Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 37, No. 8, 2001
ISSN 0735-1097/01/$20.00
PII S0735-1097(01)01290-6

Long-Term Mortality Benefit With Abciximab in Patients Undergoing Percutaneous Coronary Intervention

Keaven M. Anderson, PHD,* Robert M. Califf, MD, FACC,† Gregg W. Stone, MD, FACC,** Franz-Josef Neumann, MD, FACC,‖ Gilles Montalescot, MD,¶ Dave P. Miller, MS,§ James J. Ferguson, III, MD, FACC,‡ James T. Willerson, MD, FACC,‡ Harlan F. Weisman, MD, FACC,* Eric J. Topol, MD, FACC††

Malvern, Pennsylvania; Durham, North Carolina; Houston, Texas; San Francisco, California; Munich, Germany; Paris, France; New York, New York; and Cleveland, Ohio

OBJECTIVES The goal of this study was to test: 1) if platelet glycoprotein IIb/IIIa (GP IIb/IIIa) blockade with abciximab bolus plus 12-h infusion reduces mortality after percutaneous coronary intervention (PCI); 2) if prevention of early myocardial infarction (MI) after PCI is a mechanism for reducing mortality; and 3) for risk factors for mortality after PCI.

BACKGROUND Studies of PCI suggest that MI after intervention is predictive of mortality. Abciximab, a platelet GP IIb/IIIa receptor inhibitor, has consistently reduced the incidence of MI among PCI patients in several trials. The presumed mechanism is prevention of platelet thrombus associated with vessel wall injury and downstream embolization into the microcirculation.

METHODS In eight trials, 5,154 patients were randomized to a regimen comprising conventional therapy plus a bolus of abciximab within 1 h before PCI followed by a 12-h infusion; 4,136 controls were randomized to conventional therapy alone. Patient follow-up from six months to three years was available. Survival differences are examined using proportional hazards regression and survival curves.

RESULTS A hazard ratio of 0.71 (95% confidence interval 0.57 to 0.89; $p = 0.003$) suggests a mortality benefit with abciximab. The absolute reduction in mortality was estimated to be 0.5% through 30 days, 0.7% through six months, 0.9% through one year and 1.8% through three years. Early MI explained 18% of the observed mortality benefit at one year. Multivariate regression suggests that patients with advanced cardiovascular disease may derive the greatest mortality benefit from abciximab.

CONCLUSIONS The evidence from 9,290 randomized PCI patients shows a mortality benefit provided by abciximab bolus plus 12-h infusion. (J Am Coll Cardiol 2001;37:2059–65) © 2001 by the American College of Cardiology

Percutaneous coronary interventions (PCI) using balloon angioplasty, atherectomy or intracoronary stenting was performed to improve coronary blood flow and relieve myocardial ischemia in over one million patients worldwide in the year 2000. Complications of this procedure include death, myocardial infarction (MI) and the need for repeat revascularization (either percutaneous or surgical). The acute phase complications are a consequence of vessel wall disruption leading to arterial dissection, thrombosis with embolization to the microcirculation or a combination of these factors. Several observational studies and trials of PCI demonstrated an association between periprocedural infarction and mortality over the course of five years (1). This suggests that preventing periprocedural MI should reduce long-term mortality.

Abciximab prevented acute coronary complications of PCI in randomized trials enrolling over 12,000 patients (2–11). In the Evaluation of 7E3 in Preventing Ischemic Complications (EPIC) trial (2), a bolus of abciximab within 1 h before PCI plus a 12-h abciximab infusion prevented thrombotic events in patients at high risk for ischemic complications. Subsequently, this regimen was studied in several thousand low- and high-risk patients in seven additional randomized trials (3–9). More than a million patients have been treated with this regimen worldwide since its approval in 1994. While MI and the need for urgent repeat revascularization were reduced in individual studies, early mortality rates were low, and differences were not statistically significant.

