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Mortality Benefit of Beta-Blockade After Successful Elective Percutaneous Coronary Intervention

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OBJECTIVES The goal of this study was to evaluate the mortality benefit of beta-blockers after successful percutaneous coronary intervention (PCI).

BACKGROUND Beta-blockers reduce mortality after myocardial infarction (MI), though limited data are available regarding their role after successful PCI.

METHODS Each year from 1993 through 1999, the first 1,000 consecutive patients undergoing PCI were systematically followed up. Patients presenting with acute or recent MI, shock, or unsuccessful revascularization procedures were excluded from the analysis. Clinical, procedural, and follow-up data of beta-blocker-treated and non-beta-blocker-treated patients were compared. A multivariate survival analysis model using propensity analysis was used to adjust for heterogeneity between the two groups.

RESULTS Of the 4,553 patients, 2,056 (45%) were treated with beta-blockers at the time of the procedure. Beta-blocker therapy was associated with a mortality reduction from 1.3% to 0.8% at 30 days ($p = 0.13$) and a reduction from 6.0% to 3.9% at one year ($p = 0.0014$). This survival benefit of beta-blockers was independent of left ventricular function, diabetic status, history of hypertension, or history of MI. Using propensity analysis, beta-blocker therapy remained an independent predictor for one-year survival after PCI (hazard ratio, 0.63; 95% confidence interval, 0.46 to 0.87; $p = 0.0054$).

CONCLUSIONS Within this large prospective registry, beta-blocker use was associated with a marked long-term survival benefit among patients undergoing successful elective percutaneous coronary revascularization. (J Am Coll Cardiol 2002;40:669–75) © 2002 by the American College of Cardiology Foundation

Numerous secondary prevention trials have shown that beta-blockers prevent death and reduce the risk of reinfarction after myocardial infarction (MI) (1–10). However, most of these studies were carried out before the reperfusion era. The role of beta-blockers after successful reperfusion therapy or revascularization procedures has not been well defined. While it is hoped that revascularization reduces the need for anti-anginal medications, the use of these medications was found to be highly prevalent at six months after percutaneous coronary intervention (PCI) in clinical practice (11). By contrast with the past, when PCI and medical therapy had been considered as competitive strategies for symptomatic coronary artery disease (CAD) (12,13), we hypothesized that beta-blockers might provide complementary benefit after successful revascularization. Hence, we examined the effect of beta-blockers on mortality after PCI in a large registry and sought to define patient characteristics that might benefit from this class of medication.

METHODS

Patient selection. Each year from January 1993 through June 1999, we prospectively followed up the first 1,000 consecutive U.S. residents who underwent PCI at the Cleveland Clinic Foundation. The demographic and procedural data, including medication use, hemodynamic status, equipment use, and final results of each case were prospectively recorded in an interventional database. Serum creatine kinase (CK) was drawn routinely at 8 h and 12 to 24 h after each case, and if CK was >100 mg/dl, CK-MB levels would be obtained in the same blood sample. Clinical event data during the index hospitalization, at 30 days and at one year were collected by cardiology nurses and research coordinators through patient interview, chart review, and serial telephone contacts. Mortality data were confirmed with the United States Social Security Administration Death Master File. Patients were divided into two groups according to whether beta-blocker therapy was being received at the time of PCI procedures. Patients who presented with acute MI, recent (≤7 days) MI, cardiogenic shock, or failure of revascularization (final residual stenosis of target lesions >20% after stenting or >50% after balloon angioplasty, final TIMI [Thrombolysis in Myocardial Infarction] flow grade <3, or ongoing ischemia) in the index procedure were excluded from the analysis.

To correlate the prevalence of pre-procedural beta-blocker use with that at the time of discharge, we sampled the first 20 cases performed at the beginning of each year within the study period; hence, a total 140 cases were reviewed.

