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Evidence for Prevention of Death and Myocardial Infarction With Platelet Membrane Glycoprotein IIb/IIIa Receptor Blockade by Abciximab (c7E3 Fab) Among Patients With Unstable Angina Undergoing Percutaneous Coronary Revascularization

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Objectives. **We sought to evaluate whether patients with unstable angina undergoing coronary intervention derive particular clinical benefit from potent platelet inhibition.**

Background. **Plaque rupture and platelet aggregation are pathogenetic processes common to unstable angina and ischemic complications of percutaneous coronary intervention.**

Methods. **Of the 2,099 patients undergoing a coronary intervention in the Evaluation of 7E3 in Preventing Ischemic Complications (EPIC) trial, 489 were enrolled with the diagnosis of unstable angina and randomized to receive placebo, an abciximab (c7E3) bolus immediately before the intervention or an abciximab bolus followed by a 12-h infusion. The primary end point was a composite of death, myocardial infarction (MI) or urgent repeat revascularization within 30 days of randomization. The occurrence of death, MI or any revascularization within 6 months was also assessed.**

Results. **Compared with placebo, the bolus and infusion of abciximab resulted in a 62% reduction in the rate of the primary end point (12.8% vs. 4.8%, p = 0.012) among patients with unstable angina, due primarily to a reduction in the incidences of death (3.2% vs. 1.2%, p = 0.164) and MI (9% vs. 1.8%, p = 0.004). By 6 months, cumulative death and MI were further reduced by abciximab (6.6% vs. 1.8%, p = 0.018 and 11.1% vs. 2.4%, p = 0.002, respectively). The magnitude of the risk reduction with abciximab was greater among the patients with unstable angina than among other patients in the EPIC trial without unstable angina for the end points of death (interaction: p = 0.008 at 30 days, p = 0.002 at 6 months) and MI (interaction: p = 0.004 at 30 days, p = 0.003 at 6 months).**

Conclusions. **The syndrome of unstable angina identifies patients who will experience particularly marked reductions in the risk of death and MI with abciximab during coronary intervention.**

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Plaque fissure or rupture, occurring either spontaneously or as a result of induced arterial trauma, is a key initiating component in the pathogenesis of unstable angina (1,2) and of the ischemic complications of percutaneous coronary revascularization (3,4). Likely as a consequence of the additive thrombogenic stimuli of coronary injury induced by percutaneous revascularization techniques superimposed on the de novo plaque fissure in unstable angina, patients undergoing coronary interventional procedures in the setting of unstable angina are at elevated risk for death, myocardial infarction (MI) or recurrent ischemia compared with those undergoing revascularization for stable angina (5–8).

The central role of platelet activity in the development of ischemic complications in these settings is highlighted by several studies demonstrating unequivocal clinical benefit derived from therapy with aspirin among patients with unstable angina (9–12) and those undergoing percutaneous coronary revascularization (13,14). Yet aspirin is a relatively weak platelet inhibitor; newer strategies for more profound inhibition of platelet activity at the injured coronary plaque focus on the integrin glycoprotein (GP) IIb/IIIa receptor on the platelet surface membrane, which binds circulating fibrinogen or von Willebrand factor and cross links adjacent platelets as the final common pathway to platelet aggregation (15). The monoclonal antibody 7E3 (Centocor) (16), the first agent of the class

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Abbreviations and Acronyms

ACT	=	activated clotting time
c7E3	=	abciximab
EPIC	=	Evaluation of 7E3 in Preventing Ischemic Complications trial
EPILOG	=	Evaluation of PTCA to Improve Long-Term Outcome by c7E3 GPIIb/IIIa Receptor Blockade trial
GP	=	glycoprotein
MI	=	myocardial infarction
PTCA	=	percutaneous transluminal coronary angioplasty
TVR	=	target vessel revascularization

directed against this receptor, markedly inhibits platelet aggregation in a dose-dependent manner (17,18). A large-scale, placebo-controlled, randomized trial (Evaluation of 7E3 in Preventing Ischemic Complications [EPIC]) demonstrated that administration of abciximab (c7E3 Fab, ReoPro), a human-murine chimeric Fab fragment of this antibody, for 12 h during and after "high risk" coronary angioplasty or directional atherectomy, in addition to conventional therapy with heparin and aspirin, reduced the incidence of death, MI or urgent repeat revascularization by 35% compared with conventional therapy over 30 days (19); a 26% reduction in the need for repeat target vessel revascularization (TVR) over the subsequent 6 months was also observed (20).

