Randomized, Placebo-Controlled Trial of Platelet Glycoprotein IIb/IIIa Blockade With Primary Angioplasty for Acute Myocardial Infarction

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Background—The benefit of catheter-based reperfusion for acute myocardial infarction (MI) is limited by a 5% to 15% incidence of in-hospital major ischemic events, usually caused by infarct artery reocclusion, and a 20% to 40% need for repeat percutaneous or surgical revascularization. Platelets play a key role in the process of early infarct artery reocclusion, but inhibition of aggregation via the glycoprotein IIb/IIIa receptor has not been prospectively evaluated in the setting of acute MI.

Methods and Results—Patients with acute MI of <12 hours' duration were randomized, on a double-blind basis, to placebo or abciximab if they were deemed candidates for primary PTCA. The primary efficacy end point was death, reinfarction, or any (urgent or elective) target vessel revascularization (TVR) at 6 months by intention-to-treat (ITT) analysis. Other key prespecified end points were early (7 and 30 days) death, reinfarction, or urgent TVR. The baseline clinical and angiographic variables of the 483 (242 placebo and 241 abciximab) patients were balanced. There was no difference in the incidence of the primary 6-month end point (ITT analysis) in the 2 groups (28.1% and 28.2%, $P=0.97$, of the placebo and abciximab patients, respectively). However, abciximab significantly reduced the incidence of death, reinfarction, or urgent TVR at all time points assessed (9.9% versus 3.3%, $P=0.003$, at 7 days; 11.2% versus 5.8%, $P=0.03$, at 30 days; and 17.8% versus 11.6%, $P=0.05$, at 6 months). Analysis by actual treatment with PTCA and study drug demonstrated a considerable effect of abciximab with respect to death or reinfarction: 4.7% versus 1.4%, $P=0.047$, at 7 days; 5.8% versus 3.2%, $P=0.20$, at 30 days; and 12.0% versus 6.9%, $P=0.07$, at 6 months. The need for unplanned, "bail-out" stenting was reduced by 42% in the abciximab group (20.4% versus 11.9%, $P=0.008$). Major bleeding occurred significantly more frequently in the abciximab group (16.6% versus 9.5%, $P=0.02$), mostly at the arterial access site. There was no intracranial hemorrhage in either group.

Conclusions—Aggressive platelet inhibition with abciximab during primary PTCA for acute MI yielded a substantial reduction in the acute (30-day) phase for death, reinfarction, and urgent target vessel revascularization. However, the bleeding rates were excessive, and the 6-month primary end point, which included elective revascularization, was not favorably affected. **(*Circulation*. 1998;98:734-741.)**

Key Words: angioplasty ■ myocardial infarction ■ platelet aggregation inhibitors

Platelets play a pivotal role in the initiation of ischemic complications after percutaneous coronary intervention.[1,2] Recently, a new class of platelet antagonists directed against the platelet membrane glycoprotein IIb/IIIa receptor has undergone extensive clinical testing. One of these agents, abciximab (ReoPro, Centocor), a human-murine chimeric monoclonal antibody directed against this receptor, affects the final common pathway of platelet aggregation. In 3 large, randomized, placebo-controlled clinical trials of percutaneous coronary intervention, abciximab reduced the 30-day incidence of death, nonfatal myocardial infarction (MI), or need for urgent revascularization by 40%.[3–5]

Primary balloon angioplasty for acute MI is associated with a 5% to 15% rate of in-hospital major ischemic compli-

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cations[6–11] and subsequent repeat revascularization in 35% of patients.[12,13] Most of the acute events are related to reocclusion of the infarct artery. Marked platelet activation with increased surface expression of the IIb/IIIa receptor, present during the first few days after successful primary PTCA, contributes significantly to this process.[14] In a small subgroup of the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) trial, consisting of 64 patients undergoing catheter-based reperfusion for acute MI, a substantial clinical benefit was conferred by abciximab.[15] We hypothesized that platelet IIb/IIIa receptor blockade with abciximab would reduce both acute ischemic events, manifested by death, reinfarction, or urgent revascularization, and late restenosis, as reflected by elective revascularization. We performed a double-blind, placebo-controlled trial to test this hypothesis.

