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# Mortality Benefit of Beta Blockade in Patients with Acute Coronary Syndromes Undergoing Coronary Intervention: Pooled Results from the Epic, Epilog, Epistent, Capture and Rapport Trials

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*The effects of beta blocker therapy in the settings of heart failure and coronary artery disease have been well described, although little data exist in patients presenting with acute coronary syndromes undergoing percutaneous coronary intervention. The current study will attempt to evaluate the efficacy of beta blocker therapy in this setting. Pooled data from five randomized, controlled trials of abciximab during coronary intervention were used to analyze the clinical efficacy of beta blocker therapy. The pooled analysis evaluated the end points of all-cause mortality, myocardial infarction, repeat revascularization, and the combined endpoint of death and myocardial infarction in 2,894 patients. At 30 days, death occurred in 12 of 1,939 (0.6%) patients receiving beta blocker therapy and in 19 of 955 (2.0%) patients not receiving beta blocker therapy, ( $P < 0.001$ ). At 6 months, death occurred in 33 of 1,939 (1.7%) patients receiving beta blocker therapy and 35 of 955 (3.7%) not receiving beta blocker therapy, ( $P < 0.001$ ). After creating a propensity model and adjusting for variables predictive of mortality in the multivariable analysis, beta blocker therapy continued to be associated with a significant reduction in mortality. The findings were similar to those shown for the effects of beta blocker therapy in separate subgroups of patients with unstable angina and acute myocardial infarction. This analysis demonstrates a lower short-term mortality in patients receiving beta blocker therapy who undergo percutaneous coronary intervention for unstable angina or acute myocardial infarction. (J Interven Cardiol 2003;16:299–305)*

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## Introduction

Cardiovascular disease is the leading cause of death in the United States. Each year approximately 1.5 to 2 million people are admitted to the hospital because of acute coronary syndromes.<sup>1</sup> A significant reduction in the morbidity and mortality associated with acute coronary syndromes has been achieved over the last three decades through the use of revascularization techniques and aggressive medical therapy.<sup>2</sup>

Beta blocker therapy is pivotal in the treatment of heart disease including chronic ischemic syndromes,

acute coronary syndromes, and heart failure.<sup>3–12</sup> Beta blocker therapy given immediately following the diagnosis of acute myocardial infarction (MI) has been shown to have a favorable effect on mortality.<sup>5,10–12</sup> In the setting of congestive heart failure, beta blockers have been shown to reduce left ventricular dilation and reduce mortality.<sup>6–8</sup> A previous study has shown that beta blocker therapy limits creatine kinase MB release and lowers mortality when used following percutaneous coronary intervention, although patients undergoing percutaneous coronary intervention (PCI) for acute MI were excluded.<sup>13</sup> This current pooled analysis was performed to quantify evidence supporting the acute use of beta blocker therapy among patients presenting with unstable angina or an acute myocardial infarction who undergo percutaneous coronary intervention.

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## Methods

**Patient Population.** Patients enrolled in five randomized, placebo-controlled clinical trials of glycoprotein (GP) IIb/IIIa receptor blockade with abciximab during percutaneous coronary intervention were evaluated to determine the efficacy of beta blocker therapy among patients presenting with acute coronary syndromes.<sup>14–18</sup> The Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial enrolled 2,099 patients who were to undergo coronary angioplasty or atherectomy with high-risk clinical or angiographic characteristics.<sup>14</sup> Our pooled analysis included the 523 patients in EPIC presenting with unstable angina or acute MI. The Evaluation in PTCA to Improve Long Term Outcome With Abciximab GP IIb/IIIa Blockade (EPILOG) trial enrolled a total of 2,792 patients undergoing elective or urgent percutaneous coronary revascularization.<sup>15</sup> Patients who presented with an acute MI or unstable angina with electrocardiographic changes within the prior 24 hours were excluded. Our pooled analysis included 192 patients who presented with either acute MI or unstable angina within the prior 48 hours before randomization. The Evaluation of Platelet GP IIb/IIIa Inhibitor for Stenting (EPISTENT) trial enrolled a total of 2,399 patients with coronary lesions amenable to angioplasty or stent placement.<sup>16</sup> These patients were randomized to receive stent plus placebo, stent plus abciximab bolus and infusion, or balloon angioplasty plus abciximab bolus and infusion. Our pooled analysis included the 537 patients who presented with either acute MI or unstable angina within 48 hours before randomization. The c7E3 Fab Antiplatelet Therapy In Unstable Refractory Angina (CAPTURE) trial enrolled 1,265 patients with refractory unstable angina who had undergone prior coronary angiography with a culprit lesion amenable for angioplasty.<sup>17</sup> Our pooled analysis included the 1,233 patients presenting with unstable angina for whom data regarding beta blocker therapy was available. The ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) enrolled 483 patients who presented within 12 hours of acute MI and underwent primary angioplasty.<sup>18</sup> We included the 409 patients from RAPPORT in our pooled analysis for whom data on the use of beta blocker therapy was available.

