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## EFFECT OF BETA-BLOCKADE ON MORTALITY AMONG HIGH-RISK AND LOW-RISK PATIENTS AFTER MYOCARDIAL INFARCTION

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### ABSTRACT

**Background** Long-term administration of beta-adrenergic blockers to patients after myocardial infarction improves survival. However, physicians are reluctant to administer beta-blockers to many patients, such as older patients and those with chronic pulmonary disease, left ventricular dysfunction, or non-Q-wave myocardial infarction.

**Methods** The medical records of 201,752 patients with myocardial infarction were abstracted by the Cooperative Cardiovascular Project, which was sponsored by the Health Care Financing Administration. Using a Cox proportional-hazards model that accounted for multiple factors that might influence survival, we compared mortality among patients treated with beta-blockers with mortality among untreated patients during the two years after myocardial infarction.

**Results** A total of 34 percent of the patients received beta-blockers. The percentage was lower among the very elderly, blacks, and patients with the lowest ejection fractions, heart failure, chronic obstructive pulmonary disease, elevated serum creatinine concentrations, or type 1 diabetes mellitus. Nevertheless, mortality was lower in every subgroup of patients treated with beta-blockade than in untreated patients. In patients with myocardial infarction and no other complications, treatment with beta-blockers was associated with a 40 percent reduction in mortality. Mortality was also reduced by 40 percent in patients with non-Q-wave infarction and those with chronic obstructive pulmonary disease. Blacks, patients 80 years old or older, and those with a left ventricular ejection fraction below 20 percent, serum creatinine concentration greater than 1.4 mg per deciliter (124  $\mu$ mol per liter), or diabetes mellitus had a lower percentage reduction in mortality. Given, however, the higher mortality rates in these subgroups, the absolute reduction in mortality was similar to or greater than that among patients with no specific risk factors.

**Conclusions** After myocardial infarction, patients with conditions that are often considered contraindications to beta-blockade (such as heart failure, pulmonary disease, and older age) and those with nontransmural infarction benefit from beta-blocker therapy. (N Engl J Med 1998;339:489-97.)

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SEVERAL large trials have demonstrated that the long-term administration of beta-adrenergic blockers to patients after myocardial infarction improves survival.<sup>1-3</sup> Although the percentage of such patients receiving beta-blockade has recently increased, physicians still reportedly prescribe beta-blockers for less than one third,<sup>4</sup> and cardiologists for less than half,<sup>5</sup> of patients with myocardial infarction. Older age, impaired left ventricular function, transient heart failure, and the use of diuretic drugs predict lack of use of these drugs.<sup>6</sup> This suggests that physicians are concerned that beta-blockers may be contraindicated in a substantial proportion of patients.

The Cooperative Cardiovascular Project, a program to evaluate the care of Medicare patients with a diagnosis of myocardial infarction, provides the opportunity to evaluate the relation between treatment and outcome in unselected patients, most of whom are over 65 years of age. With more than 200,000 charts abstracted, this data base gives investigators the power to evaluate the effect of interventions in situations rarely studied before. Moreover, this data base provides information on unselected patients with conditions that often keep them out of randomized, controlled trials.

We sought to use the Cooperative Cardiovascular Project data to determine which patients benefit from the use of beta-blockers. We compared the mortality rates of patients in high- and low-risk subgroups who were treated with beta-blockers with the rates among those not given those drugs. Correcting to the extent possible for differences between the groups, we evaluated the effects of beta-blockers in patients with presumed contraindications to their use, such as old-

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er age, low ejection fraction, chronic obstructive pulmonary disease, diabetes mellitus, low blood pressure, and low heart rate. In addition, the data base provided the opportunity to look at beta-blockade in the setting of contemporary medical practice.