The objective of this study was to analyze mortality differences after PCI in the eight randomized trials including standard therapy with heparin and aspirin (placebo) and standard therapy plus an abciximab bolus within 60 min before PCI followed by a 12-h abciximab

From *Centocor, Malvern, Pennsylvania; †Duke University, Durham, North Carolina; ‡Texas Heart Institute, Houston, Texas; §Lewin-TAG, Inc., San Francisco, California; ‖Deutsches Herzzentrum, Munich, Germany; ¶Centre Hospitalier Universitaire Pitié-Salpêtrière, Paris, France; **Lenox Hill Hospital, New York, New York; and the ††Cleveland Clinic Foundation, Cleveland, Ohio. Supported by Centocor, Malvern, Pennsylvania.

Manuscript received February 22, 2000; revised manuscript received February 13, 2001, accepted March 1, 2001.

Abbreviations and Acronyms

ADMIRAL	=	Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up
CABG	=	coronary artery bypass grafting
CADILLAC	=	Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications
CAPTURE	=	C7E3 AntiPlatelet Therapy in Unstable REfractory angina trial
CHF	=	congestive heart failure
CI	=	confidence interval
EPIC	=	Evaluation of 7E3 in Preventing Ischemic Complications trial
EPILOG	=	Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIa/IIIb blockade trial
EPISTENT	=	Evaluation of Platelet Inhibition in STENTing trial
ERASER	=	Evaluation of ReoPro And Stenting to Eliminate Restenosis
GP IIb/IIIa	=	glycoprotein IIb/IIIa
HR	=	hazard ratio
ISAR-2	=	Intracoronary Stenting and Antithrombotic Regimen-2 trial
MI	=	myocardial infarction
PCI	=	percutaneous coronary intervention
PTCA	=	percutaneous transluminal coronary angioplasty
PVD	=	peripheral vascular disease
RAPPORT	=	ReoPro and Primary PTCA Organization and Randomized Trial

infusion. Follow-up of six months to three years from these trials is available. This analysis includes all follow-up from all trials.

METHODS

Population and follow-up. All follow-up data are included from all randomized, controlled studies of patients undergoing PCI where a 0.25 mg/kg bolus of abciximab within 60 min before PCI followed by a 12-h infusion of abciximab was studied. These data include the three-year follow-up from the EPIC trial (12), one-year follow-up from the Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIa/IIIb blockade (EPILOG) (13) Evaluation of Platelet Inhibition in STENTing (EPISTENT) (14) and Intracoronary Stenting and Antithrombotic Regimen-2 (ISAR-2) (7) trials and six month follow-up from the ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) (5), Evaluation of ReoPro And Stenting to Eliminate Restenosis (ERASER) (6), Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up (ADMIRAL) (8) and Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) (9) trials. All trials were randomized and controlled. All were double-blind with a placebo except the ISAR-2 and CADILLAC trials, which were open-label after randomization. In the ERASER trial, one of three arms included an infusion of abciximab that continued for 24 h after PCI. In all other active arms considered above, the abciximab infusion was 12 h. In each case, patients randomized to a common intervention were compared. Regimens with abciximab given only as a bolus or discontinued early after percutaneous transluminal coronary angioplasty (PTCA) were excluded from the emphasized analyses because of the early partial return of platelet function (15) when acute ischemic event rates are still relatively high. No incremental benefit in the rate of death, MI or urgent intervention was observed more than six h after treatment discontinuation when treatment was given as a bolus or discontinued within one h after PCI, while incremental benefit was observed after treatment when the infusion was continued (2,3,11,14). However, a complementary analysis included patients with abciximab regimens not continuing for 12 h after PCI (EPIC bolus group, C7E3 AntiPlatelet Therapy in Unstable Refractory angina [CAPTURE] pilot trial [10], CAPTURE trial [11]). Patients in the EPISTENT trial in the balloon plus abciximab treatment group were also included in this analysis even though a balloon arm without abciximab was not studied. Trials testing other compounds that block the glycoprotein IIb/IIIa (GP IIb/IIIa) receptor in the setting of PCI (16–18) were not included. The first two of these PCI studies of small molecule GP IIb/IIIa inhibitors failed to show a significant reduction of the primary end point at 30 days, suggesting differences between molecules or their dosing. The head-to-head comparison of abciximab with tirofiban found abciximab to produce superior results for the composite end point of death, MI and urgent repeat revascularization (19). In addition, the pharmacology of abciximab is distinct: platelet function recovers only gradually with abciximab, and abciximab has a dual specificity for the $\alpha_V\beta_3$ receptor on platelets, vascular smooth muscle cells and endothelial cells (20). Finally, an analysis combining all trials of GP IIb/IIIa inhibition showed no late mortality benefit with other GP IIb/IIIa inhibitors (21).