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Abbreviations and Acronyms

ACE = angiotensin-coverting enzyme
CABG = coronary artery bypass grafting
CAD = coronary artery disease
CI = confidence interval
CK = creatine kinase
COPD = chronic obstructive pulmonary disease
LVEF = left ventricular ejection fraction
MI = myocardial infarction
PCI = percutaneous coronary intervention

Statistical analysis. Continuous variables were expressed in means ± SD, and they were compared by means of Student *t* test or Mann-Whitney rank sum test. Categorical data were displayed as frequencies and percentages. Chi-square test was used for bivariate analysis for categorical data. Kaplan-Meier estimation and Cox proportional hazards modeling were used for unadjusted and adjusted survival analysis, respectively.

To attempt to adjust for the bias inherent in the decision about beta-blocker therapy before PCI, propensity analysis was performed (14,15). Propensity analysis aims to identify patients with similar probability of receiving beta-blocker therapy based on the observed clinical characteristics. Using a multivariable logistic regression model that includes the baseline characteristics as the independent variables, the probability of being assigned to beta-blocker therapy was determined. The variables that were included in the propensity score model were: age; gender; body mass index; presentation with unstable angina (angina at rest >20 min, new onset angina <2 months, angina severity equal to or greater than Canadian Cardiovascular Society classification class III, or acceleration of angina ≥1 class within two months); identification of positive ischemia on stress test (electrocardiographic, nuclear scintigraphic, or echocardiographic criteria); presence of congestive heart failure (New York Heart Association class II to IV); diabetes; hypertension; hypercholesterolemia; current cigarette smoking; renal insufficiency (serum creatinine ≥2.0 mg/dl); peripheral vascular disease; chronic obstructive lung disease (COPD); history of MI, stroke, or coronary bypass surgery (CABG); restenotic lesions; premature CAD (onset <45 years in males or <55 years in females); use of aspirin, angiotensin-converting enzyme (ACE) inhibitors, statins, calcium-channel receptor blockers, diuretics, or anti-arrhythmics; left ventricular ejection fraction (LVEF); number of diseased coronary arteries; and the years of intervention (1993 to 1994, 1995 to 1996, 1997 to 1999).

The population was then divided into deciles according to the propensity score. Within each decile, the mean propensity scores of the beta-blocker and non-beta-blocker groups were compared, as well as their clinical and procedural characteristics. To adjust for the heterogeneity between the two groups, the propensity score was then entered as a continuous variable in the Cox proportional hazards model, along with 34 potential covariates. These covariates included the baseline variables entered in the propensity score model and other procedural variables that might correlate with outcome, namely, lesion morphology (type A/B_1 vs. B_2/C), left anterior descending or saphenous vein graft intervention, number of vessels intervened, type of contrast (ionic vs. non-ionic), stent use, and glycoprotein IIb/IIIa inhibition. All statistical analyses were performed with the SAS program (version 6.12, SAS, Cary, North Carolina).

RESULTS

Baseline characteristics. During the study period, a total of 6,558 patients were followed up, and, of these, 4,553 patients were eligible for study entry. Of these, 2,056 patients (45.1%) were receiving a beta-blocker before the procedure. Table 1 shows the baseline characteristics according to beta-blocker treatment. There were important differences between the two groups. Patients who were receiving beta-blocker therapy before coronary intervention were younger, more likely to be female and more likely to have hypercholesterolemia, hypertension, prior MI, concomitant statin therapy, multi-vessel CAD, and more likely to present with unstable angina. They were less likely to receive ACE inhibitors, calcium-channel blockers, diuretics, and anti-arrhythmics. At the procedure, beta-blocker recipients were more likely to receive stents and ionic contrast. The prevalence of diabetes, renal insufficiency, prior coronary bypass surgery, history of stroke, location of lesion, glycoprotein IIb/IIIa antagonist use, and number of vessels being intervened were similar between the two groups.

Unadjusted 30-day and one-year all-cause mortality. As depicted on the Kaplan-Meier curve (Fig. 1), receiving a beta-blocker at the time of the procedure was associated with a trend toward an early (30-day) survival benefit (0.8% vs. 1.3%, hazard ratio = 0.62, log-rank p = 0.13), and the mortality difference continued to widen through the end of the first year (3.9% vs. 6.0%, hazard ratio = 0.65, log-rank p = 0.0014).