## METHODS

The Cooperative Cardiovascular Project data base includes all acute care hospital claims for patients with a principal diagnosis of acute myocardial infarction that were submitted to the Health Care Financing Administration for Medicare payment. A diagnosis of acute myocardial infarction was defined according to the coding system of the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM), as code 410, with those with a fifth digit of 2 (for episode of care), those reported by nonacute care hospitals, and those with missing medical-record numbers excluded. The national sample consisted of all discharges involving cases of acute myocardial infarction during an eight-month period, with data from the various states collected so that most discharges fell between February 1994 and July 1995.

The total number of discharges in the national sample was 201,752. The abstraction was performed by trained medical abstractors using uniform criteria to define each data item. They had access to all original hospital records. Extensive quality-control measures were applied to validate the reliability and accuracy of the abstracts. Finally, extensive checks were run against the computerized abstracts to ensure internal consistency and to enforce common data standards.<sup>7</sup>

The data were nearly complete. Serum creatinine concentrations were missing for 9575 patients, and most other data were missing for even fewer patients. The ejection fraction was obtained or documented in 134,238 patients. Patients for whom the ejection fraction was missing were analyzed as a separate subgroup. To avoid eliminating the few patients who had other missing data from the analyses, we combined patients with missing data into the largest group for all variables other than the one being analyzed.

Whenever possible, the data reflect the values obtained on admission to the hospital. The Health Care Financing Administration's survival data were based on Social Security records and were complete, with accuracy of 98 to 99 percent, at 60 days.

In this study, the Cooperative Cardiovascular Project data were used to address the question of who benefits from beta-blocker therapy. Initially, the patients prescribed and not prescribed beta-blocker therapy were compared with regard to a number of demographic and clinical variables. Patients for whom any beta-blocker at any dose had been prescribed at the time of discharge were classified as having received a beta-blocker. The means and standard deviations of continuous variables were compared. Both continuous (in categories) and discrete variables were compared with contingency-table analyses.

Comparison of mortality rates between patients receiving and those not receiving beta-blocker therapy was based on a time-to-event analysis. The Cox proportional-hazards model was used for this purpose, because it permitted estimated survival time to be controlled for differences in follow-up time and differences in covariates that might affect survival, including both confounding variables and effect modifiers. The proportional-hazards assumption was initially checked with Kaplan-Meier analyses and was found to be adequately met. Only 8464 of the total of 201,752 patients were not followed for 24 months.

Because of the size of the data set, emphasis was placed on the magnitude rather than the statistical significance of differences between groups. We recognized that very small differences could (and did) achieve statistical significance.

## RESULTS

Thirty-four percent of the patients received beta-blockers (Table 1). The percentage was lower among

the very elderly, blacks, and those patients considered the sickest according to their Acute Physiology and Chronic Health Evaluation (APACHE II)<sup>8</sup> and Killip<sup>9</sup> scores. Similarly, patients with the lowest ejection fractions, heart failure, chronic obstructive pulmonary disease, elevated serum creatinine concentrations, or type 1 diabetes mellitus were less likely to be treated with beta-blockade. Conversely, patients who had been given more aggressive treatment, including thrombolysis and angioplasty, but not bypass surgery, were more likely to be receiving beta-blockers.

As a result of these prescribing practices, patients receiving beta-blockers tended to have fewer risk factors for mortality than those not receiving beta-blockers. They were younger (mean [ $\pm$ SD] age,  $73.3 \pm 8.8$  vs.  $74.5 \pm 9.0$  years) and had lower (i.e., more favorable) APACHE II scores ( $7.9 \pm 3.4$  vs.  $9.0 \pm 4.4$ ) and lower Killip scores. Their hospital stay was shorter ( $7.2 \pm 5.1$  vs.  $7.8 \pm 7.5$  days), and their physiologic condition, as indicated by the serum creatinine concentration ( $1.3 \pm 1.0$  vs.  $1.4 \pm 1.1$  mg per deciliter [ $115 \pm 88$  vs.  $124 \pm 97$   $\mu$ mol per liter]) and left ventricular ejection fraction ( $47 \pm 13$  percent vs.  $44 \pm 14$  percent), was better. They had fewer coexisting diseases, including chronic obstructive pulmonary disease, diabetes, and congestive heart failure. Finally, they were more likely to be given thrombolytic and reperfusion therapy. The only exceptions to the favorable profile among those prescribed beta-blockers were the slightly higher proportions of patients with hypertension and of men in this group.