The types of patients studied were high-risk in the EPIC trial (acute MI, unstable angina, high-risk lesion characteristics), a broad population in the EPILOG trial (excluded only unstable angina meeting EPIC criteria and acute MI), acute MI in the RAPPORT, ISAR-2 and ADMIRAL trials, patients amenable to intracoronary stent placement in the ERASER trial, patients amenable to stent placement or angioplasty in the EPISTENT trial, acute MI patients amenable to stent in the CADILLAC study and unstable angina patients in the CAPTURE trial and its pilot.

Final follow-up was performed at a fixed, prespecified interval after randomization for all patients in each study with the exception of the EPIC trial. The EPIC follow-up was conducted primarily in 1995, while randomization was done primarily in 1992. Mortality follow-up in EPIC was complete through 2.5 to 3.5 years for 97% of patients.

Three-years of follow-up is presented here to be consistent with previous presentation (12).

At least one year of follow-up and other patient data were available from the EPIC, EPILOG and EPISTENT trials. Multivariate proportional hazards regression modeling was performed for these studies. The association of early events (MI, urgent PCI, urgent coronary artery bypass graft surgery [CABG]) within 48 h of randomization with one-year mortality was also examined in these trials.

Statistical methods. Analyses of all randomized patients (intention-to-treat) are presented. Patient survival and duration of follow-up were available on an individual patient basis. Survival of abciximab and control patients was compared using a proportional hazards regression model as implemented in the PHREG procedure (SAS Institute, Inc., Cary, North Carolina). Analyses were stratified by study and type of device (stent or balloon) to which a patient was assigned with a common hazard ratio (HR) assumed across strata. A 95% confidence interval (CI) for the HR for mortality for abciximab compared with control was computed by exponentiating the ends of the 95% CI for the regression coefficient. Corresponding p values using the Wald method are presented. For cases where no deaths occurred in the abciximab group, the partial likelihood was used to compute an exact upper 95% confidence bound for the HR. A likelihood ratio was used to test for an interaction of the treatment effect with device strategy planned at the time of randomization (stent or not); patients were stratified by device strategy in this model. A likelihood ratio test was also used to test for study-treatment interaction and to test for differential treatment effect in acute MI and other patients.

The Kaplan-Meier method was used for estimation of the probability of death in each treatment group of each study through the entire duration of follow-up. In addition, combined estimates of mortality with and without abciximab at 48 h, 7 days, 14 days, 30 days, 6 months and 1 year are presented by combining the individual Kaplan-Meier survival probability estimates. Each study was weighted by the total number of patients included (abciximab and control) in the analysis. This is analogous to the "age-adjustment" method (22) and corrects for imbalances in the proportion of patients randomized to placebo and abciximab in different studies; such imbalances could lead to a bias in estimates of treatment group differences.

Multivariate regression modeling with data from the EPIC, EPILOG and EPISTENT trials included baseline characteristics (age, gender, weight, cigarette smoking), intervention characteristics (intervention attempted, multiple segments attempted, multiple vessels attempted), history (unstable angina within 48 h, MI within seven days, PCI, CABG, peripheral vascular disease [PVD], stroke, hypertension, diabetes, congestive heart failure [CHF]) and treatment with abciximab. Models were stratified by study. As in other comparisons, bolus plus infusion abcixmab was compared with placebo for patients with a common intervention; thus, the bolus group from EPIC (no 12-h abciximab infusion after PCI) and the EPISTENT balloon arm (no control balloon arm) were excluded. Because of the large number of associations tested and the relatively small number of deaths available, interactions with treatment were not tested.