The patients in the pooled analysis were considered to be treated with beta blockers if oral beta blocker therapy was initiated during or following the admin-

istration of abciximab or following PCI. Though the exact timing of beta blocker therapy was not recorded, therapy was initiated within 24 hours of randomization. Statistical modeling was used to adjust for differences between beta blocker initiation among the different trials. Information regarding the specific beta blocking agents administered was not available from the trial databases. Patients in the beta blocker group were all discharged from the hospital on beta blocker therapy. The clinical trial databases do not contain data regarding whether or not patients continued to receive beta blocker therapy by 30-day and 6-month follow-up.

**Study End Points.** The end points used in the pooled analysis consisted of all-cause mortality, MI, repeat revascularization, and the composite of death and MI. These end points were evaluated in all patients and separately in the cohorts presenting with unstable angina or acute MI at 30 days and 6 months following trial entry. In the hospital myocardial infarction was defined by one of two criteria: new clinically significant Q waves in two or more contiguous electrocardiographic leads or elevation in creatine kinase or the creatine kinase MB isoenzyme to at least three times the upper limit of normal. After hospital discharge, MI was defined by the occurrence of new Q waves in two or more contiguous electrocardiographic leads or an elevation of creatine kinase or the creatine kinase MB isoenzyme to more than twice the upper limit of normal. Repeat revascularization included any percutaneous or surgical revascularization for recurrent myocardial ischemia performed during the follow-up period of 30 days or 6 months.

**Statistical Analysis.** The primary comparison was between patients receiving beta blockers and those not receiving beta blockers in the setting of an acute coronary syndrome. The patients were all classified as acute coronary syndrome and subsequently stratified according to acute myocardial infarction and unstable angina. The effect of receiving beta blocker therapy was compared in the subgroups of patients presenting with an acute MI, unstable angina, and those who received abciximab or placebo. The effect of receiving abciximab was compared in the subgroups of patients who did or did not receive beta blockers. A secondary analysis was performed to evaluate for the presence of an interaction between beta blockers and abciximab.

Mortality was further evaluated by adjusting for differences between patients who received beta blockers and those who did not. Initially, a propensity model for beta blocker use was developed, which incorporated

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the demographic data. The variables incorporated into the model included age, diabetes, peripheral vascular disease, prior MI, prior PCI or coronary artery bypass grafting, and body mass index. The propensity model for beta blocker use was not only used to adjust for differences between patient characteristics, but also pre-hospital medications that may have had an impact on the outcome. The medications included in the propensity model were pre-hospital beta blockers, aspirin, nitrates, and oral anticoagulants. Also, procedure type, pre-procedure coronary artery stenosis, and TIMI flow were included in the model, each of which may have affected the outcome. Adjustments for whether or not a person received PTCA or PTCA/stent or bail-out stenting were included. A second model was created, which adjusted for differences in baseline characteristics using a multivariable analysis (Cox Proportional Hazard Model). The parameters included in the multivariable analysis were propensity scores and variables predictive of mortality, which included age, hypertension, diabetes, peripheral vascular disease (PVD), prior revascularization, prior MI, randomization to abciximab, pre-procedure aspirin, anticoagulant or nitrate use, and body mass index. Dichotomous variables are presented as percentages and continuous variables as means  $\pm$  standard deviation unless otherwise indicated. Differences between treatment groups are reported using unadjusted and adjusted hazard ratios; confidence intervals and P values for the significant variables are also listed. The causes of death were also evaluated at 30 days and 6 months. These were divided into cardiac death, which included MI and arrhythmia; vascular death, which included stroke and peripheral vascular disease; noncardiac death; and unknown death.

All analyses were performed using the SAS statistical package, version 6.12 (SAS Institute, Inc., Cary, NC).