Propensity analysis. Within the propensity score analysis, variables that predicted the prescription of beta-blocker before PCI were (in descending order): concomitant statin therapy, hypertension, presentation with unstable angina, and prior MI (Table 2). On the other hand, independent predictors against a prescription of beta-blocker included (in descending order) concomitant anti-arrhythmic agents, calcium-channel antagonist, COPD, ACE-inhibitor use, LVEF ≤35%, congestive heart failure, positive stress test, and male gender. The goodness of fit of the propensity score was given by the *c* statistic (or area under the receiver operating characteristic curve) being 0.68. Within each decile of the study population, the propensity scores and baseline characteristics were similar among the beta-blocker-treated and non-beta-blocker-treated groups.

Multivariate analysis of six-month mortality. Using Cox proportional hazards model to adjust for all potential

Table 1. Baseline Characteristics and Procedural Data of the Patients at the Time of PCI

Characteristics	Beta-Blocker (n = 2,056)	No Beta-Blocker (n = 2,497)
Age (yrs)*	62.9 ± 11.0	64.1 ± 10.4
Female (%)*	30	25
Body mass index (kg/m^2)	30.9 ± 9.6	28.7 ± 9.1
Heart rate (beats/min)*	69.3 ± 13.1	73.7 ± 13.2
Risk factors		
Current smoker (%)	17	15
Diabetes mellitus (%)	27	27
Hypercholesterolemia (%)*	51	45
Hypertension (%)*	66	57
Premature CAD (%)	30	30
Comorbidity		
Prior MI (%)*	47	41
Prior coronary bypass surgery (%)	35	32
History of congestive heart failure (%)*	7.4	11
NYHA class I/II/III/IV	3.5/2.5/0.7/0.7	4.0/3.5/2.3/1.6
Renal insufficiency (%)	3.9	4.2
Peripheral vascular disease (%)*	7.1	8.8
Prior stroke (%)	8.4	7.7
Chronic obstructive lung disease (%)*	3.7	8.3
Medications		
Aspirin (%)	96	95
ACE inhibitor (%)*	16	20
Calcium-channel blocker (%)*	34	52
HMG-CoA reductase inhibitor (%)*	32	22
Diuretic (%)*	16	18
Antiarrhythmia (%)*	1.4	3.3
Positive stress test*	42	58
Procedural profile		
Unstable angina (%)*	73	65
LVEF <35 (%)*	8.3	11
Number of diseased vessels (>50% severity) (%)*		
1	34	37
2	31	31
3	35	32
Lesion location (%)		
LAD	42	43
RCA	36	36
Circumflex	35	35
Number of vessels treated (%)		
1	85	85
2	13	14
3	0.7	0.7
Restenotic lesion(s) (%)	19	20
SVG intervention (%)	13	11
Ionic contrast (%)*	77	73
Stent(s) (%)*	45	41
GP IIb/IIIa antagonist (%)	48	48
Peri-procedural MI		
CK-MB > 1x upper limit of normal	15	15
CK-MB > 3x upper limit of normal	4.1	5.1

*$p < 0.05$.
ACE = angiotensin-converting enzyme; CAD = coronary artery disease; CK = creatine kinase; GP = glycoprotein; HMG-CoA = 3-hydroxy-3-methylglutaryl–coenzyme A; LAD = left anterior descending; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; RCA = right coronary artery; SVG = saphenous vein graft.

variables, beta-blocker therapy at the time of PCI remained an independent predictor for survival at one year (hazard ratio = 0.62, 95% confidence interval [CI]: 0.45 to 0.87, p = 0.0048) (Table 3). When the propensity score was included in the model with all the covariates to adjust also for the chance of prescription of beta-blocker, the effect of beta-blocker pre-treatment on one-year survival did not change significantly (hazard ratio = 0.63, 95% CI: 0.46 to 0.87, p = 0.0054). Other predictors for mortality are listed in Figure 2. Diabetes, age ≥75 years, triple-vessel CAD, poor left ventricular (LV) systolic function, diuretic use, COPD, renal insufficiency, and low body mass index were independent predictors for mortality at one year. Aspirin use at the time of procedure was associated with survival benefit at one year.

