

Cardioprotective Effect of Prior β -Blocker Therapy in Reducing Creatine Kinase-MB Elevation After Coronary Intervention

Benefit Is Extended to Improvement in Intermediate-Term Survival

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Background—Both retrospective studies and prospective randomized trials have shown that β -blockers improve survival and reduce the risk of reinfarction in patients with myocardial infarction. To evaluate whether β -blockers exert similar protective benefits during and after coronary intervention, we studied the incidence of postprocedure creatine kinase (CK)-MB elevation in patients with or without prior β -blocker therapy and its effect on intermediate-term (≈ 1 year) survival.

Methods and Results—We prospectively analyzed 1675 consecutive patients undergoing coronary intervention; of these patients, 643 (38.4%) were on β -blocker therapy before the intervention. The incidence of CK-MB elevation after coronary intervention was 13.2% in patients on β -blocker therapy before intervention and 22.1% in patients who were not on β -blockers ($P < 0.001$). Patients with prior β -blocker therapy had lower persistent/recurrent postprocedure chest pain and lower preprocedure and postprocedure heart rates and mean blood pressures compared with patients who were not on β -blockers ($P < 0.001$). Multiple linear regression analysis revealed prior β -blocker therapy as the sole independent factor for lower CK-MB release after coronary intervention. During intermediate-term follow-up at 15 ± 3 months, patients on β -blocker therapy before intervention had lower mortality rates compared with those not on β -blockers (0.78% versus 1.96%; $P = 0.04$), although the benefit was independent of the reduction in CK-MB release.

Conclusions—Our nonrandomized, prospective analysis suggests that prior β -blocker therapy has a cardioprotective effect in limiting CK-MB release after coronary intervention and that it is associated with a lower mortality at intermediate-term follow-up. (*Circulation*. 2000;102:166-172.)

Key Words: creatine kinase ■ β -blocker ■ angioplasty ■ myocardial infarction ■ prognosis

Creatine kinase (CK)-MB isoenzymes are elevated after 6% to 30% of percutaneous coronary interventions.¹⁻³ The clinical relevance of periprocedural CK-MB elevation after coronary intervention and its impact on intermediate (≈ 1 year) and long-term (2 to 5 years) survival has been a matter of intense debate. Numerous earlier reports, mostly involving balloon angioplasty, have shown CK-MB elevation is associated with higher subsequent cardiac events and mortality.⁴⁻⁷ Recent trials involving newer devices have shown a higher incidence of postprocedure CK-MB elevation but no definite increase in intermediate-term mortality.⁸⁻¹¹ The causes of CK-MB elevation after otherwise successful coronary intervention are multiple and include side branch closure, slow flow, transient vessel closure, spasm, distal thromboembolism, and prolonged ischemia by balloon inflations.¹¹⁻¹⁴ In some cases, increased myocardial oxygen de-

mand due to the tachycardia and hypertension caused by heightened sympathetic discharge in response to ischemia and pain may also contribute to CK-MB elevation.

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Both retrospective studies and prospective randomized trials have shown that β -blockers improve survival, limit infarct size and CK release, and reduce the risk of reinfarction in patients with a previous myocardial infarction (MI), predominantly by blunting the sympathetic response, reducing arrhythmia, decreasing ischemia, and limiting infarct extension.^{15,16} It is not known whether prior β -blocker therapy exerts a similar protective effect after coronary intervention—a state of heightened sympathetic tone. The present study was conducted with the following objectives: (1) to evaluate the incidence of CK-MB elevation after various

Received November 15, 1999; revision received January 13, 2000; accepted February 11, 2000.

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Presented in part at the 48th Annual Scientific Sessions of the American College of Cardiology, New Orleans, La, March 1999.

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coronary interventions in relation to prior β -blocker therapy and (2) to determine if prior β -blocker therapy has a beneficial effect on intermediate-term survival after coronary intervention.