The one-year EPIC, EPILOG and EPISTENT data were also used to estimate the portion of mortality benefit explained by the early reduction in MI that abciximab provided. The proportion of patients who had both an early event (death, MI or urgent repeat revascularization) and died within one year was estimated for each treatment group using the Kaplan-Meier method; all patients were censored except those that had an event within 48 h of randomization and later died. The difference between treatment groups was divided by the overall difference in mortality between treatment groups at one year to estimate the portion of mortality reduction explained by the treatment reduction of early events.

RESULTS

Table 1 compares mortality among PCI patients randomized to standard therapy (placebo) or to an abciximab bolus immediately before PCI followed by a 12-h infusion using a proportional hazards regression model. Lower mortality with abciximab was observed in each study, with a significant reduction at one year in the EPISTENT trial when abciximab was combined with stenting ($p = 0.043$). Combining studies increased the strength of evidence for a reduction in mortality with the abciximab bolus plus 12-h infusion compared with standard therapy as indicated by an HR of 0.71 (95% CI: 0.57, 0.89; $p = 0.003$). When the analysis in the bottom line of Table 1 was repeated, eliminating follow-up after one year, the association remained (HR 0.74; 95% CI: 0.58, 0.94; $p = 0.012$). The association remained significant after including all follow-up of all randomized patients according to randomized treatment assignment including all abciximab regimens (HR 0.79; mortality in 193/4,801 placebo patients, 234/7,305 abciximab patients; 95% CI: 0.65, 0.96; $p = 0.017$). This included the EPIC bolus group (54 deaths/695 randomized), the CAPTURE pilot (10) with 12 weeks of follow-up (0/30 deaths abciximab; 1/30 deaths placebo), CAPTURE (11) with six months of follow-up (17/630 deaths abciximab; 14/635 deaths placebo) and the EPISTENT balloon plus abciximab group (17/796 deaths). Excluding any single trial from the final analysis in Table 1 results in a p value of no higher than 0.013. No treatment-study interaction was found (the four smaller studies were combined for this analysis; $p = 0.64$).

Patients assigned to receive a primary stent (by randomization in EPISTENT, the stent substudy in EPILOG and CADILLAC; by protocol in ERASER, ISAR-2 and ADMIRAL) and those who were not were also analyzed separately (Table 1). The 'All balloon' group includes those

Table 1. Intention-to-Treat Analysis of Mortality Reduction With Abciximab in Studies Randomizing Patients to Standard Therapy or Standard Therapy Plus Abciximab With a 12-h Infusion After PCI

Study	Follow-up	Indication	Placebo Death		Abciximab Death		Hazard Ratio (95% CI)	p Value
			n	%	n	(%)		
EPIC	3 years	High-risk	696	59 (8.6%)	708	47 (6.8%)	0.78 (0.53, 1.14)	0.201
EPILOG*	1 year	High/low-risk	939	24 (2.6%)	1,853	32 (1.7%)	0.67 (0.40, 1.15)	0.144
EPISTENT	1 year	Stent	809	19 (2.4%)	794	8 (1.0%)	0.43 (0.19, 0.97)	0.043
RAPPORT	6 months	MI	242	11 (4.6%)	241	10 (4.2%)	0.91 (0.38, 2.13)	0.821
ERASER*†	6 months	Stent	71	1 (1.5%)	154	0	0 (0, 8.36)	—
ISAR-2	1 year	MI/stent	200	17 (8.5%)	201	12 (6.0%)	0.69 (0.33, 1.45)	0.331
ADMIRAL	6 months	MI/stent	151	11 (7.3%)	149	5 (3.4%)	0.45 (0.16, 1.29)	0.144
CADILLAC	6 months	MI	1,028	36 (3.5%)	1,054	32 (3.1%)	0.86 (0.53, 1.38)	0.532
All balloon		Balloon	2,372	116	3,293	101	0.72 (0.55, 0.94)	0.016
All stent		Stent	1,764	62	1,861	45	0.71 (0.48, 1.04)	0.082
All MI		MI	1,644	80	1,670	62	0.76 (0.54, 1.06)	0.100
All non-MI		Non-MI	2,492	98	3,484	84	0.68 (0.51, 0.92)	0.012
All combined		All	4,136	178	5,154	146	0.71 (0.57, 0.89)	0.003