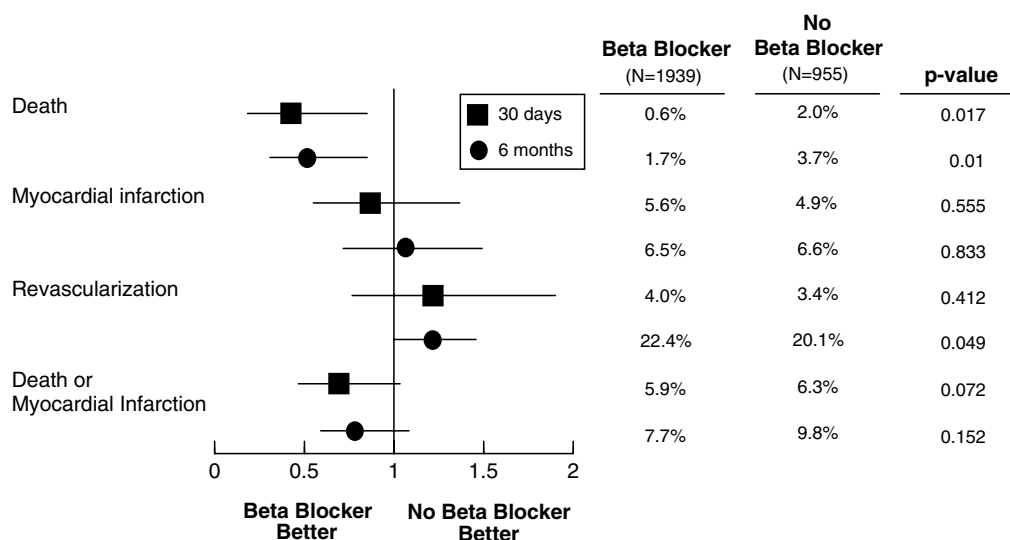
### Results

Patient demographics are summarized in Table 1. There were 1,960 patients who presented with unstable angina and 934 patients who presented with an acute myocardial infarction. In the study cohort, 1,939 patients received beta blocker therapy and 955 did not. The patients who did not receive beta blocker therapy were significantly older, had lower body weight, and had higher incidences of congestive heart failure, peripheral vascular disease, and diabetes. The groups were otherwise comparable.

**Pooled Analysis.** At 30 days, all-cause mortality was significantly lower in patients receiving beta blockers than among those not treated with beta blockers. Mortality was 2.0% in the non-beta-blocker group and 0.6% in the group receiving beta blocker therapy (unadjusted hazard ratio, 0.402; 95% confidence interval (CI), 0.19 to 0.849,  $P = 0.017$ ), (Figure 1). After adjusting for the propensity score and predictive variables, the apparent benefit of beta blocker therapy persisted (adjusted hazard ratio 0.248; 95% CI, 0.108 to 0.57,  $P = 0.001$ ). This mortality difference also was seen after the groups were categorized according to unstable angina and acute myocardial infarction (Table 2). In patients presenting with unstable angina, mortality was 0.56% in the beta blocker group and 1.55% in the group not receiving beta blockers at 30 days. In patients presenting with an acute MI, mortality was 0.72% in the beta blocker group and 3.32% in the group not receiving beta blockers.

**Table 1.** Patient Demographics

Parameters	No Beta Blocker ( <i>n</i> = 955)	Beta Blocker ( <i>n</i> = 1939)	P value
Age in years ( $\pm$ SD)	61.1 (10.6)	59.5 (10.87)	<0.001
Male	71.5	70.4	0.533
Weight in kilograms ( $\pm$ SD)	79.5 (15.15)	80.8 (15.76)	0.034
Prior myocardial infarction	43.2	46.3	0.114
Prior coronary artery bypass grafting	6.2	5.7	0.586
Prior percutaneous intervention	17.8	16.1	0.25
Congestive heart failure	5.3	3.6	0.038
Peripheral vascular disease	9.6	7.2	0.029
Diabetes	20.6	16.8	0.012
Smoking or quit within 1 year	37.6	40.4	0.145
Stroke	2.0	1.8	0.729
Hypertension	48.5	49.5	0.631



**Figure 1.** Unadjusted hazard ratio and incidence of end points at 30 days and 6 months in all acute coronary syndrome patients.

At 6 months, the differences in mortality persisted: 3.7% in non-beta-blocker group and 1.7% in the group that received beta blockers (unadjusted hazard ratio of 0.516; 95% confidence interval, 0.312 to 0.853,  $P = 0.01$ ) (Figure 1). After adjusting for the propensity score and predictive variables, the mortality advantage associated with beta blockers persisted (adjusted hazard ratio, 0.525; 95% confidence interval, 0.293 to 0.94,  $P = 0.03$ ). Among patients presenting with acute MI or unstable angina the mortality benefit of beta blockers persisted at 6 months (Table 2). There were no significant differences in rates of MI, or the composite of death and MI at 30 days or 6 months between patients

who did and did not receive beta blockers. However, the incidence of repeat revascularization was significantly higher in patients receiving beta blockers at 6 months, as demonstrated by the unadjusted hazard ratio (unadjusted hazard ratio, 1.21; 95% confidence interval, 1.0 to 1.46).