Methods

Patient Enrollment and Study Protocol

Enrollment took place from November 16, 1995, to February 2, 1997, in 36 centers (see Appendix). Patients within 12 hours of the onset of acute MI, referred for primary angioplasty, were randomly assigned to abciximab, administered as a 0.25-mg/kg bolus followed by a 12-hour infusion of 0.125 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (maximum, 10 μg/min), or to matching placebo, in a double-blind fashion. Study drug administration before diagnostic angiography was permitted.

Acute MI was defined as ischemic chest pain lasting >20 minutes and accompanied by significant ST-segment elevation in 2 contiguous leads or by a new complete left bundle-branch block pattern. Before angioplasty, a 100-U/kg heparin bolus was given, followed by additional weight-adjusted doses to maintain an activated clotting time >300 seconds during the procedure. Only balloon angioplasty and directional atherectomy were permitted as catheter-based strategies. Stent implantation was discouraged but was allowed for large residual dissections with >50% stenosis and for abrupt or threatened vessel closure. Early (<6 hours) sheath removal was strongly encouraged.[4,16] Avoidance of routine venous sheath placement was recommended. Heparin could be continued for a maximum of 48 hours, with an activated partial thromboplastin time of 60 to 85 seconds maintained. All patients received aspirin, and the rest of their medical regimen was left to the investigator's discretion.

Patients were excluded from the study for severe thrombocytopenia, baseline prothrombin time >1.2 times control, ongoing internal bleeding or recent major surgery, previous stroke, severe uncontrolled hypertension, PTCA of the infarct artery within 3 months, cardiogenic shock or prolonged resuscitation, vasculitis, prior administration of abciximab or fibrinolytic therapy, or inability to give written informed consent. The protocol was approved by the Institutional Review Board at each participating site.

Study End Points

The primary efficacy end point was the composite of death from any cause, nonfatal reinfarction, or any (percutaneous or surgical) repeat target vessel revascularization within 6 months. The acute-phase end points were the composite of death, reinfarction, or urgent target vessel revascularization at 7 and 30 days. Safety was assessed by the incidence of major bleeding (intracerebral hemorrhage or a >5 g% adjusted decline in hemoglobin).

All clinical end points were independently adjudicated by a clinical events committee, who reviewed the case report forms, hospital records, and ECG and enzymatic data. All angiograms were reviewed by a central angiographic laboratory. Reinfarction within 24 hours of randomization was defined as a reelevation of CK-MB by at least 33% or 100% from the preceding nadir (which was ≥2 or <2 times normal, respectively) and reached at least a >3 times normal value in association with ischemic symptoms. After 24 hours, reinfarction was defined as new pathological Q waves, or reelevation of CK-MB to >3 times normal (24 hours to discharge) or >2 times normal (after hospital discharge). Urgent target vessel revascularization (TVR) was defined as repeat percutaneous coronary intervention or CABG performed within 24 hours of severe recurrent ischemic symptoms. Repeat angiography and revascularization were performed, in general, in response to clinical signs of recurrent ischemia.

TABLE 1. Baseline Demographic and Hemodynamic Characteristics

Characteristic	Placebo (n=242)	Abciximab (n=241)
Age, y	62 (53,71)	60 (52,70)
Weight, kg	84 (72,94)	80 (70,93)
Male, %	72	73
Diabetes, %	22	23
Hypertension, %	50	46
Current smoker,* %	41	41
Previous MI, %	21	17
Any prior revascularization,† %	14	14
Systolic BP, mm Hg	132 (115,150)	135 (120,150)
Heart rate, bpm	78 (65,91)	78 (67,88)

Values listed are medians with 25% and 75% quartiles unless otherwise indicated.

*Currently smoking or within 1 year of discontinuation.

†CABG or PTCA.

