary end point in the abciximab group and the stenting only group.

The results of three earlier randomized trials comparing stenting alone and stenting plus abciximab are conflicting.

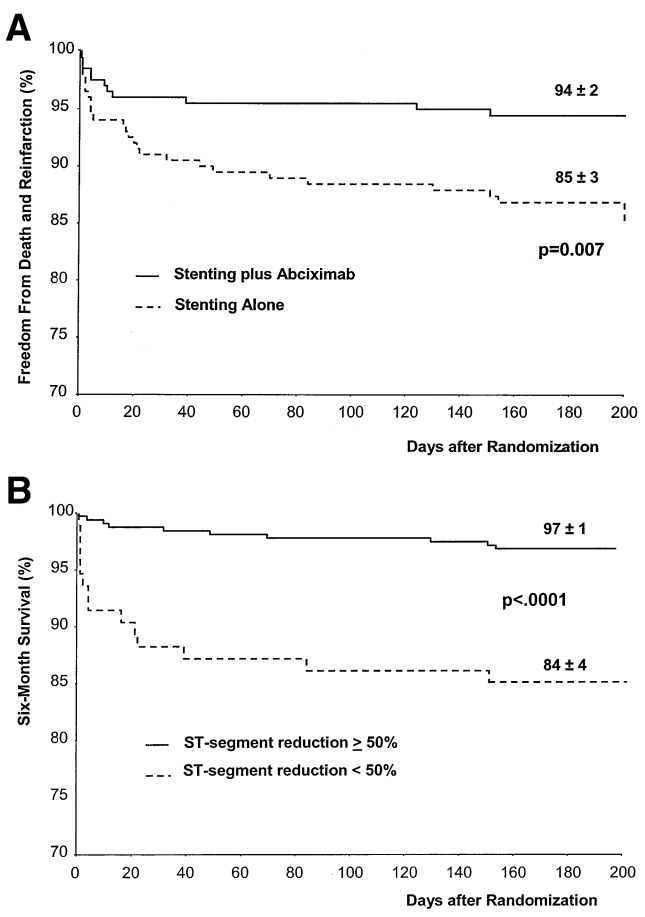

Figure 2. (A) Kaplan-Meier curves for the composite of death and reinfarction at six months in the abciximab group and the stenting only group. **(B)** Kaplan-Meier curves for six-month mortality in patients with and without ST-segment reduction.

The Intracoronary Stenting and Antithrombotic Regimen (ISAR)-2 trial, based on a sample of 401 patients, showed a benefit of abciximab in terms of a reduction in the composite of death, reinfarction, and TVR at one month (5.0% vs. 10.5%, p = 0.038), but this benefit was no longer evident at 12 months (7). The Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up (ADMIRAL) trial, based on a sample of 300 patients, showed a significant reduction in the composite of death, reinfarction, and urgent TVR at one month, and this benefit was maintained at six months (7.4% vs. 15.9%, p = 0.02) (8). Finally, the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial, based on a sample of 2,082 patients, compared angioplasty with stenting, with or without abciximab. The primary end point of the study was the composite of six-month mortality, reinfarction, TVR, and disabling stroke. The study showed a strong benefit of coronary stenting, as compared with coronary angioplasty, with or without abciximab, and no adjunctive benefit of abciximab in the stenting arm (primary end point rate 11.5% in the stenting only group [n = 512] and 10.2% in the stenting plus abciximab group [n = 524]) (6). It might be hypothesized that the lack of effect of abciximab in the stenting arm of the CADILLAC trial was due to the very early administration of ticlopidine or clopidogrel.

Major differences in study designs prevent a direct comparison of the results of our study with those of earlier trials. We did not use stringent quantitative criteria for definition of reinfarction, as in CADILLAC trial (CK >50% higher than the previous values obtained during hospitalization). However, in all cases of reinfarction, the diagnosis was based on recurrence of chest pain, CK re-elevation, and evidence of occlusive thrombosis or dissection of the target vessel. Moreover, several features of our trial should be highlighted to put the results of the study into proper perspective. In our study, more than one-third of patients were over 70 years old; 66% were "not low risk"; the more frequent location of the AMI was anterior; diffuse disease or multiple lesions within the IRA resulted in multiple stent implantation in 25% of patients; and patients with CS on admission were included, as well as patients with coronary anatomy at high risk. The inclusion of high-risk patients who were poorly represented or excluded from previous trials may explain the positive study results, because it may be very difficult or even impossible to show the efficacy of treatment in low-risk patients. Moreover, the overall compliance with the protocol was excellent: coronary stenting was attempted in all patients and, in nearly all cases, was successful when using a last-generation passive coating stent, although the incidence of crossover to bailout abciximab in patients randomized to stenting alone was very low. The study design resulted in the enrollment of a population whose characteristics are consistent with those of large survey studies on AMI (17,18). Thus, the study sample can be considered representative of the entire population of patients with ST-segment elevation AMI. As a consequence, the study results, showing a strong benefit of abciximab as adjunctive treatment to coronary stenting, are applicable to the generality of patients undergoing primary stenting for ST-segment elevation AMI.

Study limitations. This study was not blinded. However, for the component of the primary end point of TVR, the need for reintervention was recurrent ischemia due to stent thrombosis or dissection revealed on the emergency angiogram. Thus, the potential bias in the need for emergency TVR was avoided in all cases.

Another potential limitation of the study is the different duration of postprocedural heparin treatment in the two arms. The rationale for this different duration is based on the fact that platelet inhibition may be considered completed within 12 h with abciximab treatment, whereas it needs at least 48 h with ticlopidine alone.

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APPENDIX

The following investigators and institutions participated in the Abciximab and Carbostent Evaluation (ACE) trial: *Steering Committee:* D. Antoniucci (Chairman), A. Rodriguez, A. Hempel, A. Bartorelli, A. Colombo; *Data Monitoring* (ARCARD Foundation, Careggi Hospital, Florence): E. V. Dovellini (Director), G. Cerisano, P. Buonamici; *Electrocardiographic Core Laboratory* (Division of Cardiology, Careggi Hospital, Florence): A. Migliorini (Director); *Nuclear Medicine Core Laboratory* (Nuclear Medicine Institute, University of Florence): A. Pupi (Director); *Angiographic Core Laboratory* (Milan Cardiovascular Research Foundation): C. Di Mario (Director).