Throughout the 6 months of follow-up, a total of 68 patients died: 33 in the beta blocker group and 35 in the non-beta-blocker group. Cardiovascular mortality accounted for 64% of the deaths in the beta blocker group and 77% in the non-beta-blocker group. Vascular mortality accounted for 6% of the deaths in the beta blocker group and 11% in the non-beta-blocker group.

**Table 2.** Thirty-Day and 6-Month End Points for Unstable Angina and Acute MI

End Points	Time	Unstable Angina (n = 1960)		P value	Acute MI (n = 934)		P value
		No Beta Blocker (n = 714)	Beta Blocker (n = 1246)		No Beta Blocker (n = 241)	Beta Blocker (n = 693)	
Death	30 days	1.6	0.6	0.029	3.3	0.7	0.003
	6 months	3.1	1.4	0.009	5.6	2.3	0.02
Myocardial infarction	30 days	5.3	4.7	0.56	3.4	6.8	0.97
	6 months	7.1	6.7	0.73	5.2	6.0	0.63
Revascularization	30 days	3.3	4.4	0.26	3.8	3.5	0.81
	6 months	23.5	22.9	0.12	21.6	21.6	0.97
Death and myocardial infarction	30 days	6.3	5.1	0.24	6.3	7.2	0.12
	6 months	9.6	7.8	0.16	10.3	7.6	0.25

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**Table 3.** Thirty-Day and 6-Month End Points by Beta Blocker Treatment

End Points	Time	No Beta Blocker (n = 955)		P value	Beta Blocker (n = 1939)		P value
		Abciximab (n = 539)	Placebo (n = 416)		Abciximab (n = 1110)	Placebo (n = 829)	
Death	30 days	2.0	1.9	0.9	0.5	0.8	0.272
	6 months	4.1	3.2	0.442	1.3	2.3	0.08
Myocardial infarction	30 days	3.0	7.3	0.002	2.9	11	0.001
	6 months	4.7	9.0	0.008	5.3	8.0	0.012
Revascularization	30 days	2.4	4.6	0.065	3.3	5.0	0.055
	6 months	19	21.6	0.37	22	23	0.488
Death and myocardial infarction	30 days	4.5	8.7	0.007	3.2	11.4	0.001
	6 months	8.3	11.7	0.069	6.2	9.8	0.002

The combined noncardiac and unknown mortality was 30% of deaths in the beta blocker group and 12% in the non-beta-blocker group. The reduction in mortality seen in the beta blocker group thus appeared to be due to lower cardiac mortality.

Among patients who received abciximab, beta blocker therapy was associated with a significantly lower rate of death at 30 days and 6 months. However, in the group of patients who received placebo, the differences in rates of death at 30 days and 6 months were not as marked and did not reach statistical significance. However, there were no statistically significant interactions between the protective effect of beta blocker therapy whether the patients received abciximab or placebo. The treatment effect of abciximab in reducing myocardial infarction and urgent revascularization events was present independently of the use of beta blockers (Table 3).

### Discussion

The effects of beta blocker therapy were evaluated in this pooled group of patients presenting with acute MI or unstable angina who underwent PCI. We observed that mortality was reduced by approximately 50% at 30 days and 6 months in patients receiving beta blockers. There were baseline differences between the groups of patients that received and those that did not receive beta blocker therapy. Patients treated with beta blockers were younger and had a lower incidence of diabetes, congestive heart failure, peripheral vascular disease, and prior revascularization. It is plausible that

beta blocker therapy in this cohort may have been a marker for more aggressive therapy in a population that is less critically ill. With these factors in mind, a propensity model and the Cox Proportional Hazard model were constructed, which corrected for baseline factors as well as differences in pre-hospital medication and the severity of coronary artery disease. The mortality benefit persisted after these adjustments, with a reduction in both cardiovascular and vascular mortality. Beta blockers were not shown in this study to be associated with a beneficial effect on the incidence of MI. A significant increase in repeat revascularization rates at 6 months with beta blockers was demonstrated by the unadjusted hazard ratio. However, this was a significant borderline finding that was not subjected to multivariable analysis, and likely represents random statistical chance. Beta blocker therapy appeared to have an enhanced effect when used in combination with abciximab, although the multivariable analysis did not show a statistically significant interaction between the two therapies. The clinical benefit of abciximab was independent of beta blocker use.