Data Management and Statistical Analysis

Data were collected on case report forms by the site coordinators and forwarded to study monitors for verification. The investigators, central adjudication committees, and sponsors remained blinded to treatment allocation until the database was finalized and the prespecified analyses were performed. The study sample size and power were determined by Bayesian calculations[17] based on 5 distributions of the incidence of the primary end point in the EPIC trial population as a whole,[3] the EPIC MI subgroup,[15] and 3 other uniform priors. In all cases, 450 patients yielded a >80% chance to conclude that there was a 90% probability that abciximab is better than placebo, assuming trial event rates of 20% and 30% in the 2 groups, respectively. The final enrollment goal was extended to 500 patients to yield at least 450 analyzable sets of data, assuming a 10% rate of protocol violations and incomplete follow-up. The primary analysis was performed according to the intention-to-treat (ITT) principle, with Bayesian analysis for the primary 6-month end point. A prespecified secondary analysis was designed to assess the true effect of the strategy, tested by including only patients who received study drug and underwent PTCA. Categorical variables were analyzed by Cochran-Mantel-Haenszel χ^2 test, Pearson χ^2 test, and log-rank test for event-free survival analysis. Continuous variables were described as medians with interquartile range and were compared by ANOVA, with effects for treatment, site, and treatment-by-site interaction.

Results

Patient Population

A total of 483 patients were randomized. As shown in Table 1, there were no significant differences in baseline demographic or clinical characteristics between the groups. For the secondary analysis of actual treatment (AT) with study drug and PTCA, 74 patients (51 in the placebo and 23 in the abciximab groups) were excluded for the following reasons: PTCA not performed in 33 and 21, incorrect or no study drug administration in 16 and 0, and inclusion criteria not met in 2

TABLE 2. Angiographic and Procedural Variables in the 2 Treatment Groups

Variable	Placebo (n=242)	Abciximab (n=241)
Multivessel (>1) disease, %	62	57
Symptom onset to study drug, h	3.7 (2.5,5.5)	3.6 (2.6,4.8)
Infarct artery,* %	n=191	n=218
Left anterior descending	42	33
Left circumflex	17	19
Right coronary	38	45
Bypass graft	3	3
Procedural variables*	n=191	n=218
Symptom onset to PTCA, h	3.9 (2.9,5.7)	3.9 (2.8,5.0)
Duration of PTCA, min	66 (47,92)	60 (44,82)
≥2 sheaths inserted	52	53
>1 segment treated	20	13
Procedural complications,†	31	28
Unplanned stenting,‡	20	12
Final diameter stenosis, %	37 (27,48)	38 (28,46)
Final TIMI 3 flow	85	85

Values listed are medians with 25% and 75% quartiles unless otherwise indicated.

*Pertains to patients who received study drug and underwent PTCA.

†Major or minor dissection, embolization, side-branch closure, transient occlusion, new thrombus, failure to dilate, spasm, or reduction in TIMI flow by ≥1 grade.

‡P=0.008.

and 2, leaving 191 and 218 patients in the 2 groups, respectively. Early drug administration (≥30 minutes before first balloon inflation) occurred in 19% and 21% of the 2 groups, respectively. Follow-up was complete in 99.2% of patients at 30 days and 97.7% at 6 months.

Angiographic and Procedural Data

The anatomic and procedural features are summarized in Table 2. As determined by the central angiographic laboratory, Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow was achieved in 84.8% and 85.3% of the placebo- and abciximab-treated patients with attempted intervention, respectively, P=0.57. The need for bail-out stenting was reduced in the abciximab group by 33% and 42% (ITT and AT analysis, respectively).

Acute-Phase Clinical Events: 7- and 30-Day Outcomes

As shown in Tables 3 (ITT analysis) and 4 (AT analysis), the composite end point of death, repeat MI, or urgent TVR was significantly less common in patients treated with abciximab compared with placebo. The AT analysis revealed further amplification of the benefit observed in the whole cohort. As shown in Figure 1, the event curves for the 30-day composite end point separated as early as day 1. Much of the composite end point benefit afforded by abciximab was related to a 75% decrease in urgent TVR, which inherently substantially affected (29% to 44%) the incidence of total TVR (urgent and elective). Nevertheless, the rate of elective TVR, mostly via coronary bypass surgery, was not significantly different between the 2 groups. The 3% to 5% difference in total TVR favoring the abciximab group and due to less urgent TVR observed at 7 days was maintained at 30 days, without incremental benefit.