Subgroup analysis. The mortality benefits among subgroups are shown in Figure 3. Of note, beta-blocker therapy was associated with a survival benefit in most of the subgroups, except for patients who underwent successful PCI for single-vessel CAD (Breslow-Day test for single-vessel vs. multi-vessel CAD, p value = 0.067). In addition, beta-blocker therapy was shown to be associated with a marked survival benefit among patients with renal insufficiency (Breslow-Day test for renal insufficiency vs. preserved renal function, p = 0.049). Despite a relatively small number of patients treated with rotational atherectomy, a significant survival benefit was associated with beta-blocker treatment. On the other hand, beta-blocker use did not prevent peri-procedural myonecrosis (defined as total CK or CK-MB fraction >1× upper normal limit in two sequential samples, 15.5% vs. 15.3%, p = NS), or peri-procedural MI (defined as total CK or CK-MB fraction >3 times the upper normal limit in 2 sequential samples, 4.1% vs. 5.1%, p = NS).

Pre-procedural beta-blocker use and use at the time of discharge. Among the 140 cases that were sampled, 73 of 80 patients who were receiving beta-blockers at the time of the procedure were discharged also receiving beta-blockers, and 52 of 60 patients not pre-treated with beta-blockers were not discharged with beta-blockers. Hence, there was an 89% correlation of pre-procedural beta-blocker use and use of beta-blocker after discharge.

DISCUSSION

Within this large prospective interventional registry, beta-blocker therapy was associated with an early mortality reduction after successful elective PCI, and the benefit increased during the first year of follow-up. This treatment effect was present to a similar extent across the majority of the subgroups regardless of age, diabetic status, history of MI, lesion type, or LV systolic function. In addition to the patients who had a history of MI, a striking survival benefit was also found in patients with renal insufficiency and those who underwent multi-vessel PCI. Importantly, the mortality benefit of beta-blockers observed at one year was independent of peri-procedural MI. Furthermore, beta-blockers offered no protection against peri-procedural MI.

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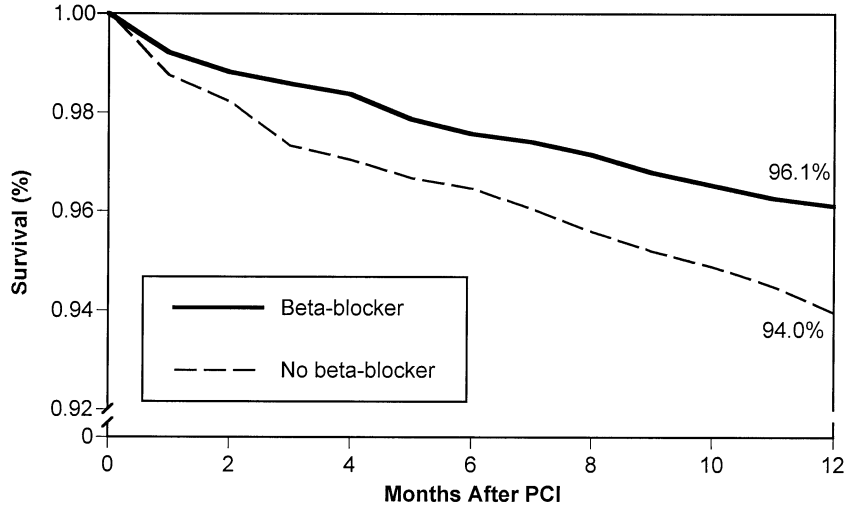

Figure 1. Kaplan-Meier estimation of the survival rates within the first year after percutaneous coronary intervention (PCI).