The current analysis was carried out to evaluate the hypothesis that patients with unstable angina undergoing percutaneous coronary revascularization in the EPIC trial, in whom both spontaneous and induced mechanisms of platelet activation are operative, might achieve particular benefit from platelet GP IIb/IIIa blockade.

Methods

Patient group. As previously reported (19,20), 2,099 patients undergoing high risk coronary balloon angioplasty or directional atherectomy were enrolled at 56 clinical sites throughout the United States into the EPIC trial. Criteria constituting high risk status for entry into the trial included acute or recent MI, unstable angina or complex target lesion angiographic morphology in association with advanced age, female gender or diabetes mellitus. *Unstable angina* was defined by the presence of early (within 7 days) postinfarction angina, at least two episodes of angina occurring at rest or angina occurring despite heparin and nitrate therapy. Transient electrocardiographic ST-T wave changes accompanying these clinical presentations were required to confirm the diagnosis of unstable angina. Patients were excluded if they were over 80 years of age or for known bleeding diatheses, a major operation within 6 weeks or stroke within the previous 2 years. Patients provided written informed consent, and the protocol was approved by the Institutional Review Board at each clinical site.

Study protocol. The study protocol has been previously described (19). Briefly, patients were treated with aspirin and a sufficient bolus of heparin to achieve an activated clotting time (ACT) of 300 to 350 s before and throughout the coronary intervention. Patients were randomized in a double-blind fashion to one of three intravenous treatment regimens: 1) placebo bolus followed by placebo infusion for 12 h; 2) 0.25-mg/kg bolus of abciximab followed by placebo infusion for 12 h; or 3) 0.25-mg/kg bolus of abciximab followed by 10-μg/min infusion of abciximab for 12 h. Coronary angioplasty or directional atherectomy was carried out according to standard techniques. Heparin infusion was continued for the 12-h duration of the study drug, and vascular sheaths remained in place until 6 h after discontinuation of the study drug infusion and 4 h after discontinuation of heparin infusion, whichever occurred later.

Study end points. End point classifications made by a clinical events committee in blinded manner were used for the final analyses. The primary efficacy end point of the trial was a prespecified composite of any of the following events occurring within 30 days of randomization: death from any cause, MI or reinfarction, urgent surgical or repeat percutaneous coronary revascularization for recurrent ischemia, stent implantation to treat threatened or abrupt closure of the target vessel or insertion of an intraaortic balloon pump for recurrent ischemia in patients for whom repeat revascularization was contraindicated. A secondary efficacy end point was the occurrence of death, MI or any surgical or repeat percutaneous revascularization (urgent or elective) by 6 months after randomization. Patient treatment allocations remained double-blinded until completion of 6-month follow-up in all patients. Definitions of MI have been described previously (19). Bleeding events occurring during the hospital period were classified as major, minor or insignificant according to the criteria used in the Thrombolysis in Myocardial Infarction trial (21). To account for the influence of red blood cell transfusions on measured hemoglobin values, estimated decreases in hemoglobin were adjusted according to the technique suggested by Landefeld et al. (22).

Economics substudy. A prospective economics substudy was conducted within the EPIC trial (23). Bills were collected for the baseline hospital period and for subsequent hospital admissions within 6 months of study entry. Medicare cost-to-charge ratios for each study site were used to convert billed charges to hospital costs, and physician fees were estimated using the Physician 1994 Medicare Fee Schedule (Cigna).

Data management and statistical analysis. Data were collected on case report forms by study coordinators at the clinical sites and verified with source medical records by study monitors. Investigators, study coordinators and the trial sponsor (Centocor) remained blinded to treatment allocation until the analysis plan and primary end point data entry were finalized.

Categoric variables are summarized by percentages; continuous variables are summarized by medians and interquartile ranges. Pairwise comparisons of 30-day outcome, 6-month outcome and bleeding events were performed between each of the two abciximab treatment groups and the placebo group according to the intention-to-treat principle (randomized pa-

tients) as well as by analysis of only those patients who actually received the study drug (treated patients). The p values for dose response were computed by coding the placebo group as 0, the abciximab bolus group as 1 and the abciximab bolus and infusion group as 2. A trend test was computed using the generalized log-rank statistic. The p values for pairwise comparisons of placebo to abciximab bolus and infusion were similar to the dose-response p values and are therefore not presented.