Methods

Patients

All patients who underwent percutaneous coronary interventions at Mount Sinai Hospital in New York from January 1997 to February 1998 were included in the study except those who had a coronary intervention within 24 hours of acute MI ($n=82$), an elevated preprocedure CK-MB ($n=16$), and incomplete CK-MB values ($n=32$) and those who were on unknown medications ($n=33$). Patients who had major complications, which were defined as emergency bypass surgery and persistent refractory closure causing MI or death, while inside the catheterization laboratory were also excluded ($n=8$); only 2 of these patients were on β -blocker therapy. The study population consisted of 1675 consecutive patients who had preprocedure and 6- to 8-hour and 16- to 24-hour postprocedure CK-MB values available for analysis. Of these 1675 patients, 643 (38.4%) were on β -blocker therapy before the intervention, and 1032 (61.6%) were not taking β -blockers. Patients who received β -blockers during the interventional procedure ($n=24$; 5 before and 19 during the intervention) or after the coronary intervention ($n=64$) were included in the no β -blocker group. Baseline clinical history and medications were recorded before coronary intervention, during the hospital stay, and at discharge.

Protocol

All patients had blood drawn for CK-MB measurements at the time of sheath insertion and had a baseline 12-lead ECG within the 24 hours before the procedure. Interventional procedures were performed in a standard fashion, and procedural complications such as coronary spasm, arterial dissection, thromboembolism, transient vessel closure, abrupt closure, slow flow, side branch closure, prolonged hypotension (systolic blood pressure <80 mm Hg lasting for >5 minutes), prolonged balloon inflation (>5 minutes), and persistent chest pain (>30 minutes postprocedure) were recorded. Subsequently, blood samples were drawn at 6 to 8 hours and 16 to 24 hours after the procedure for cardiac enzyme determination and complete blood cell counts. A 12-lead ECG was routinely recorded after the procedure and on the following morning. In cases of an adverse clinical outcome or recurrent chest pain, further blood tests and ECGs were performed as deemed clinically necessary. All ECGs were independently analyzed for ST segment and T wave changes and for the appearance of new Q waves.

CK and CK-MB Measurements

Total CK was measured by a Hitachi 747 analyzer, and CK-MB levels were measured by immunoinhibition using a Johnson & Johnson Vitros 950 analyzer. If CK-MB was abnormal (absolute total ≥ 16 U or $\geq 10\%$ of total CK), then the measurement was further confirmed with an enzyme mass immunoassay using a Baxter Stratus-2 analyzer. Final CK-MB values of mass immunoassay were used for the analysis. CK-MB <16 U was considered normal, and any value ≥ 16 U was considered elevated, with a CK-MB of 16 to 48 U as 1 to $3\times$ normal, a CK-MB of 49 to 80 U as 3 to $5\times$ normal, and a CK-MB of >80 U as $5\times$ normal.

Intervention

All patients received 325 mg of aspirin orally and a 70 to 100 U/kg intravenous bolus of heparin. Subsequently, periodic intravenous heparin boluses were given to maintain an activated clotting time between 250 to 350 seconds throughout the procedure, with a trend toward lower values (225 to 250 seconds) if abciximab was used. Abciximab was used in 38.8% of coronary interventions; its use was based on clinical and angiographic lesion complexity and was not randomized. An appropriately sized (6 to 10 French) guiding catheter

was used to accommodate the selected interventional device. The distribution of various devices for coronary interventions was as follows: balloon angioplasty, 10.4%; rotational atherectomy, 25.1%; stent, 28.5%; rotational atherectomy followed by stenting, 31.9%; and other devices (directional coronary atherectomy, transluminal extraction catheter, or Angiojet alone or in combination with stent), 4.1%.

All interventions were performed using conventional techniques, and the selection of a particular device was at the discretion of the operator. The arterial access sheath was removed 3 to 6 hours after intervention, except in cases of recurrent chest pain or a staged next-day procedure. Coronary interventions were classified as single vessel (80%) if the intervention was done in one native coronary vessel distribution (including branches), as multivessel (11%) if the intervention was done in ≥ 2 native coronary vessels, and as graft (9%) if the intervention involved an arterial or venous bypass graft. Complete angiographic vessel and lesion characteristics and procedural results were recorded after each coronary intervention. In cases of multiple lesions undergoing intervention, patients were classified according to the most complex lesion characteristic. Various periprocedural events were recorded for each patient, and multiple occurrences of one procedural complication was counted only once.