Comparison with other beta-blocker and MI studies. The effect of beta-blockade for the secondary prevention of MI has been established in numerous studies (1–10). Mortality reduction with beta-blockade after acute MI is mainly mediated by its negative chronotropic and inotropic effects, leading to reduction of arterial blood pressure, reduction of myocardial oxygen demand, and anti-arrhythmogenesis. Overall, mortality rates were reduced by 25% to 35% within the first year in these trials. Most of these studies were performed before the widespread use of fibrinolytics or PCI for reperfusion therapy. The use of beta-blockers after successful percutaneous revascularization has not been addressed in the American College of Cardiology/American Heart Association clinical guidelines. The importance of the appropriate medical therapy after PCI may be less emphasized in the modern era when procedure-oriented strategies receive substantial attention. Using the data from a large interventional database, this analysis suggests a mortality benefit and reinforces the utility of beta-blockers after elective revascularization. By contrast with the clinical trials in which a mortality benefit with beta-blockers was confined to patients with prior MI, our study observed a benefit extending to patients who did not have a history of MI. Similar to the study by Sharma et al. (16), our study concluded that the mortality reduction at one-year was not mediated by the cardioprotection within the subgroup of patients who had peri-procedural MI. However, by contrast with the same study, our data did not detect a cardioprotective effect against peri-procedural MI with beta-blockade (17).

Observation from subgroup analyses. Consistent with studies about beta-blockade in high-risk populations (18–21), survival benefits were also found in patients whose conditions would be considered a contraindication for this therapy 20 years ago, such as ischemic cardiomyopathy, diabetes, and presence of peripheral vascular disease. Furthermore, this benefit was present regardless of the type of diabetes. Interestingly, our study revealed a striking mortality benefit of beta-blockers in patients with renal insufficiency, an observation that is contrary to the previously held belief that these agents reduced cardiac output, leading to a reduction in renal blood flow and glomerular filtration rate (22). Conversely, renal impairment is associated with chronic hypertension, diabetes, presence of peripheral vascular disease, multi-vessel CAD, and LV dysfunction (23), and these factors were linked to benefits from beta-blockers

Table 2. Factors Associated With the Propensity of Beta-Blocker Prescription

Factors	Odds Ratio	p Value
More likely prescribed with beta-blocker		
Statin	1.58	0.0001
Hypertension	1.54	0.0001
Unstable angina	1.47	0.0001
Prior MI	1.40	0.0001
Year 1995–1996	1.39	0.0001
Less likely prescribed with beta-blocker		
Anti-arrhythmic agents	2.68	0.0001
Calcium-channel blocker	2.48	0.0001
Chronic obstructive lung disease	2.20	0.0001
Congestive heart failure	1.80	0.0004
ACE inhibitor	1.59	0.0001
Left ventricular ejection fraction ≤35%	1.37	0.0001
Positive stress test	1.24	0.0027
Male	1.18	0.0320
Area under ROC curve (c-statistic)	0.68	

ACE = angiotensin-converting enzyme; MI = myocardial infarction; ROC = receiver operating characteristic.

Table 3. Survival Benefit Associated With Beta-Blocker Use After PCI

	Hazard Ratio	95% CI	p Value
Unadjusted	0.64	0.49–0.84	0.0015
Adjusted for covariates	0.62	0.45–0.87	0.0048
Adjusted for propensity score	0.68	0.50–0.93	0.0164
Adjusted for covariates and propensity score	0.63	0.46–0.87	0.0054

CI = confidence interval; PCI = percutaneous coronary intervention.