Outcome through 6 months was assessed separately for all events from baseline to 6 months or for events occurring after 30 days in patients with an initially successful intervention (defined as achievement of final stenosis <50% without an ischemic complication). Events taking place before the 30-day cutoff in the latter analysis were excluded in order to focus on clinical benefit incremental to that encompassed by the primary 30-day end point analysis.

Proportional hazards (Cox) regression models were fit to test for differences in treatment effects in the unstable angina subgroup compared with the other patient groups. All patients were included in the models testing the interaction between treatment effects and unstable angina. Effects were estimated for treatment (abciximab bolus and infusion vs. placebo) and subgroup (unstable angina vs. no unstable angina). A likelihood ratio test was used to test for the significance of treatment–subgroup interaction for each end point studied (24).

Economic data are presented as average total costs (hospital plus physician) by treatment group, separately for the baseline hospital period and for the combined follow-up hospital periods. Pairwise comparisons were made between the abciximab treatment groups and the placebo group using the Wilcoxon two-sample test among patients treated with the study drug.

Results

Patient group. Of the total 2,099 patients enrolled in the EPIC trial, 489 had a diagnosis of unstable angina on entry and form the basis of this analysis. Study drug was administered to 470 patients; 19 patients did not receive the study agent because of the operator's decision not to perform a coronary intervention (n = 7), the investigator's decision to withhold the study drug (n = 3), an adverse event or bleeding before study drug administration (n = 3), inappropriate randomization (n = 2), thrombocytopenia (n = 2), withdrawal of consent (n = 1) or inability to obtain the study drug from a pharmacy (n = 1).

The selected baseline demographic and procedural characteristics of the 489 randomized patients with unstable angina are summarized in Table 1. There were no important differences among the treatment groups with respect to baseline or procedural variables. Activated clotting times tended to be lower among patients receiving placebo than among those treated with abciximab, reflecting the previously reported modest elevation in ACT induced by this platelet GP IIb/IIIa receptor antagonist (25). Patients with unstable angina more frequently received preprocedural heparin than did those without unstable angina (68% vs. 44%), but there were no other substantial differences between the two groups with regard to baseline characteristics.

Outcome through 30 days. Clinical efficacy end points occurring within 30 days of study entry are summarized in Table 2 for the three treatment groups. Among the 489 patients with unstable angina randomized in the trial, a graded effect on the rate of the primary composite end point was observed, with a 39% reduction among patients randomized to abciximab bolus compared with placebo and a 62% reduction among patients randomized to abciximab bolus and infusion (12.5% vs. 7.8% vs. 4.8%, respectively, p = 0.012 for dose response). The incidence of MI (particularly Q wave MI) was significantly diminished by abciximab bolus and infusion, with a consistent trend toward a reduction in the other components of the composite end point as well.

The magnitude of benefit derived from abciximab among patients with unstable angina was more apparent when only the 470 patients who actually received the study drug were considered (Table 2). The rate of the primary composite efficacy end point was decreased by 71% among patients treated with the abciximab bolus and infusion compared with those receiving placebo. The relative risk reduction of the most serious end points of death and MI was 94% with the abciximab bolus and infusion (11.1% in the placebo group vs. 5.0% in the abciximab bolus group vs. 0.6% in the abciximab bolus and infusion group; p < 0.001).

Figure 1 illustrates the efficacy of therapy with abciximab among patients with unstable angina in relation to the outcome among the other 1,610 patients in the EPIC trial who were enrolled *without* the diagnosis of unstable angina. Placebo group rates of death or MI were higher among the patients with unstable angina, whereas other end point event rates were comparable between the two groups. Treatment with abciximab bolus and infusion was particularly effective compared with placebo in reducing mortality (62% reduction) and MI (80% reduction) among patients with unstable angina. Tests for subgroup interactions suggested that the magnitude of the treatment effect was larger among patients with unstable angina than among other patients (p = 0.150 for mortality, p = 0.035 for MI). The evidence for treatment subgroup interaction was substantially strengthened when only patients treated with the study agent were considered (p = 0.008 for mortality, p = 0.004 for MI). There were trends toward less reduction in urgent intervention with abciximab bolus and infusion in patients with unstable angina than in other patients. Although there was a 62% proportionate reduction in the 30-day primary composite end point in the unstable angina group compared with a 27% reduction in the other patient groups, the difference in the magnitude of the treatment effect for this end point did not reach statistical significance (p = 0.127).