The current pooled analysis suggests that beta blockers are effective in patients undergoing percutaneous intervention for an acute coronary syndrome. Beta blocker therapy has previously been shown to be beneficial in the settings of acute myocardial infarction, unstable angina and to a certain extent percutaneous coronary intervention. Beta blockade reduces myocardial workload and hence oxygen demand through a reduction in heart rate and blood pressure. These agents also reduce free fatty acid levels and shift myocardial metabolism from fatty acids to glucose, thereby

further decreasing oxygen demand. Beta blockade also reduces catecholamine levels and can produce favorable redistributions of blood flow, with greater diversion to the subendocardial regions where ischemia is often severe.<sup>20</sup> These mechanisms along with a number of clinical studies provide scientific evidence supporting the use of beta blocker therapy in acute coronary syndromes.

Beta blocker therapy in the setting of myocardial infarction has been shown to improve mortality along with reducing recurrent ischemia and infarct size. The International Study of Infarct Survival 1 (ISIS-1) trial randomized 16,027 patients with suspected MI, prior to the era of reperfusion, to placebo or atenolol. The trial showed that vascular mortality was reduced by 15% in the atenolol group after 7 days.<sup>11</sup> The Metoprolol In Acute Myocardial Infarction (MIAMI) trial randomized patients presenting with acute MI shortly after arrival into the hospital to placebo or to intravenous metoprolol. Although, this trial did not show a mortality benefit, beta blocker therapy did reduce recurrent ischemia and limit infarct size after 15 days of follow-up.<sup>5</sup> The Beta Blocker Heart Attack Trial (BHAT) research group evaluated the long-term effects of beta blocker therapy, randomizing patients who were 5-to-21 days post MI to receive placebo or propranolol. The patients were followed for an average of 25 months, and propranolol was found to reduce mortality by 26%.<sup>12</sup>

Trials evaluating beta blocker therapy in patients with unstable angina have shown a reduction in myocardial infarction and recurrent ischemia. In a study involving 43 patients presenting with "threatened MI," randomized to receive propranolol or conventional therapy, those treated with propranolol had fewer completed infarcts as assessed by serial electrocardiograms, a lower frequency of serum CK levels above the normal range and a lower peak serum CK.<sup>9</sup> The Holland Interuniversity Nifedipine Metoprolol Trial (HINT) research group randomized 515 patients presenting with unstable angina to placebo, metoprolol, nifedipine, or nifedipine and metoprolol.<sup>21</sup> After 48 hours, the group of patients receiving metoprolol was found to have a reduction in rates of recurrent ischemia or myocardial infarction. A systematic overview from five randomized trials, which included over 4,700 patients, showed that there was a 13% reduction in the risk of developing MI in patients who received initial intravenous beta blockade followed by 1 week of oral beta blockade.<sup>22</sup>

There are few data on beta blockers in patients undergoing percutaneous coronary intervention. However,

a nonrandomized study evaluating beta blockers following PCI suggested that prior beta blocker therapy limits CK-MB release after coronary intervention.<sup>13</sup> This study retrospectively evaluated patients undergoing PCI, excluding patients who were within 24 hours of acute MI. Beta blocker therapy was associated with a decreased incidence of CK-MB release after PCI and lesser mortality at 15 month follow-up.

Data from the current pooled analysis support the literature regarding the mortality benefit of beta blockers in patients with acute MI, unstable angina, and those undergoing percutaneous coronary intervention. However, prior studies have shown a reduction in myocardial infarction associated with beta blocker use following unstable angina and acute MI, which was not shown in our current study. It is not clear why this pooled analysis did not show a reduction in MI associated with beta blocker therapy, although statistical chance is certainly an important possibility. This finding may also be related to the fact that PCI may alter the natural history over this relatively short period of follow-up, resulting in a clustering of MI events in the periprocedural period that would not be affected by beta blocker therapy. Previous studies were not PCI studies, in contrast to those included in our pooled analysis.

**Study Limitations.** This pooled analysis shares the limitations that are common to post hoc, nonrandomized subgroup analyses. The primary comparison was not randomized and the difference seen in mortality may be attributable to underlying differences between patient populations, despite adjustment in the multivariable analysis. There also was a lack of uniform definitions of acute coronary syndromes across the different trials. No information was available regarding the type of beta blockers used. Therefore, some beta blockers may have been nonselective or may have had alpha blocking or intrinsic sympathomimetic properties that may have affected outcome.

## Conclusion

Beta blocker therapy is associated with a significant reduction in short-term mortality in patients who are undergoing percutaneous coronary intervention presenting with acute coronary syndromes. There were no significant interactions seen between abciximab and beta blocker therapy. These findings provide further support for the role of beta blocker therapy in the broad spectrum of patients treated for ischemic heart disease.

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