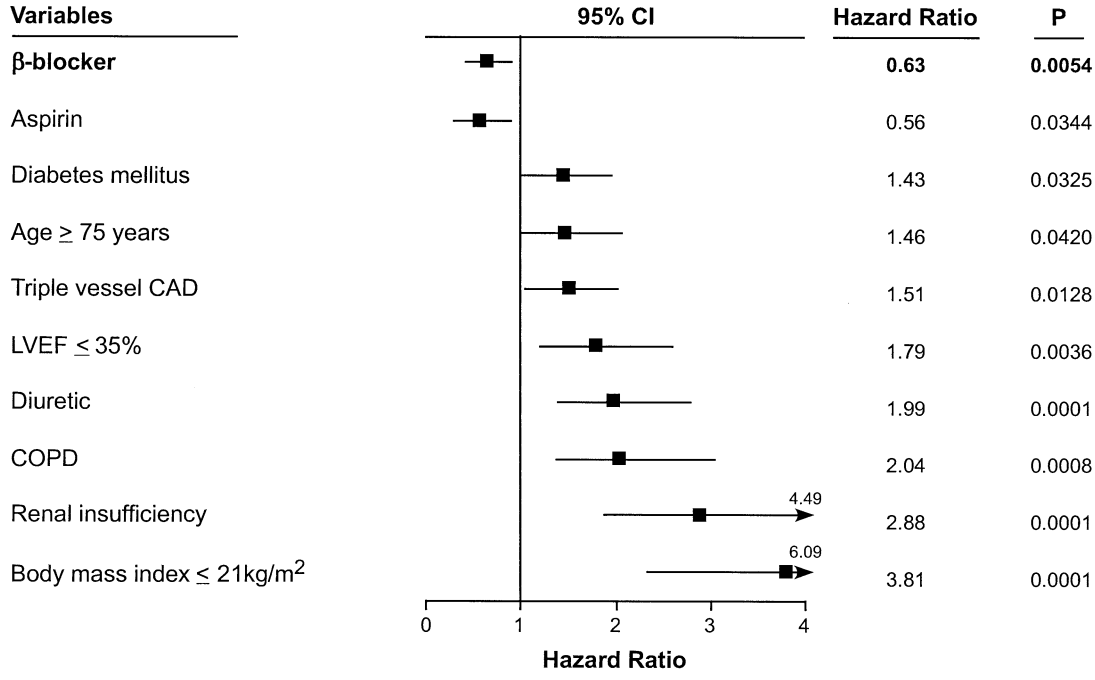

Figure 2. Independent predictors for mortality at one year after percutaneous coronary intervention. CAD = coronary artery disease; CI = confidence interval; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction.

in this study. Regardless, renal insufficiency was an independent predictor for mortality in our model even after adjusting for all these factors. The explanation of the mechanics of the survival benefits associated with beta-blockers in these patients may warrant further exploration.

Traditionally, rotational atherectomy has been implicated in post-procedure CK-MB elevation. Although the benefits of beta-blockers did not appear to be mediated by myocardial protection after an incidence of myonecrosis, beta-blockade was associated with a significant mortality reduction at one year after rotational atherectomy. The association between atherectomy use, beta-blocker use, and mortality reduction may be confounded by factors such as diffuse coronary and systemic atherosclerosis because patients with these lesion characteristics may derive a greater benefit from the use of beta-blockers. In view of a greater benefit of beta-blockers among patients with prior MI, prior CABG, LVEF ≤35%, multi-vessel CAD, and multi-vessel PCI than among without these factors, our study suggests that the benefits of beta-blockers are largely proportional to the extent of the cardiovascular disease burden in these patients.

Observations from multivariate analysis. Importantly, our study highlights the independent predictors for one-year mortality after elective PCI. The factors were similar to the ones reported from the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty (NHLBI PTCA) Registry (24). Disappointingly, other than beta-blocker and aspirin administration, which were associated with survival benefit, many of these independent risk factors are non-modifiable. Consistent with the other reports (25,26), very low body mass index was noted to be the most powerful predictor for mortality at one year in contemporary PCI.

Study limitations. This study has limitations inherent to any registry data. The use of beta-blockers at the time of intervention was not randomized. Despite the use of the conventional and appropriate statistical methods for adjusting for the heterogeneity between the two groups and physicians' decisions to prescribe the drugs, beta-blocker use may still be a surrogate marker for better care, and this may contribute, in part, to a better outcome. In addition, the duration of treatment with beta-blockers before the procedure was unknown. However, the presence of an inadequate beta-blockade before the procedure would lead only to an underestimation of the benefit of beta-blockers. Similarly, the compliance of beta-blockers after hospital discharge was unrecorded. When we sampled our population systemically, we noted that the correlation of pre-procedural beta-blocker use and use at discharge was close to 90%. In addition, a previous study of 3,831 patients reported that >90% of patients continued to receive beta-blockers at six months despite complete revascularization with PCI (11). Moreover, because our study was based on beta-blocker status at the time of intervention, any crossover of beta-blocker use between the two groups would lead to an underestimation of the effect of beta-blockers in the reduction of mortality.