Late Clinical Events: 6-Month Outcome

At 6 months, the primary end point occurred in 28.1% of the placebo and 28.2% of the abciximab patients (P=0.97, Table 3, Figure 2) by ITT analysis and in 31.9% and 28.0%, respectively (P=0.36, Table 4) by AT analysis. On the basis of Bayesian analysis, there was an 80% probability that abciximab is superior to placebo and a 38% probability that this advantage exceeded 5% in absolute terms. Early drug administration was not associated with better outcome.

Compared with placebo, the cumulative need for urgent TVR at 6 months was significantly reduced by abciximab, 8.7% versus 3.3%, P=0.02 (ITT analysis) and 10.5% versus 3.7%, P=0.006 (AT analysis). Total TVR (urgent and elective) was not significantly affected by abciximab, showing equivalent rates of repeat procedures in both groups from hospital discharge onward. Approximately one third of the revascularization procedures in each group (6.6% of placebo and 8.3% of abciximab patients) consisted of CABG, reflecting the high incidence of diffuse, multivessel coronary disease in this cohort.

Unplanned Stent Implantation

Treatment allocation did not affect the primary 6-month end point in patients undergoing only PTCA (n=359) or unplanned stenting (n=70). Compared with PTCA, unplanned stent use, independently of treatment allocation, was associated with a lower incidence of death, MI, or TVR (35.7% versus 17.1%; odds ratio, 0.43; CI, 0.21 to 0.87; P=0.01). Most of the advantage was related to a decreased need for TVR (12.9% versus 26.2%). The same proportion of patients in the 2 treatment groups received ticlopidine after hospital discharge (19.8% and 16.2% between days 7 and 30 and 8.7% and 9.1% between day 30 and 6-month visit).

Bleeding Complications

Abciximab resulted in a 27-second prolongation of the median activated clotting time compared with placebo (364 versus 337 seconds, respectively). The sheath dwell time was 17 (8, 25) and 19 (9, 26) hours, respectively, P=0.08. We observed an excess of major bleeding (16.6% versus 9.5%, P=0.02) and blood product transfusion (13.7% versus 7.9%, P=0.04) in the abciximab cohort (Table 5). There were no intracranial hemorrhages. Most of the excess major bleeding was confined to the access site.

Discussion

This is the first dedicated randomized trial of platelet IIb/IIIa blockade for patients with acute MI. Despite a lack of effect on late elective revascularization, abciximab yielded a marked acute-phase benefit with respect to major ischemic events, significantly reducing reinfarction and urgent revascularization by 5 to 6 events for each 100 patients treated. Although it lacked power to detect statistically significant

TABLE 3. Outcome in the Treatment Groups by ITT Analysis

End Point	Placebo, % (n=242)	Abciximab, % (n=241)	OR (95% CI)	Log-Rank *P* Value
7 Days				
Death	1.7	1.2	0.75 (0.17, 3.39)	0.70
Reinfarction	3.3	1.7	0.49 (0.15, 1.66)	0.24
Death/repeat MI	5.0	2.1	0.41 (0.14, 1.17)	0.09
Urgent TVR	5.4	1.2	0.22 (0.06, 0.79)	0.01
Any TVR	9.1	6.2	0.66 (0.34, 1.31)	0.19
Death/MI/urgent TVR	9.9	3.3	0.31 (0.14, 0.71)	0.003
Death/MI/any TVR	12.4	8.3	0.64 (0.35, 1.16)	0.11
30 Days				
Death	2.1	2.5	1.21 (0.36, 4.02)	0.77
Reinfarction	4.1	3.3	0.80 (0.31, 2.05)	0.61
Death/repeat MI	5.8	4.6	0.78 (0.35, 1.75)	0.52
Urgent TVR	6.6	1.7	0.24 (0.08, 0.72)	0.006
Any TVR	12.4	9.1	0.71 (0.40, 1.27)	0.22
Death/MI/urgent TVR	11.2	5.8	0.49 (0.25, 0.96)	0.03
Death/MI/any TVR	16.1	13.3	0.80 (0.48, 1.32)	0.32
6 Months				
Death	4.5	4.1	0.91 (0.38, 2.18)	0.82
Reinfarction	7.4	6.6	0.88 (0.44, 1.78)	0.70
Death/repeat MI	11.2	8.7	0.76 (0.42, 1.39)	0.36
Urgent TVR	8.7	3.3	0.36 (0.16, 0.83)	0.01
Any TVR	21.9	20.7	0.93 (0.60, 1.44)	0.68
Death/MI/urgent TVR	17.8	11.6	0.61 (0.36, 1.02)	0.048
Death/MI/any TVR	28.1	28.2	1.01 (0.68, 1.50)	0.90