*Two abciximab treatment groups are combined for EPILOG and ERASER; †Two placebo deaths were reported for ERASER (6); only one occurred within six months of follow-up.

For acronym definitions, see Abbreviations and Acronyms box.

CI = confidence interval; MI = myocardial infarction; PCI = percutaneous coronary intervention.

who received provisional or bailout stents since balloon angioplasty (or atherectomy in a small number of cases) was prespecified as the primary mode of intervention. There was no difference in the abciximab mortality reduction between patients assigned balloon or stent treatment ($p = 0.97$). Among balloon patients, the HR was 0.72 with 95% CI (0.55, 0.94), whereas, among stent patients, the HR was 0.71 with 95% CI (0.48, 1.04). Similarly, no interaction was noted in the abciximab effect among patients with MI at baseline compared with others ($p = 0.65$).

Figure 1 shows a relatively high mortality rate in each treatment group in the first two weeks after randomization with a somewhat lower mortality rate thereafter through six months. The relative mortality reduction with abciximab compared with placebo was not statistically different ($p = 0.80$) in the first two weeks (HR: 0.68; 95% CI: 0.46, 1.01) than it was after two weeks (HR: 0.73; 95% CI: 0.56, 0.96). Table 2 displays mortality rates for different time periods. Analyses for fixed durations of six months ($p = 0.040$) and one year ($p = 0.031$) reached nominal significance. The EPIC trial is the only trial with follow-up after one year. Between one and three years, the absolute mortality reduction with abciximab grew from 0.21% (4.45% placebo, 4.24% abcixmab) to 1.81% (8.58% placebo, 6.77% abciximab [12]).

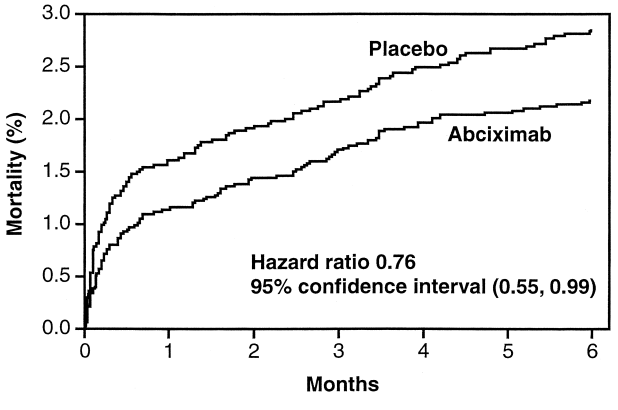

Figure 1. Mortality over six months for all studies combined by patient randomization to standard therapy (placebo) versus standard therapy plus abciximab bolus within 1 h before percutaneous coronary intervention followed by a 12-h infusion.