The rates of bleeding complications during the initial hospital period are contrasted for patients with and without unstable angina in Table 3. There was a dose-related increase

Table 1. Baseline and Procedural Characteristics of Patients With Unstable Angina in the EPIC Trial

Variable	Placebo (n = 156)	Abciximab Bolus (n = 168)	Abciximab Bolus and Infusion (n = 165)	Total (n = 489)
Age (yr)	63 (54–69)	61 (53–69)	60 (50–67)	61 (52–68)
Weight (kg)	84 (73–92)	83 (71–93)	80 (71–91)	82 (71–92)
Male gender	65	65	68	66
Diabetes mellitus	21	24	24	23
Hypertension	54	59	54	55
Elevated cholesterol	53	61	48	54
History of smoking	71	71	74	72
Peripheral vascular disease	9	9	12	10
Previous myocardial infarction	54	59	63	59
Previous coronary angioplasty	22	22	17	20
Previous bypass surgery	13	14	10	12
Single-vessel coronary artery disease	55	52	61	56
Interventional procedure				
Balloon angioplasty	93	89	86	89
Atherectomy	5	5	7	6
Both	2	5	7	5
Target artery				
LAD	42	38	43	41
LCx	22	28	27	26
RCA	35	40	30	35
Bypass graft	4	4	5	4
Preprocedural heparin therapy	69	64	71	68
Thrombolytic agent used	4	5	1	3
Duration of procedure (min)	54 (33–82)	58 (41–87)	53 (32–78)	55 (35–83)
Contrast agent used (ml)	200 (140–270)	200 (150–275)	200 (150–275)	200 (150–275)
Preintervention ACT (s)	348 (299–405)	380 (336–435)	403 (339–454)	377 (326–440)

Dichotomous variables are expressed as percent of total and continuous variables as median (interquartile range). ACT = activated clotting time; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

in the incidence of major bleeding and the need for blood transfusions associated with abciximab therapy in the EPIC trial (19,26), but rates of bleeding complications were not different among patients with or without unstable angina.

Outcome through 6 months. Clinical follow-up was 98% complete in the group of patients with unstable angina. Clinical events occurring between study entry and 6 months among randomized or treated patients with unstable angina are summarized in Table 4. Administration of abciximab bolus and infusion was associated with a substantially lower rate of death or MI in this patient group over the 6 months after the coronary intervention; among those actually receiving the study drug, the relative risk reduction for death or MI by 6 months was 88% (16.6% in the placebo group vs. 8.1% in the abciximab bolus group vs. 2.0% in the abciximab bolus and infusion group; $p < 0.001$). By considering only those ischemic events occurring beyond the 30-day period of the primary outcome analysis (Table 5), it is suggested that administration of abciximab resulted in an *amplification* over 6 months of the reduction in death and MI, not merely a maintenance of early (30-day) benefit. In contrast, there was less long-term effect of abciximab therapy on the rates of repeat surgical or percutaneous coronary revascularization in patients with unstable angina (Tables 4 and 5). The incidence of "clinical restenosis," as determined by the need for TVR, was not significantly reduced by abciximab among patients with unstable angina in this trial.

Figure 2 compares the patients with unstable angina with those without unstable angina in the EPIC trial with regard to the 6-month efficacy of abciximab bolus and infusion. As with the 30-day end point (Fig. 1), placebo group event rates occurred with roughly equal frequency in the two patient groups, except for a substantially higher incidence of death in patients with unstable angina. Death and MI events over 6 months were reduced chiefly among the patients with unstable angina: the clinical benefit imparted by abciximab bolus and infusion was greater among patients with unstable angina than among those without unstable angina for the end points of death (interaction between unstable angina and treatment effect: $p = 0.002$ for treated patient analysis), MI ($p = 0.003$) and death or MI ($p < 0.001$). In contrast, long-term benefit in terms of a diminished necessity for repeat coronary revascularization and a reduction in clinical restenosis appeared largely confined to those patients without unstable angina.