Conclusions. In summary, this large observational study performed in the era of PCI demonstrated a survival benefit at one year with the use of beta-blockers at the time of PCI, and this benefit was present across the majority of the patient subgroups. Because the aim of medical care is to

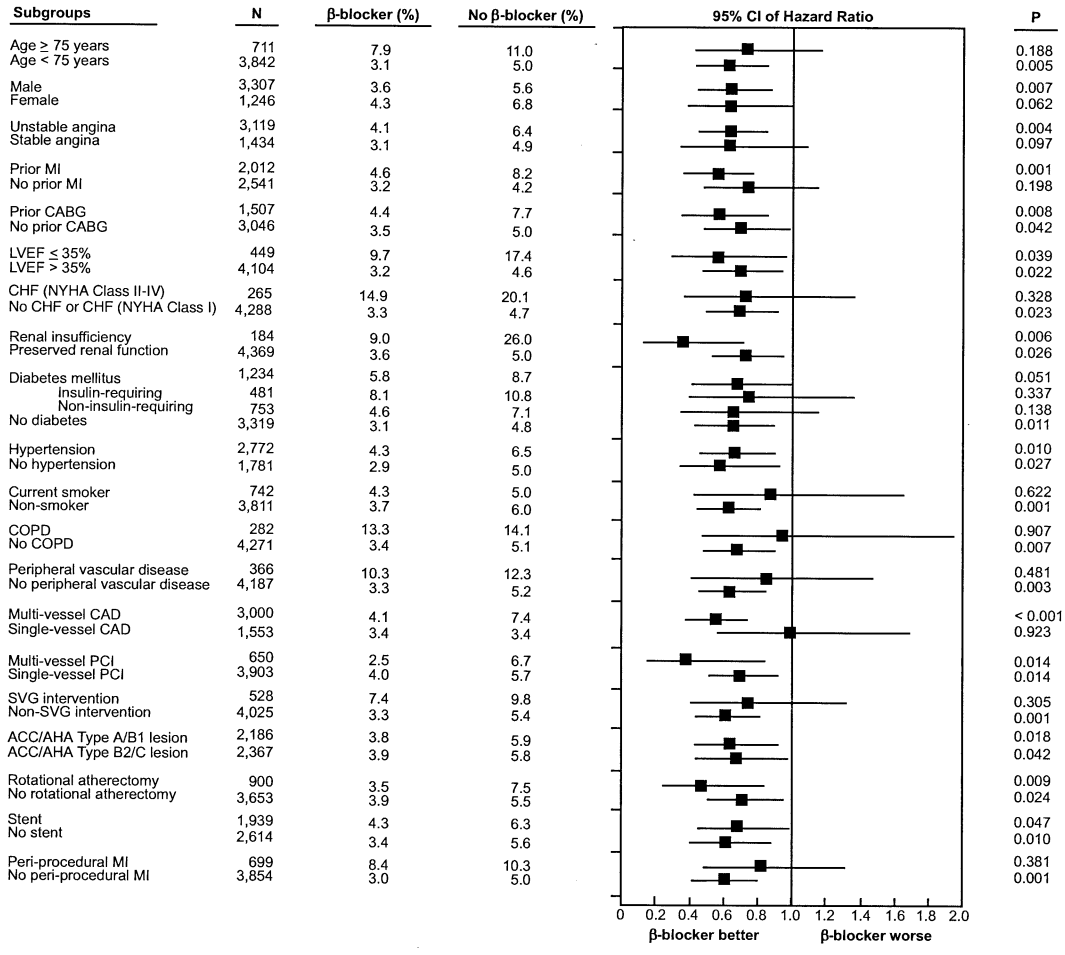

Figure 3. Subgroup comparisons of the one-year survival rates among patients who were treated with beta-adrenergic blocking agents with those who were not treated with beta-blockers at the time of percutaneous coronary intervention (PCI). ACC/AHA = American College of Cardiology/American Heart Association; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CHF = congestive heart failure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; SVG = saphenous vein graft.

reduce mortality and morbidity of our patients, medical therapy with beta-blockers and percutaneous coronary revascularization should be considered as complementary strategies.

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