In-Hospital Course

All patients were monitored in-hospital for major complications (Q-wave MI, emergent bypass surgery, or in-hospital death), recurrent chest pain, heart failure, arrhythmia (atrial or ventricular), ECG changes, acute or subacute closure, and the need for repeat catheterization, repeat intervention, and/or in-hospital bypass surgery. Patients with normal CK-MB levels who were clinically stable were discharged the following day on aspirin only (325 mg daily) in the absence of stent implantation or on aspirin (325 mg daily) plus ticlopidine (250 mg twice daily for 4 weeks) if a stent was implanted.

Follow-Up

All patients discharged from the hospital were followed for adverse cardiac events and survival at 1, 6, 12, and 18 months by telephone contact to the patient or private physician. Survival data were cross-checked with the New York State interventional database, which monitors the mortality of all interventional patients. Clinical follow-up was available in 99.1% ($n=637$) of the prior β -blocker therapy patients and in 98.8% ($n=1020$) of the group without previous β -blocker therapy.

Statistics

The data were entered in a Microsoft Excel database and transferred to the statistical program StatView 4.1 for analysis. Results are presented as mean $\pm$ SD or n (%). Comparisons between the 2 groups were done using χ^2 analysis or Fischer's exact test for categorical variables and a 2-tailed Student's t test for continuous variables. Significant univariate variables with $P<0.1$ were included in the multiple logistic regression analysis for odds ratios and 95% confidence intervals.

Results

For the 1675 patients and 4068 lesions, the rates of overall angiographic lesion success (94.5%), clinical success (96.3%), and major complications (0.72%, including 1 death in each group) were not different between the prior β -blocker and no β -blocker groups. The incidence of CK-MB elevation was 18.7% for the entire group, 13.2% in the prior β -blocker therapy group, and 22.1% in no β -blocker group ($P<0.001$). Patients on prior β -blocker therapy had a lower incidence and magnitude of CK-MB elevation, which was basically due to a significant reduction in the group with a 1 to $3\times$ normal CK-MB elevation, compared with the no β -blocker group (Figure 1). The mean peak CK-MB level postprocedure was

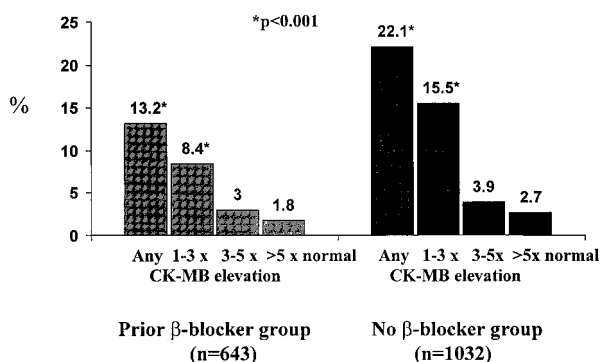


Figure 1. Incidence and magnitude of CK-MB elevation in prior β -blocker therapy versus no β -blocker therapy groups.

29 ± 18 U in the β -blocker therapy group and 38 ± 24 U in the no β -blocker group ($P < 0.002$). The time to peak CK-MB release was 6 to 8 hours in 69% of cases, 16 to 24 hours in 23% of cases, and >24 hours in 8% of cases; time was not different between the 2 groups.

Important clinical and angiographic variables and the incidence of CK-MB elevation in relation to β -blocker therapy are shown in Table 1. Mean age was not different

between the 2 groups, but mean ejection fraction was significantly higher in the no β -blocker group ($53 \pm 11.4\%$ versus $43 \pm 8.6\%$ in the prior β -blocker group). The following clinical variables were significantly higher in the group with previous β -blocker therapy: male sex, hypertension, absence of diabetes, rest angina, prior MI, prior bypass surgery, multivessel disease, and absence of heart failure. Prior β -blocker therapy was protective in most of the clinical categories, despite the higher incidence of adverse clinical features in most subgroups compared with the no β -blocker group. The presence of significant collaterals (≥ 2 by Rentrop classification) was comparable in the 2 groups (8.6% versus 8.1% in the no β -blocker versus prior β blocker group; $P = \text{NS}$), as was the mean number of lesions with intervention (2.6 ± 0.3 versus 2.3 ± 0.3 in the no β -blocker versus prior β -blocker group; $P = \text{NS}$). The mean peak activated clotting time in patients with or without abciximab was not different between the 2 groups. Prior β -blocker therapy was protective with most of the interventional devices except for rotational atherectomy.