differences between the 2 groups regarding the individual components of the composite end points, the trial demonstrated a consistent favorable effect of IIb/IIIa blockade on each of the individual major adverse outcomes. Patients receiving active study drug and PTCA had a more pronounced effect with respect to reinfarction. As in other IIb/IIIa trials,[3–5] the lower rate of reinfarction was tightly coupled with the lesser need for urgent revascularization. This consistent relationship between the 2 outcomes confirms the validity of urgent revascularization as a surrogate for "harder" end points, such as reinfarction, in the setting of acute MI. A marked reduction in the need for urgent revascularization is especially crucial in patients undergoing primary angioplasty, who are at high risk for early ischemic events related to reocclusion. In many patients, the strategy of repeat revascularization was used to prevent an impending reinfarction.

Comparison With Other Trials of Glycoprotein IIb/IIIa Blockade in Interventional Cardiology

Acute-Phase Benefit

Our data confirm the significant (50%) decrease in the 30-day composite end point of death, repeat MI, or need for urgent TVR observed in the other 3 large randomized trials of abciximab given during coronary angioplasty.[3–5] Importantly, this is the first study to document the effectiveness of this strategy in patients with acute MI. The extent and magnitude of the benefit across the trials of abciximab in interventional cardiology is remarkably consistent and has been confirmed, in part, for other IIb/IIIa inhibitors in various clinical settings.[18,19]

Lack of Effect on Elective Revascularization

At the time the ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) was designed, data from EPIC suggested a potential beneficial effect of abciximab on the need for elective revascularization at 6 months. Since the present trial was initiated, 2 other large studies, with less critically ill patients, have not supported this putative benefit. Thus, it was very unlikely that a much smaller trial in a population with a high incidence of restenosis would reach a different conclusion. The consistency of these 3 recent trials with respect to the composite incidence of death, reinfarction, or the need for revascularization at 6 months is remarkable: 26% versus 23% in Evaluation of PTCA to Improve Long-Term Outcome With Abciximab IIb/IIIa Blockade (EPILOG), 31% versus 31% in c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE), and 28% versus 28% in RAPPORT, for placebo and abciximab, respectively. In contrast, in the EPIC trial, patients continued to have a significant reduction in this composite end point at 6 months (from 35% for placebo to 27% for abciximab, $P=0.001$) and at 3 years (from 47.2% to 41.1%, $P=0.009$).

TABLE 4. Outcome in the Treatment Groups by AT Analysis

End Point	Placebo, % (n=191)	Abciximab, % (n=218)	OR (95% CI)	Log-Rank *P* Value
7 Days				
Death	1.0	0.9	0.88 (0.12, 6.27)	0.91
Reinfarction	3.7	0.9	0.24 (0.05, 1.19)	0.06
Death/repeat MI	4.7	1.4	0.28 (0.08, 1.06)	0.047
Urgent TVR	6.3	1.4	0.21 (0.06, 0.75)	0.008
Any TVR	11.0	6.4	0.56 (0.27, 1.13)	0.08
Death/MI/urgent TVR	10.5	2.8	0.24 (0.10, 0.62)	0.001
Death/MI/any TVR	13.6	7.8	0.54 (0.28, 1.02)	0.042
30 Days				
Death	1.6	1.8	1.17 (0.26, 5.30)	0.85
Reinfarction	4.7	2.3	0.47 (0.16, 1.44)	0.17
Death/repeat MI	5.8	3.2	0.54 (0.21, 1.43)	0.20
Urgent TVR	7.9	1.8	0.22 (0.07, 0.67)	0.004
Any TVR	14.7	9.6	0.62 (0.34, 1.13)	0.11
Death/MI/urgent TVR	12.0	4.6	0.35 (0.16, 0.76)	0.005
Death/MI/any TVR	17.8	12.4	0.65 (0.38, 1.13)	0.10
6 Months				
Death	4.7	3.2	0.67 (0.24, 1.84)	0.43
Reinfarction	8.4	5.5	0.64 (0.29, 1.38)	0.23
Death/repeat MI	12.0	6.9	0.54 (0.27, 1.07)	0.07
Urgent TVR	10.5	3.7	0.33 (0.14, 0.76)	0.006
Any TVR	26.2	22.5	0.82 (0.52, 1.29)	0.32
Death/MI/urgent TVR	19.9	10.6	0.45 (0.26, 0.80)	0.004
Death/MI/any TVR	31.9	28.0	0.83 (0.54, 1.27)	0.31