Economic analysis. Hospital cost data were obtained in 96% of patients with unstable angina in the trial. Average costs for the baseline hospital period among the 470 patients with unstable angina actually receiving the study drug were

Table 2. Thirty-Day Outcome Among Patients With Unstable Angina in the EPIC Trial

	Placebo	Abciximab Bolus	Abciximab Bolus and Infusion	p Value for Dose Response
Randomized patients (n = 489)	156	168	165	
Primary end point (%)	12.8	7.8	4.8	0.012
Death	3.2	0.6	1.2	0.164
MI	9.0	4.2	1.8	0.004
Q wave MI	4.5	0.6	0	0.002
Non–Q wave MI	4.5	4.2	1.8	0.197
Urgent PTCA	3.9	1.8	1.8	0.238
Urgent CABG	3.8	2.4	1.2	0.129
Urgent PTCA or CABG	5.8	4.2	3.0	0.223
Treated patients (n = 470)	153	161	156	
Primary end point (%)	13.1	8.1	3.8	0.004
Death	3.3	0.6	0	0.011
MI	9.2	4.3	0.6	0.001
Q wave MI	4.6	0.6	0	0.002
Non–Q wave MI	4.6	4.3	0.6	0.052
Urgent PTCA	4.0	1.9	1.9	0.259
Urgent CABG	3.9	2.5	0.6	0.057
Urgent PTCA or CABG	5.9	4.4	2.6	0.145

CABG = coronary artery bypass graft surgery; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty or atherectomy.

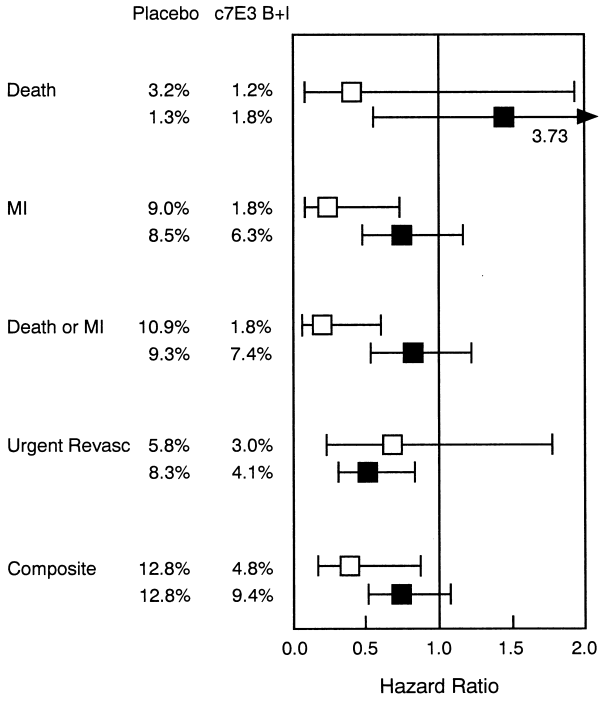

Figure 1. Comparison of relative reductions in 30-day end point events by abciximab bolus and infusion (c7E3 B+I) among randomized patients with (n = 489, **open squares**) and without (n = 1,601, **solid squares**) unstable angina. A hazard ratio of 1 denotes no clinical benefit of abciximab bolus and infusion for a particular end point; a hazard ratio <1 denotes a reduction of risk with abciximab therapy; and a hazard ratio >1 denotes higher risk with abciximab. Confidence intervals (95%) intersecting a hazard ratio of 1 represent a nonsignificant influence of abciximab on outcome. Of note is that three deaths in the abciximab bolus and infusion group (two patients with unstable angina and one patient without unstable angina) were among patients who were randomized but did not receive the study drug. Composite = death, MI, urgent repeat revascularization (Revasc) for ischemia or stent or intraaortic balloon pump placement.

$13,929 ± 6,474 vs. $15,072 ± 18,374 for the abciximab bolus and infusion group compared with the placebo group, respectively (p = 0.130). The cost of abciximab is not included in this estimate, as the study drug was provided free of charge during the trial. Average hospital costs over the subsequent 6-month follow-up period were $3,508 ± 8,889 versus $4,625 ± 9,893 in the abciximab bolus and infusion group and placebo group, respectively (p = 0.430). Total hospital costs for the patients with unstable angina in the EPIC trial therefore tended to be reduced by an average of $2,170 (p = 0.355) by therapy with abciximab.