Important procedural complications and in-hospital events in the 2 groups are listed in Table 2. Patients on prior β -blocker therapy had lower persistent/recurrent postproce-

TABLE 1. Clinical, Angiographic, and Procedural Variables and Incidence of CK-MB Elevation

Characteristics	Prior β -Blocker Therapy (n=643)		No β -Blocker Therapy (n=1032)		P for CK-MB Elevation
	n (%)	Incidence of CK-MB Elevation	n (%)	Incidence of CK-MB Elevation	
Female sex	160 (24.9)	17.5%	370 (35.8)	23.8%	0.02
Hypertension	486 (75.6)	14.0%	689 (66.8)	21.8%	<0.01
Diabetes mellitus	108 (16.8)	17.6%	309 (29.9)	16.8%	NS
Smoking	105 (16.3)	16.2%	185 (17.9)	22.7%	0.04
Rest angina	311 (48.3)	19.6%	301 (29.2)	33.9%	<0.01
Prior myocardial infarction	316 (49.1)	16.1%	266 (25.8)	24.1%	<0.01
Infarction in <30 days	152 (23.6)	18.4%	82 (7.9)	28.0%	<0.01
Prior bypass surgery	169 (26.3)	14.8%	88 (8.5)	23.9%	<0.01
Systemic atherosclerosis	42 (6.5)	28.6%	148 (14.3)	26.4%	NS
Congestive heart failure	41 (6.4)	21.9%	142 (13.8)	20.4%	NS
Abciximab use	268 (41.7)	25.4%	382 (37.0)	23.8%	NS
Multivessel disease	291 (45.2)	15.5%	260 (25.2)	28.5%	<0.01
Multivessel intervention	54 (8.4)	20.4%	131 (12.7)	22.9%	NS
LAD lesion	273 (42.4)	15.8%	359 (34.8)	21.4%	0.07
Vein graft lesion	81 (12.6)	24.7%	70 (6.8)	27.1%	NS
ACC/AHA type C lesion	141 (21.9)	22.0%	224 (21.7)	32.6%	0.03
Total or subtotal occlusion	98 (15.2)	16.3%	145 (14.0)	19.3%	NS
Moderate/heavy calcification	156 (24.2)	18.6%	242 (23.4)	18.6%	NS
Thrombotic lesion	64 (9.9)	26.6%	70 (6.8)	18.6%	NS
Device used					
Rotablator	142 (22.1)	19.0%	278 (26.9)	14.4%	0.1
Stent	171 (26.6)	11.7%	306 (29.7)	25.5%	<0.01
RotaStent	231 (35.9)	14.2%	333 (29.3)	23.7%	<0.01

ACC indicates American College of Cardiology; AHA, American Heart Association; and LAD, left anterior descending artery.

TABLE 2. Important Procedural Complications and In-Hospital Events in Groups

Events	Prior β -Blocker Therapy (n=643)	No β -Blocker Therapy (n=1032)	P
Side branch closure	64 (9.9)	101 (9.8)	NS
Slow flow	15 (2.3)	12 (1.2)	0.06
Spasm	10 (1.6)	6 (0.6)	0.05
Transient vessel closure	6 (0.9)	16 (1.6)	NS
Distal embolization	5 (0.8)	8 (0.8)	NS
NHLBI dissection grade C–F	5 (0.8)	19 (1.8)	0.11
Prolonged balloon inflation	8 (1.2)	13 (1.3)	NS
Prolonged hypotension	7 (1.1)	7 (0.7)	NS
Persistent chest pain postprocedure	18 (2.8)	51 (4.9)	0.03
Preprocedure heart rate, bpm	62 $\pm$ 32	84 $\pm$ 26	<0.01
Preprocedure blood pressure, mm Hg	108 $\pm$ 32	128 $\pm$ 40	<0.01
Postprocedure heart rate, bpm	78 $\pm$ 21	96 $\pm$ 30	<0.01
Postprocedure blood pressure, mm Hg	96 $\pm$ 18	114 $\pm$ 28	<0.01
Peak activated clotting time, s	282 $\pm$ 72	278 $\pm$ 68	NS
Major complications	5 (0.7)	7 (0.7)	NS
Abrupt closure/stent thrombosis	5 (0.8)	10 (1.0)	NS
Recurrent chest pain	42 (6.8)	129 (12.5)	<0.01
ECG ST-T changes	66 (10.3)	70 (6.5)	<0.01
Congestive heart failure	52 (8.1)	59 (5.7)	0.06
Reintervention	5 (0.8)	16 (1.6)	0.12
Hospital stay, days postprocedure	2.4 $\pm$ 1.5	3.2 $\pm$ 1.7	0.05