It should be noted, however, that the angioplasty performed in the era of the EPIC trial (1992) was much more conservative and less effective due to unavailability of stents. This is highlighted by the almost identical rate of adverse events in the active-treatment groups (28% and 27%), whereas the placebo group in RAPPORT fared significantly better than its counterpart in EPIC (28% versus 35%). Furthermore, the very positive effect of bolus and infusion of abciximab in acute MI patients in EPIC was based on only 22 patients, an extremely small population, in which the play of chance can substantially distort the true significance of the results.

Bleeding Complications

Reminiscent of the EPIC trial,[20] the incidence of major bleeding associated with the strategy tested in this trial was significantly higher in the abciximab group, reflecting both the intensity of anticoagulation used during and after the procedure and the long interval between angioplasty and sheath removal. The latter was undoubtedly affected by the double-blind design of the study, which made investigators reluctant to stop heparin for early sheath removal. Nevertheless, most excess bleeding was confined to the access site. As in other trials of primary angioplasty,[21] the overall rate of major bleeding was higher than that observed during elective

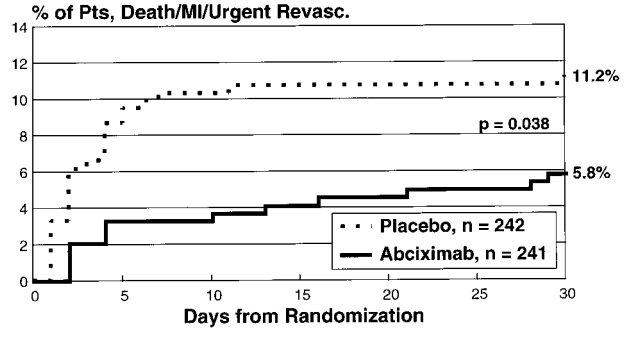

Figure 1. Probability of death, repeat MI, or urgent TVR (Revasc.) within 30 days in abciximab (solid line) and placebo (dashed line) groups by ITT analysis. Kaplan-Meier plot. Pts indicates patients.

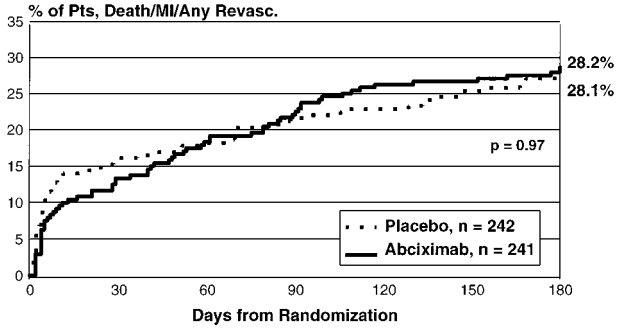

Figure 2. Probability of death, repeat MI, or TVR (Revasc.) within 6 months in abciximab (solid line) and placebo (dashed line) groups by ITT analysis. Kaplan-Meier plot. Pts indicates patients.