Survival regression was performed for patients randomized to a 12-h infusion of abciximab after PCI and corresponding controls from EPIC, EPILOG and EPISTENT; the EPISTENT balloon/abciximab arm was excluded since no placebo/balloon arm was studied. Three years of follow-up from EPIC and one year of follow-up from EPILOG and EPISTENT were included. Univariate regression demonstrated the following associations with increased mortality: increased age ($p < 0.001$), female gender ($p = 0.047$), low body weight ($p = 0.013$), history of CABG ($p < 0.001$), history of CHF ($p < 0.001$), history of diabetes ($p = 0.004$), history of cancer ($p < 0.001$, this was assumed to be negative for EPISTENT patients as the data were not collected), history of hypertension ($p < 0.001$), no history of previous PCI ($p = 0.018$), history of PVD ($p < 0.001$), no PCI attempted ($p = 0.003$), multiple vessels attempted ($p < 0.001$) and placebo treatment ($p = 0.011$). Association of mortality with the following did not reach conventional ($p < 0.05$) levels of significance: cigarette smoking ($p = 0.085$, lower risk for smokers), MI within seven days before study entry ($p = 0.50$), multiple segments attempted ($p = 0.071$), unstable angina within 48 h before entry ($p = 0.92$), and history of stroke ($p = 0.089$). Backwards stepwise regression was used to select variables associated ($p < 0.05$) with mortality. The variables selected were: age ($p < 0.001$), history of CHF ($p < 0.001$), history of cancer ($p < 0.001$), history of hypertension ($p = 0.012$), history of PCI ($p = 0.006$; lower risk for patients with previous PCI), history of PVD ($p = 0.008$), multiple vessels attempted ($p = 0.005$), intervention not attempted ($p =$

Table 2. Mortality Over Time Among All Patients in PCI Studies Randomizing Patients to Standard Therapy or Standard Therapy Plus Abciximab With a 12-h Infusion After PCI (Excludes Patients Not Randomized to a Common Intervention [EPISTENT PTCA/Abciximab Group])

Follow-up	Placebo	Abciximab	Absolute Difference	Hazard Ratio	95% CI	p Value
48 h	0.54%	0.34%	0.20%	0.64	(0.34, 1.19)	0.157
7 days	1.01%	0.72%	0.29%	0.71	(0.45, 1.10)	0.125
14 days	1.36%	0.93%	0.43%	0.68	(0.46, 1.01)	0.055
30 days	1.61%	1.14%	0.47%	0.71	(0.50, 1.01)	0.056
6 months	2.86%	2.18%	0.74%	0.76	(0.59, 0.99)	0.040
1 yr*	3.33%	2.39%	0.94%	0.72	(0.53, 0.97)	0.031
2 yr†	6.62%	5.24%	1.38%	0.79	(0.51, 1.21)	0.280
3 yr†	8.58%	6.77%	1.81%	0.78	(0.53, 1.14)	0.201

*EPIC, EPILOG, EPISTENT, ISAR-2 only; †EPIC only.
CI = confidence interval; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty. For acronym definitions, see Abbreviations and Acronyms box.

0.006) and placebo treatment (p = 0.010). Thus, the mortality benefit with abciximab was not altered by adjustment for other factors.

The rate of early end point events (death, MI, urgent PCI, urgent CABG within 48 h of randomization) was reduced from 9.5% in the placebo group to 4.9% in the abciximab group in the combined EPIC, EPILOG and EPISTENT analysis. The risk of dying between 48 h and one year was higher (HR 3.18; 95% CI: 2.18, 4.63) among the patients alive at 48 h who already had experienced an early MI or urgent intervention compared with those who did not. This increased risk associated with early end point events is similar to the results reported in previous studies (1). Nevertheless, most of the observed mortality from randomization to one year was among patients who did not have early end point events. In the placebo group, 73% of deaths within one year were among patients without early events (2.17% of patients had no early event and died within one year of a total of 2.97% of placebo patients who died); this figure was 70% in the abciximab group (1.5% of 2.14%) (Fig. 2). Furthermore, most mortality benefit with abciximab was observed among the patients who did not have early events: 0.83% absolute mortality benefit was observed in the abciximab group overall (2.97% − 2.14%), with 0.67% (2.17% − 1.5%) or 82% of the total mortality difference observed among the patients without death, MI or urgent PCI or CABG within 48 h of randomization. In order to test the association of mortality with treatment among patients without early events, patients were censored at the time of an event (death, MI or urgent PCI or CABG within 48 h of randomization): one year of follow-up was used for EPISTENT and EPILOG and three years for EPIC. Among patients without early events, the HR for mortality with abciximab compared with placebo patients was 0.60 (p = 0.002).