Values are n (%) or mean $\pm$ SD. NHLBI indicates National Heart, Lung, and Blood Institute.

chest pain and lower preprocedure and postprocedure heart rates and mean blood pressures. Also, patients on prior β -blocker therapy had a significantly lower incidence of discernible ST segment depression (6.8%) or T-wave inversion (3.5%) compared with the no β -blocker group (11.4% and 5.1%, respectively; $P<0.01$). A trend toward a higher incidence of slow flow, coronary spasm, and congestive heart failure existed in the prior β -blocker therapy group. Medications at the time of discharge were not significantly different between the no β -blocker versus previous β -blocker groups, except for the use of β -blockers; medications included lipid-lowering agents (42.8% versus 44.1%, respectively), ticlopidine (62.4% versus 60.1%) and calcium channel blockers (22.4% versus 24.1%). The use of β -blockers was 95.8% in the prior β -blocker therapy group and 10.6% in the no β -blocker group ($P<0.001$).

On multiple logistic regression analysis (Figure 2), rest angina, multivessel disease, diffuse coronary artery disease, systemic atherosclerosis, stent use, and vein graft intervention were independent predictors of CK-MB release, but only prior β -blocker therapy was correlated with lower CK-MB release. Female sex, hypertension, prior MI, diabetes mellitus, abciximab use, prior ticlopidine use, multivessel intervention, balloon angioplasty, rotational atherectomy, and peak activated clotting time were not predictive of CK-MB elevation.

During a mean follow up of 15 $\pm$ 3 months (Figure 3), 5 deaths (4 cardiac, 1 noncardiac; 0.78%) occurred in the prior β -blocker group at a mean of 245 days after discharge; in the

no β -blocker group, 20 deaths (16 cardiac, 4 noncardiac; 1.96%) occurred at a mean of 266 days after discharge ($P=0.04$). The incidence of sudden cardiac death with an implied possible arrhythmic cause was significantly lower in the prior β -blocker group than in the no β -blocker group (0.16% versus 0.98%; $P=0.04$). The incidence of death in relation to CK-MB elevation was not different between the 2

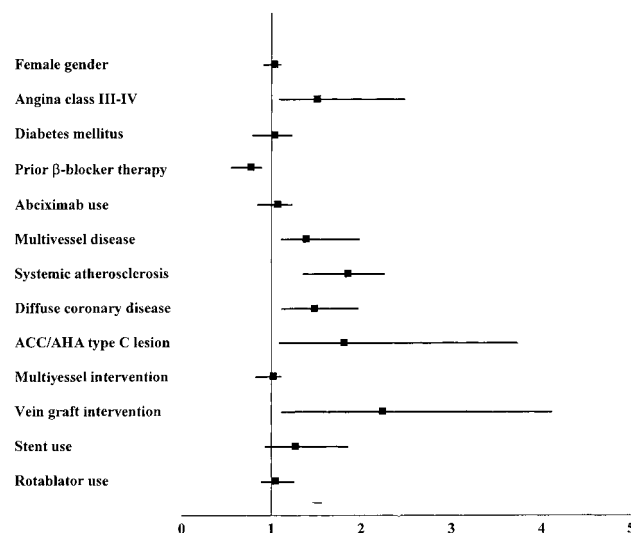


Figure 2. Important multivariate predictors of CK-MB elevation with odds ratios and 95% confidence intervals. ACC indicates American College of Cardiology; AHA, American Heart Association.