Discussion

Despite considerable research into pharmacologic and revascularization treatments for the acute coronary ischemic syndromes, outcome among patients hospitalized with unstable angina remains unsatisfactory. Recently reported large-scale randomized trials, for example, have demonstrated that the risk of death or MI within the first 4 to 6 weeks after development of unstable angina is as high as 9% to 11% (27,28). Although percutaneous myocardial revascularization has been advocated as a means of reducing morbidity in this group of patients, particularly those with symptoms refractory to medical therapy (29), several studies have suggested that patients undergoing a coronary intervention in the setting of unstable angina are at elevated risk for ischemic complications compared with patients treated by revascularization for more stable indications (5–8).

The current study evaluated clinical outcome in the subgroup of 489 patients who met rigorous criteria for unstable angina in the randomized, placebo-controlled EPIC trial assessing the efficacy of a new potent antiplatelet agent, the GP IIb/IIIa receptor antagonist abciximab, in preventing ischemic complications associated with percutaneous coronary intervention. Nearly 11% of the patients with unstable angina who received placebo in the trial died or had an MI within 30 days of study enrollment, confirming the high risk profile of this patient group. Treatment of these patients with abciximab during and for 12 h after coronary revascularization, however, resulted in an extraordinary and durable improvement in the prognosis for this disease process, with a relative reduction in the incidence of death or MI by 94% over the first 30 days and by 88% over 6 months. The magnitude of benefit with regard to these two most serious clinical end points was substantially greater among patients with unstable angina than among those undergoing coronary revascularization for stable ischemic symptoms. These findings support the concept that potent platelet inhibition by GP IIb/IIIa receptor blockade more completely attenuates ischemic risk among patients undergo-

Table 3. Bleeding Complications and Hematologic Values for Patients With and Without Unstable Angina in the EPIC Trial

	Placebo	Abciximab Bolus	Abciximab Bolus and Infusion	p Value for Dose Response
Patients with unstable angina (n = 489)	156	168	165	
Major bleeding (%)*	4.5	7.7	9.7	0.075
Blood transfusions (%)*	9.6	10.1	15.8	0.087
Nadir hemoglobin (mg/dl)†	12.0 (10.4, 12.9)	11.4 (9.9, 12.5)	11.0 (9.6, 12.4)	0.021
Patients without unstable angina (n = 1,610)	540	527	543	
Major bleeding (%)*	3.0	8.9	10.9	<0.001
Blood transfusions (%)*	3.5	12.0	13.1	<0.001
Nadir hemoglobin (mg/dl)†	12.0 (10.7, 13.1)	11.7 (10.0, 12.8)	11.4 (9.8, 12.8)	<0.001

*Major bleeding and blood transfusions unrelated to coronary artery bypass graft surgery. †Adjusted for transfusions by the Landefeld index (22). Nadir hemoglobin values are medians (25th and 75th percentiles).

ing a coronary intervention for unstable angina, in whom periprocedural complications are most likely to be related to the thrombotic milieu present before the intervention at the complex arterial plaque, than among patients with stable ischemic syndromes, in whom adverse sequelae of percutaneous revascularization may be more frequently associated with mechanical arterial disruption. Enhanced clinical benefit observed in patients with unstable angina was not associated with a heightened gradient of risk; hemorrhagic complications were more frequent as a result of abciximab administration (19,26)

Table 4. Outcome Among Patients With Unstable Angina From Study Entry Through 6 Months

	Placebo	Abciximab Bolus	Abciximab Bolus and Infusion	p Value for Dose Response
Randomized Patients (n = 489)	156	168	165	
Composite end point (%)	35.0	26.9	25.4	0.045
Death	6.6	1.2	1.8	0.018
MI	11.1	6.6	2.4	0.002
PTCA	19.5	16.2	15.6	0.361
CABG	11.4	10.3	8.7	0.404
PTCA or CABG	26.1	23.4	23.6	0.556
Target vessel repeat revascularization (%)	22.0	19.9	18.7	0.480
Treated patients (n = 470)	153	161	156	
Composite end point (%)	35.0	26.8	24.3	0.024
Death	6.7	1.2	0.7	0.002
MI	11.3	6.9	1.3	<0.001
PTCA	19.9	16.3	15.1	0.254
CABG	10.9	9.5	7.8	0.340
PTCA or CABG	26.0	23.2	23.0	0.466
Target vessel repeat revascularization (%)	22.2	19.8	18.3	0.410

Abbreviations as in Table 2.