DISCUSSION

Summary. An abciximab bolus within 1 h before PCI plus a 12-h infusion is estimated to reduce mortality with a HR of 0.71 compared with standard treatment without abciximab (p = 0.003, 95% CI: 0.57, 0.89). This result was derived using a proportional hazards model combining maximum follow-up available for all studies with patients undergoing PCI where randomization occurred between placebo and an abciximab bolus within 1 h before PCI plus a 12-h infusion thereafter. Excluding deaths during the first two weeks of follow-up or excluding patients with death, MI or urgent intervention within 48 h of randomization, there was still a significant reduction in mortality with abciximab. The association between abciximab and reduced mortality remained statistically significant after adjusting for demographics, medical history and the nature of the intervention. One year of follow-up of the EPIC, EPILOG, EPISTENT and ISAR-2 trials showed a 0.94% absolute mortality benefit of abciximab treatment compared with placebo or nine lives saved per 1,000 patients randomized.

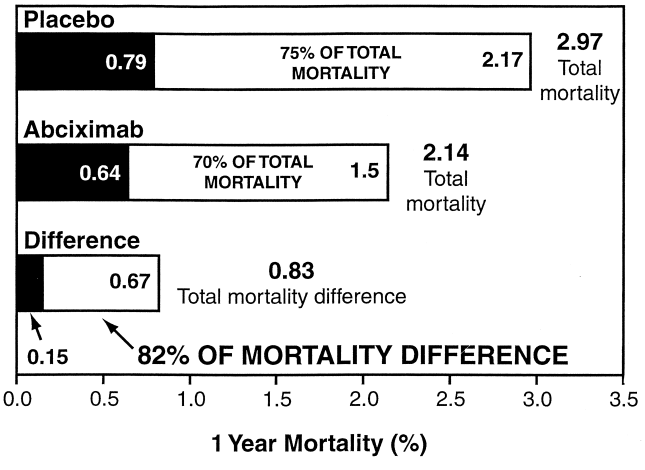

Figure 2. Difference in one-year mortality in the EPIC, EPILOG and EPISTENT trials by randomized treatment assignment partitioned among patients with and without an early end point event (death, myocardial infarction or urgent percutaneous coronary intervention or coronary artery bypass grafting within 48 h of of randomization). **Solid box** = with event < 48 h; **open box** = without event < 48 h. For acronym definitions, see Abbreviations and Acronyms box.

The mortality benefit was similar whether a stenting or balloon angioplasty was performed.

Multivariate regression suggested that patients with more advanced cardiovascular disease (older age, with CHF, hypertension, and/or multivessel disease) were at higher risk of mortality. Treatment interactions with risk factors for mortality were not tested because of the relatively large number of factors and the relatively small number of deaths in the combined studies. The model suggests that patients without any of these risk factors would have a low risk of mortality regardless of treatment: that the mortality benefit is greatest among patients with advanced cardiovascular disease. An analysis specifically examining diabetics in the combined EPIC, EPILOG and EPISTENT trials suggests that diabetics might receive a particular mortality benefit from abciximab (23). The three-year EPIC follow-up suggested that those with severe unstable angina might have a greatly reduced mortality after abciximab treatment (24). Since patients with angina this severe were excluded from EPILOG and may have been preferentially eliminated from EPISTENT, the results presented here do not clarify the relative mortality benefit among patients with acute coronary syndromes at the time of PCI.

Selection of analysis presented. Although a meta-analysis of all GP IIb/IIIa inhibition studies using many agents in both PCI and medical therapy for unstable angina/non-Q-wave MI showed no mortality benefit at six months (21), differences in mortality rates among the agents included in the meta-analysis were not presented. In this study, the HR estimation assumed both early and late mortality were equally reduced by abciximab. We emphasized the abciximab regimen that has been most widely studied, has demonstrated the greatest acute benefit (19,20) and is in use worldwide. Abciximab regimens with concurrent placebo controls using the same interventional strategy were emphasized, excluding the EPISTENT PTCA/abciximab group. However, an intention-to-treat analysis of PCI studies comparing all abciximab regimens to placebo using all available mortality follow-up confirmed the results presented.