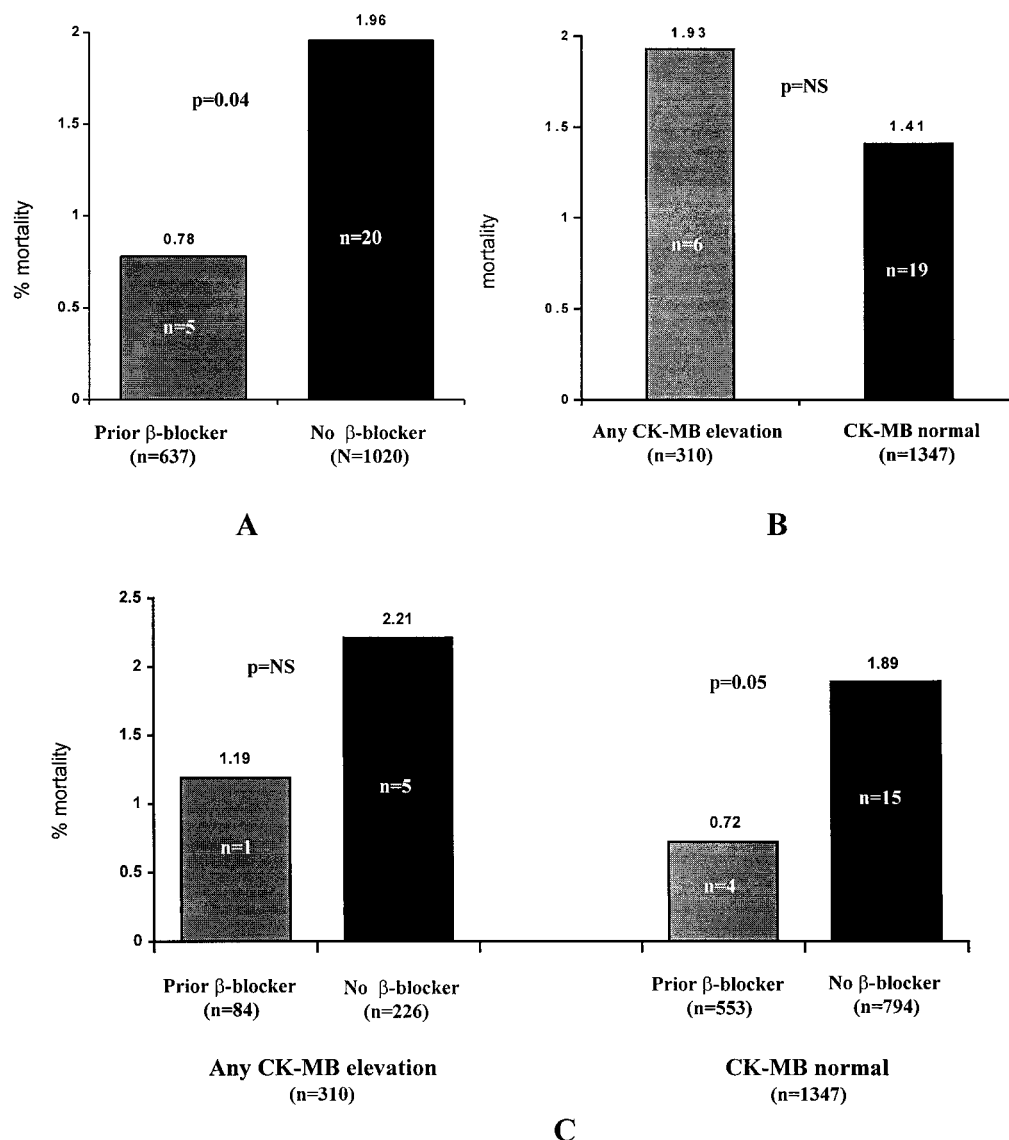


Figure 3. Intermediate-term mortality in relation to prior β -blocker therapy and CK-MB elevation. A, Mortality in relation to prior β -blocker therapy at the time of intervention. B, Mortality in relation to CK-MB levels. C, Mortality in relation to prior β -blocker therapy and CK-MB levels.