Table 5. Outcome Among Patients With Unstable Angina From 30 Days Through 6 Months

	Placebo	Abciximab Bolus	Abciximab Bolus and Infusion	p Value for Dose Response
Randomized patients (n = 418)	125	149	144	
Composite end point (%)	20.2	18.1	16.8	0.463
Death	3.5	0.6	0.6	0.049
MI	2.3	2.6	0.6	0.283
PTCA	12.1	13.7	10.2	0.614
CABG	6.5	6.4	6.4	0.969
PTCA or CABG	16.4	17.5	16.6	1.000
Target vessel repeat revascularization (%)	17.5	17.1	15.9	0.762
Treated patients (n = 405)	123	143	139	
Composite end point (%)	20.5	18.2	17.4	0.508
Death (%)	3.5	0.6	0.7	0.053
MI (%)	2.3	2.7	0.7	0.295
PTCA (%)	12.3	13.6	10.5	0.637
CABG (%)	6.6	6.0	6.0	0.842
PTCA or CABG (%)	16.6	17.6	17.1	0.941
Target vessel repeat revascularization (%)	17.7	17.0	15.5	0.661

Abbreviations as in Table 2.

but occurred with roughly equal frequency among patients with and without unstable angina.

Antithrombotic approaches to unstable angina. Amplification of the clinical benefit derived from platelet GP IIb/IIIa receptor blockade among patients with unstable angina in the EPIC trial is concordant with data from earlier studies emphasizing the key role of platelet activity in the pathogenesis of unstable angina and its ischemic complications. Of the various pharmacologic strategies that have been tested for efficacy in the management of unstable angina, those directed at inhibition of platelet aggregation have been most consistently associated with an unequivocal therapeutic benefit, with a relative reduction in the risk of progression to death or MI of 30% to 50% by aspirin in placebo-controlled trials (9–12). Data supporting such a role for other antithrombotic approaches have thus far been less reproducible. Randomized studies did not demonstrate a durable reduction in death or MI among patients treated with heparin (12,30), low molecular weight heparin (28), the direct thrombin inhibitors hirudin (31) and hirulog (32) or thrombolytic agents (27,33) in the setting of unstable angina.

Repeat revascularization. Notably, the enhancement of clinical benefit observed among patients with unstable angina treated with abciximab in the EPIC trial was largely confined to a reduction of death and MI. Repeat revascularization events, particularly those occurring over the 6-month period after the baseline hospital period, were less effectively suppressed by abciximab in patients with unstable angina than in those without unstable angina. A possible explanation for this observation is that the 18- to 24-h period of intense platelet inhibition produced by the 12-h abciximab infusion (18) may have been too short to completely attenuate the exaggerated

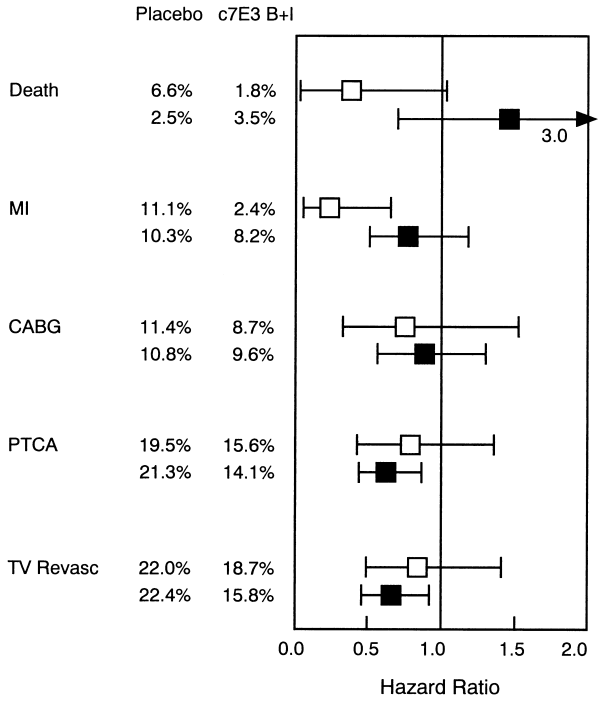

Figure 2. Comparison of relative reductions in 6-month end point events by abciximab bolus and infusion (c7E3 B+I) among randomized patients with (n = 489, **open squares**) and without (n = 1,610, **solid squares**) unstable angina. See Figure 1 for explanation of hazard ratios. TV Revasc = target vessel revascularization by coronary artery bypass graft surgery (CABG) or percutaneous transluminal coronary angioplasty.