Possible mechanisms of benefit. It is likely that the most frequent triggering for periprocedural MI is atherosclerotic particulate material that is microembolized in the coronary vasculature coupled with local vasoconstriction associated with a platelet aggregation response (25). Abciximab blocks platelet aggregation both at the site of plaque injury and downstream at the site of vascular embolism. Thus, marked lessening of necrosis is likely and the chance for developing arrhythmic foci is reduced, which are a likely cause of the excess late sudden death events reported in multiple series (1). However, only 18% of the mortality benefit was estimated to be attributable to early events, and abciximab significantly reduced mortality ($p = 0.002$) compared with placebo among patients without early events. Thus, although patients with events within 48 h after PCI are more likely to die during follow-up, most late deaths occur among patients without these early events. Therefore, the survival benefit of abciximab benefit is twofold. First, early events associated with increased mortality are prevented. Second, survival is improved among the majority of patients undergoing PCI who do not experience early events.

The measurement of early MI using routine enzyme measurement may not detect all early benefit provided by abciximab. There is a possibility that some platelet emboli not causing an infarction as defined in the trials are eventually clinically significant and are prevented by abciximab. However, other possible factors explaining the abciximab mortality benefit among patients without early MI may be related to pharmacologic characteristics of abciximab other than the immediate prevention of platelet aggregation in the periprocedural period. These include prolonged, gradually tapering platelet inhibition during the first two to three weeks after PCI (20). This enhances microcirculatory blood flow and improves ventricular function in patients with ongoing plaque instability after PCI, as has been reported in patients with acute MI undergoing intracoronary stenting with abciximab (7). Other possibilities contributing to improved survival include beneficial effects on longer-term arterial passivation. Abciximab blocks not only GP IIb/IIIa on platelets but also has equivalent blocking affinity for the $\alpha_V\beta_3$ receptor (20,26) on platelets, vascular smooth muscle cells and endothelial cells and, in addition, has demonstrable inhibition of the Mac-1 receptor on activated monocytes and macrophages (27). These integrin receptors and cells have been implicated in both the acute and chronic response to arterial plaque injury and atherothrombosis (28–31). By blocking these receptors with tapered recovery after PCI, abciximab may affect long-term vessel healing and stability.

Study limitations. Analysis of mortality across studies was not prespecified. Only the EPIC trial had follow-up of more than one year. The patient populations in these studies varied in their enrollment characteristics. The nature of PCI changed over the span of several years when these studies were conducted, with stenting rarely being used at the time of EPIC to its becoming a standard of care at the time of EPISTENT. Although there have been over 20,000 patients in studies of GP IIb/IIIa inhibitors cited here, there are still too few deaths in these studies to adequately assess whether there is a differential mortality benefit between agents, regimens and patient populations. Analyses where early follow-up is excluded should be considered descriptive. Despite these limitations, a mortality reduction was observed consistently across time periods, devices and trials, suggesting that the results can be generalized to a broad patient population undergoing PCI with the abciximab bolus plus 12-h infusion regimen.

Conclusions. The accumulated data from randomized clinical trials provides robust evidence of a mortality benefit provided by a bolus of abciximab within 1 h before PCI followed by a 12-h infusion. Further follow-up to extend the long-term observational window would be worthwhile.

Acknowledgments

The authors acknowledge the following individuals who have contributed data or provided review of the manuscript. Rotterdam: Maarten Simoons; Eli Lilly, France: Philippe Pinton; Centocor: Elliot Barnathan, Richard Melsheimer.

Reprint requests and correspondence: Dr. Keaven Anderson, Centocor, Inc., 200 Great Valley Parkway, Malvern, Pennsylvania 19355-1307. E-mail: andersonk@centocor.com.

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