groups (1.93% in CK-MB elevation group versus 1.41% in the group with a normal CK-MB; $P=NS$). However, the major benefit of β -blocker therapy was observed in the normal CK-MB group (0.72% in prior β -blocker versus 1.89% in no β -blocker group; $P=0.05$), whereas in the CK-MB elevation group, no statistically significant difference existed with respect to prior β -blocker therapy (1.19% versus 2.21% in prior β -blocker versus no β -blocker groups; $P=0.48$). This beneficial trend on intermediate-term mortality of prior β -blocker therapy was observed in subsets of patients with or without a history of previous MI or hypertension (Figure 4). The incidence of nonfatal MI was lower in the prior β -blocker group (5.2% versus 8.1%; $P=0.02$), whereas the rate of revascularization (repeat or de novo), after excluding staged interventions, was comparable between the 2 groups (23.1% in β -blocker versus 20.2% in no β blocker group; $P=NS$).

Discussion

Several reports have shown that CK-MB elevation after coronary intervention is associated with higher late cardiac events of MI and death.³⁻⁶ Most of these data were gathered in the era of percutaneous transluminal coronary angioplasty. CK-MB elevation during the interventional procedure is device-dependent, with higher enzyme release for nonballoon devices.⁴⁻⁷ Recent trials with newer devices have shown a higher incidence of CK-MB release with otherwise successful coronary interventions.⁸⁻¹² The cause of CK-MB enzyme release is multifactorial and results from various procedural events, of which side branch closure and distal thromboembolism are the most frequent.^{3,5,6,13,14} Despite numerous minor procedural adverse events, CK-MB elevation occurs even in the absence of discernible complications (51% of cases in the present study). The heightened sympathoadrenal tone associated with coronary interventions, which is caused

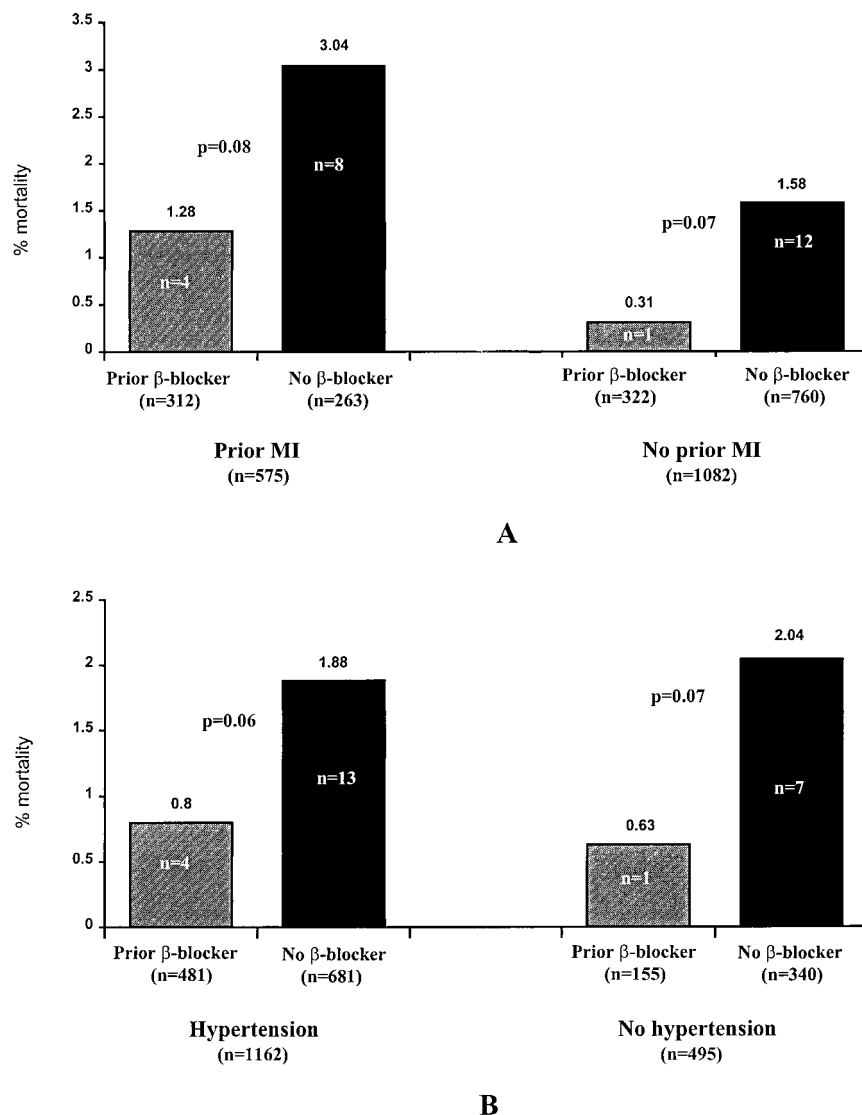


Figure 4. Intermediate-term mortality in patients with a history of MI and hypertension in relation to prior β -blocker therapy. A, Mortality in relation to history of MI. B, Mortality in relation to presence/absence of hypertension.