Because of the better risk-factor profile among those treated with beta-blockers, it was necessary to hold each risk factor constant when comparing mortality among those treated and those not treated with beta-blockers. Each of the subsequent analyses took direct account of or held constant the following factors: age; race or ethnic group; sex; APACHE II score; length of hospital stay; Killip score; physiologic condition at admission, as reflected by the systolic blood pressure, pulse rate, and serum creatinine concentration; left ventricular ejection fraction; presence or absence of coexisting diseases, including diabetes, congestive heart failure, chronic obstructive pulmonary disease, and asthma; type of myocardial infarction (anterior, inferior, or non-Q-wave); history of myocardial infarction, revascularization, or heart failure; and treatment, including aspirin, angiotensin-converting-enzyme inhibitors, calcium-channel blockers, heparin, thrombolytic agents, coronary angioplasty, and bypass surgery.

Table 2 shows the 24-month adjusted risks and relative risks of death among patients prescribed beta-blockers and those not prescribed the drugs. After demographic and physiologic measures and coexisting diseases were accounted for, patients treated with beta-blockade had substantially lower

TABLE 1. CHARACTERISTICS OF PATIENTS WHO RECEIVED OR DID NOT RECEIVE BETA-BLOCKERS AT HOSPITAL DISCHARGE.\*

CHARACTERISTIC	No. OF PATIENTS	No BETA-BLOCKER		CHARACTERISTIC	No. OF PATIENTS	No BETA-BLOCKER	
		BETA-BLOCKER	no. (%)			BETA-BLOCKER	no. (%)
Total	201,752	69,153 (34.3)	132,599 (65.7)	Serum creatinine			
Age				<1.2 mg/dl	119,557	44,094 (36.9)	75,463 (63.1)
<75 yr	106,496	39,312 (36.9)	67,184 (63.1)	1.2–1.4 mg/dl	27,464	8,979 (32.7)	18,485 (67.3)
75–84 yr	71,426	23,467 (32.9)	47,959 (67.1)	1.5–1.9 mg/dl	27,026	7,866 (29.1)	19,160 (70.9)
≥85 yr	23,830	6,374 (26.7)	17,456 (73.3)	≥2.0 mg/dl	18,129	4,691 (25.9)	13,438 (74.1)
Sex				Heart rate			
Male	109,193	38,236 (35.0)	70,957 (65.0)	<60/min	17,788	6,397 (36.0)	11,391 (64.0)
Female	92,559	30,917 (33.4)	61,642 (66.6)	60–79/min	67,651	26,970 (39.9)	40,681 (60.1)
Race or ethnic group				80–99/min	65,343	22,421 (34.3)	42,922 (65.7)
White	180,320	62,531 (34.7)	117,789 (65.3)	100–119/min	31,782	8,898 (28.0)	22,884 (72.0)
Black	13,681	4,394 (32.1)	9,287 (67.9)	≥120/min	18,756	4,350 (23.2)	14,406 (76.8)
Hispanic	5,832	1,660 (28.5)	4,172 (71.5)	Myocardial infarction			
Other	1,919	568 (29.6)	1,351 (70.4)	Q-wave	116,734	40,715 (34.9)	76,019 (65.1)
APACHE II score†				Non-Q-wave	85,018	28,438 (33.4)	56,580 (66.6)
<8	95,698	37,517 (39.2)	58,181 (60.8)	COPD	41,814	9,228 (22.1)	32,586 (77.9)
8–10.9	61,402	21,150 (34.4)	40,252 (65.6)	Asthma	3,819	676 (17.7)	3,143 (82.3)
11–12.9	18,023	5,074 (28.2)	12,949 (71.8)	Diabetes mellitus			
≥13	26,629	5,412 (20.3)	21,217 (79.7)	Receiving insulin	21,578	6,115 (28.3)	15,463 (71.7)