local platelet activity and arterial thrombus formation in these patients with unstable angina. Large-scale clinical trials are currently under way to test the potential for prolonged therapy (1 to 3 days) with GP IIb/IIIa receptor antagonists to achieve greater clinical benefit in patients with unstable angina. Alternatively, repeat revascularization events in the setting of unstable angina may represent a shift toward less severe and more stable manifestations of coronary artery disease produced by therapy with abciximab in patients who otherwise would have died or had an MI. Finally, it is conceivable that *mechanical* factors at the lesion site, such as greater plaque instability or a heightened propensity for arterial spasm and recoil, rather than mechanisms mediated by the platelet–thrombus, may play a dominant role in the process of arterial renarrowing in patients with unstable angina. In this regard, stent implantation with concomitant abciximab therapy among patients with unstable angina may be a most effective means of limiting both the ischemic and repeat revascularization events among patients with unstable angina. The potential complementarity of glycoprotein IIb/IIIa inhibition in the setting of elective stent implantation was not addressed in the EPIC study, in which planned stenting was an exclusion criterion, but is the subject of the ongoing Evaluation of PTCA to Improve Long-Term Outcome by c7E3 GP IIb/IIIa Receptor Blockade (EPILOG) stent trial.

Economic impact. Because of the suppression of clinical ischemic events, treatment with abciximab in patients with unstable angina in the EPIC trial was associated with an apparent reduction in economic hospital costs by $2,170 over the 6-month period after trial entry. This difference in costs between treatment groups did not reach statistical significance ($p = 0.355$), reflecting the wide variability among patients and the relatively small size of the unstable angina cohort within the trial, but nevertheless compares favorably with the $1,231 cost reduction estimated for the overall trial group (23). With the mean wholesale pharmacy cost per dose of commercially available abciximab (ReoPro) of $1,407 (23), potential net cost savings would be approximately $763; use of abciximab in patients with unstable angina undergoing a coronary intervention may thus be a "dominant strategy" from the economic standpoint ("dominant strategy" defined as one that reduces both clinical events and cost). Moreover, with bleeding rates associated with abciximab reduced below levels observed in the EPIC trial by modification of heparin dosing and other measures, as observed in the recent EPILOG trial (34), the economic profile of this therapy in patients with unstable angina may be even more favorable.

Study limitations. Although the entry criteria for unstable angina in the EPIC trial were precisely defined and the patients with unstable ischemic syndromes constituted one of the few subgroups prospectively identified for evaluation, any such subgroup analysis within a randomized trial is subject to the limitation that apparent differences in treatment effect in one subset of patients versus another may merely be a spurious finding due to chance. In fact, differences in treatment benefit cannot be assessed by simply determining whether p values for treatment effect are "more significant" in one patient subset than another; these p values are influenced not only by the magnitude of the treatment effect, but also by the sample size of the patient group under evaluation, and thus provide a very limited perspective on the differences in treatment effect between subsets of a study group. In the current study, however, the *interaction* between treatment effect and unstable angina was formally tested by Cox proportional hazards regression modeling, demonstrating that the magnitude of clinical benefit with abciximab in reducing death or MI by 30 days and 6 months was strongly associated with the presence of unstable angina.

Conclusions. The adoption of new medical therapeutics that may be associated with safety risk and economic cost will optimally be focused on those patients who are likely to experience the greatest clinical benefit. Although the EPIC trial established efficacy of therapy with abciximab among patients considered to be at "high risk" for coronary intervention according to a number of different criteria, it is the clinical syndrome of unequivocal unstable angina that appears to identify a group of patients who are at high risk for death or MI and who will experience a particularly marked improvement in outcome with adjunctive platelet inhibition by abciximab. Administration of abciximab holds promise as an effective means of allowing coronary revascularization to be carried out

in a safe, expeditious and cost-effective manner in patients with unstable ischemic syndromes.

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