by ischemia or pain, may induce increased oxygen demand by increasing heart rate, blood pressure, and contractility. β -blockade decreases oxygen demand by preventing increases in heart rate and blood pressure, as is shown in the present study. Although speculative, this may be the mechanism most responsible for preventing periprocedural CK-MB release in patients on prior β -blocker therapy.

Other effects of β -blockade, which were not measured in the present study, such as the redistribution of blood flow to the ischemic myocardium, a decrease in platelet aggregation, and an improvement of the oxygen dissociation curve, may also contribute to this protective effect.¹⁶ The incidence of certain procedural events, such as slow flow and spasm, was slightly higher in the prior β -blocker therapy group; this was probably mediated by the increased coronary vascular resistance caused by sympathetic blockade. The effect of these minor procedural events was counteracted by decreased periprocedural chest pain, heart rate, and blood pressure. This cardioprotective effect of β -blocker therapy was observed, despite the higher incidence of adverse clinical and lesion characteristics in the prior β -blocker therapy group. In addition,

a lower incidence of ECG ST-T changes in the prior β -blocker therapy group may reflect the final outcome of a complex interplay between heart rate, blood pressure, and periprocedural ischemia.

The long-term use of β -blockers in patients with coronary artery disease, especially after MI, decreases mortality through infarct size reduction and decreased arrhythmia.^{15,16} Despite their proven benefit on survival, it has been reported that less than one-third of patients with coronary artery disease are on β -blockers, as was noted in the present study.¹⁷ In our study, patients on β -blockers before the intervention had lower mortality compared with patients not on β -blockers. This beneficial effect of β -blockers did not seem to be mediated by the prevention of CK-MB elevation, because a statistically significant benefit was observed only in patients with normal CK-MB values. More likely, this benefit represents a secondary prevention of cardiac events, especially sudden death, in patients with coronary artery disease who received β -blockers; a beneficial trend on mortality was observed in patient subgroups with or without prior MI or hypertension.

A recent analysis of the cooperative cardiovascular project by Gottlieb et al¹⁸ also showed a reduction in mortality at 2 years after coronary intervention in high-risk patients after MI who were prescribed β -blockers versus those not on β -blockers (9.2% versus 15.2%; 95% confidence interval, 0.57 to 0.63). To our knowledge, this intriguing observation of a cardioprotective effect of β -blockers by reducing CK-MB elevation after coronary intervention and an improvement in intermediate-term survival is reported here for the first time. On the basis of these preliminary observations, a randomized trial of metoprolol versus placebo before intervention in patients not on β -blockers at the time of the procedure is being formulated.

Study Limitations

This was a prospective observational but not randomized study. Two sets of CK-MB values (6 to 8 and 16 to 24 hours) after intervention were routinely measured, and it is possible that in some cases, CK-MB might be elevated after 24 hours of intervention. Some patients on β -blocker therapy might not have taken β -blockers on the day of procedure; however, they were nevertheless included in the intention-to-treat analysis. Also, if patients were started on β -blockers during or after the intervention, they were included in the no β -blocker group. The present study did not evaluate the effect of different types of β -blockers, although metoprolol was the most common (76%). Cardiac troponins (I or T), which are more sensitive markers of myocardial necrosis, were not measured in the present study because the assay was not available at our center at the time of the study.¹⁹

In conclusion, this observational study suggests that β -blocker therapy has a cardioprotective effect when the drugs are administered before coronary intervention. β -blockers given in this way seem to limit CK-MB elevation and improve intermediate-term survival after various coronary interventions. A randomized trial of β -blocker administration before intervention is warranted to confirm this apparent beneficial effect.

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