TABLE 5. Incidence and Site of Bleeding Complications

Event	Placebo, % (n=242)	Abciximab, % (n=241)	*P*	Placebo, % (n=191)	Abciximab, % (n=218)	*P*
Major bleeding	9.5	16.6	0.02	7.3	13.3	0.07
Intracranial	0	0		0	0	
Access site	3.7	12.0	<0.001	2.6	11.0	0.001
CABG associated	5.4	5.0	0.78	3.7	1.8	0.14
Gastrointestinal	1.2	3.7	0.08	0.5	3.7	0.04
Minor bleeding	22.7	29.9	0.06	20.4	30.7	0.02
Transfusions*	7.9	13.7	0.04	6.3	12.4	0.04

*Includes transfusion during CABG.

angioplasty. The substantially lower incidence of bleeding associated with less intense anticoagulation and early sheath removal[4,16] would indicate that this important drawback of IIb/IIIa blockade can be alleviated without any compromise in efficacy. In fact, there was a doubling of efficacy from the original trial to EPILOG, when the bleeding was markedly reduced.[4]

Role of Platelet IIb/IIIa Receptor Blockade in Primary Angioplasty

Iwabuchi et al[22] recently showed that intravascular ultrasound performed after angiographically successful primary angioplasty can detect predictors of abrupt vessel closure, such as smaller lumen and greater plaque areas, and especially the presence of disrupted plaque and thrombus. Pharmacological and mechanical interventions may be needed to prevent this event. On one hand, because platelets avidly aggregate on the disrupted vessel surface created by the initial plaque rupture[23] and subsequent balloon-induced wall trauma, effective blockade of platelet aggregation at the site of injury may substantially reduce the risk of abrupt closure. On the other hand, coronary stent implantation can restore the vessel integrity and improve flow. Preliminary data from 5 small studies[24–28] comparing balloon angioplasty with stenting for acute MI indicated that stenting reduced the rate of repeat in-hospital revascularization (usually due to infarct artery reocclusion) by 50% to 75%, from between 6% and 11% to between 2% and 4%. Importantly, abciximab in the present trial demonstrated a beneficial effect of a similar magnitude, which translated to an incidence of urgent revascularization of only 1.2% at 7 days and 1.7% at 30 days. Thus, the use of platelet inhibitors may be particularly valuable in patients who are not candidates for stenting.

Besides affecting the patency of the infarct vessel, platelet aggregates can also be embolized distally and impair the microvasculature of the infarcted territory. Neumann et al[29] compared the outcomes of 200 patients undergoing primary or rescue stenting of the infarct artery with or without adjunct abciximab. As in our study, at 30 days, the abciximab-treated patients had less death, reinfarction, and urgent revascularization (2% versus 9%, $P=0.031$) than the usual-care group. In addition, by 14 days, abciximab-treated patients demonstrated higher peak flow velocity in the infarct artery and improved wall motion index score and global ejection fraction independently of the acute angiographic results. These preliminary data suggested that platelet blockade can reduce early recurrent ischemia and lessen the degree of microcirculatory dysfunction, even in patients treated with stents. Two ongoing trials, Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) and Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-term Follow-up (ADMIRAL), are currently evaluating the long-term effect of the combination of abciximab and primary stenting for acute MI.

Limitations of the Study

The low overall mortality and the baseline characteristics of the patients suggest that the more ill patients, for whom the investigators believed that IIb/IIIa blockade was beneficial, may have been excluded from enrollment. Without systematic follow-up of patients who were not enrolled at each institution, we are unable to address this salient issue. The high incidence of major bleeding in the abciximab arm was due in part to the double-blind trial design, which led to the operator's unwillingness to discontinue heparin anticoagulation immediately after the procedure for early sheath removal. Despite these potential limitations, the present trial is still one of the largest trials of primary angioplasty for acute MI with rigorous and blinded adjudication of clinical and angiographic end points.

In summary, compared with placebo, platelet IIb/IIIa receptor blockade with primary angioplasty for acute MI does not affect the incidence of death, reinfarction, or any revascularization of the infarct vessel at 6 months. This is attributable to a lack of effect on subsequent elective revascularization. However, this strategy markedly reduces the incidence of death, reinfarction, and urgent revascularization during the acute phase, and this benefit was sustained throughout the follow-up period. The magnitude and direction of the effect are highly consistent with previous trials of platelet inhibition in interventional cardiology in the elective setting. These findings have important implications for improving outcomes in the large number of patients undergoing catheter-based reperfusion for acute MI.

Appendix

Participating Institutions (Alphabetical Order), Principal Investigators, and Coordinators

Baptist Medical Center, Little Rock, Ark: Randal F. Hundley, MD, Vicki Mabry; Brookwood Medical Center, Montclair Baptist Hospi-

tal, Birmingham, Ala: Eric D. Cohen, MD, Larry Maske; Cardiology Foundation of Lankenau Hospital, Wynnewood, Pa: Timothy Shapiro, MD, Ann Marie Chikowski; Crozer Chester Medical Center, Upland, Pa: Ancil A. Jones, MD, Susan Curry, RN; Geisinger Medical Clinic, Danville, Pa: James Blankenship, MD, Lee Demko; Hackensack Medical Center, Hackensack, NJ: Pranay Vaidya, MD, Sarah Timmapuri, MD; High Point Regional Hospital, High Point, NC: H. Barrett Cheek, MD, Karen Resh; Hospital of the Good Samaritan, Los Angeles, Calif: Thomas L. Shook, MD, Beverly Firth; Huntington Memorial, Pasadena, Calif: Paul Maher, MD, Donna Lynn Ujllge; Lenox Hill Hospital, New York, NY: Jeffrey W. Moses, MD, Nancy Cohn; Long Beach Memorial Hospital, Long Beach, Calif: Rex Winters, MD, Kathy Lee; Medical University of South Carolina, Charleston, SC: Bruce Usher, MD, Michael Miller, MD, Betty Owens; Mercy General and Sutter Memorial Hospitals, Sacramento, Calif: David Roberts, MD, Lucy Lindsey; Mercy Hospital Medical Center Iowa Heart Center, Des Moines, Iowa: Mark Tannenbaum, MD, Dawn Stangl; Heart and Vascular Institute, Ypsilanti, Mich: James Bengston, MD, Mary Adolphson; Midwest Heart Research, Lombard, Ill: Lawrence Barr, MD, Peter M. Kerwin, MD, Elaine Enger, Ann Burns; Milwaukee Cardiovascular Research Foundation, Milwaukee, Wis: Anita Arnold, MD, Tim Sommers; North Shore University Hospital, Manhasset, NY: Stanley Katz, MD, Patrice Hilepo; Washington University Medical Center, St Louis, Mo: John M. LaSala, MD, Kim Myers, Amy Campbell; Presbyterian Health Care Center, Albuquerque, NM: Harvey J. White, MD, Roann Sexon; Providence Medical Center, Seattle, Wash: Fredric M. Tobis, MD, Manau Blennan, RN; Riverside Methodist Hospital, Columbus, Ohio: Barry S. George, MD, Denise Smith, Christine Gilliland; St Joseph's Hospital, Savannah, Ga: Philip C. Gainey, MD, Sandra Arsenault; St Louis University Hospital, St Louis, Mo: Frank V. Aguirre, MD, Carol Meechem; St Patrick Hospital Western Montana Clinic, Missoula, Mont: Mark Sanz, MD, Dale Mayer; Swedish Medical Center, Seattle, Wash: R. Jeffrey Westcott, MD, Verna Harms, RN; The Christ Hospital, Cincinnati, Ohio: Dean Kereiakes, MD, David Lausten; The Cleveland Clinic Foundation, Cleveland, Ohio: Eric Topol, MD, Sorin Brener, MD, Susan Hejl, RN; University of California at Davis Medical Center, Sacramento, Calif: Gary Gershony, MD, Katie Pittenger; Medical Center of Southern Nevada, Las Vegas, Nev: Harry Thomas, Jr, MD, Yvette Seaton, RN; University of California at San Francisco Moffitt Hospital: Christopher Wolfe, MD, Cindi Klinski, RN; University of Massachusetts Medical Center, Worcester, Mass: Bonnie Weiner, MD, Marie Borbone; University of Pittsburgh Medical Center, Presbyterian University Hospital, Pittsburgh, Pa: Jeb Burchenal, MD, Kathy Jacobs, RN; University of Washington Division of Cardiology, Seattle, Wash: Douglas K. Stewart, MD, Renee Devine.

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