Highest Killip score†				Not receiving insulin	37,867	12,521 (33.1)	25,346 (66.9)
1 or 2	113,151	46,547 (41.1)	66,604 (58.9)	No diabetes	139,150	49,477 (35.6)	89,673 (64.4)
3	82,346	21,336 (25.9)	61,010 (74.1)	Prior CHF	39,838	8,633 (21.7)	31,205 (78.3)
4	6,255	1,270 (20.3)	4,985 (79.7)	Prior myocardial infarction	63,142	21,046 (33.3)	42,096 (66.7)
Left ventricular ejection fraction				Prior CABG	26,872	9,735 (36.2)	17,137 (63.8)
<20%	2,812	412 (14.7)	2,400 (85.3)	Prior PTCA	16,532	6,216 (37.6)	10,316 (62.4)
20–29%	13,284	2,975 (22.4)	10,309 (77.6)	Treatment during current hospitalization			
30–39%	23,968	7,595 (31.7)	16,373 (68.3)	CABG	18,947	5,946 (31.4)	13,001 (68.6)
40–49%	33,860	13,350 (39.4)	20,510 (60.6)	PTCA	31,576	14,365 (45.5)	17,211 (54.5)
≥50%	60,314	24,787 (41.1)	35,527 (58.9)	Thrombolytic agents	29,642	11,755 (39.7)	17,887 (60.3)
Missing data	67,514	20,034 (29.7)	47,480 (70.3)	ACE inhibitors	60,382	19,619 (32.5)	40,763 (67.5)
Systolic blood pressure				Calcium-channel blockers	65,609	20,206 (30.8)	45,403 (69.2)
<100 mm Hg	10,457	2,679 (25.6)	7,778 (74.4)	Aspirin	166,650	61,953 (37.2)	104,697 (62.8)
100–119 mm Hg	29,910	9,512 (31.8)	20,398 (68.2)				
120–139 mm Hg	48,950	16,838 (34.4)	32,112 (65.6)				
≥140 mm Hg	111,926	40,000 (35.7)	71,926 (64.3)				

\*APACHE denotes Acute Physiology and Chronic Health Evaluation, COPD chronic obstructive pulmonary disease, CHF congestive heart failure, CABG coronary-artery bypass graft, PTCA percutaneous transluminal coronary angioplasty, and ACE angiotensin-converting-enzyme. To convert values for creatinine to micromoles per liter, multiply by 88.4.

†Lower scores denote less severe illness.

mortality in every subgroup. Among patients with myocardial infarction and no other complications, treatment with beta-blockers was associated with a 40 percent reduction in mortality during the follow-up period. Mortality was also reduced by 40 percent among patients with non-Q-wave infarction (Fig. 1) and patients with chronic obstructive pulmonary disease (Fig. 2). However, the reduction in mortality among those treated with beta-blockers was smaller among black patients (28 percent). Older patients (Fig. 3) and those with a left ventricular ejection fraction below 20 percent (Fig. 4), a serum creatinine concentration higher than 1.4 mg per deciliter, or diabetes mellitus also had a smaller percentage reduction in mortality. However, because of the higher mortality rates in these subgroups, the use of beta-blockers actually resulted in an absolute reduction in mortality similar to or greater than that in patients with no specific risk factors.

## DISCUSSION

Patients who received beta-blockers had a 40 percent lower mortality rate than those who did not have beta-blockers prescribed at the time of discharge from the hospital. This reduction was even greater than the 22 percent reduction found in a meta-analysis of 23 trials.<sup>10</sup> Furthermore, all subgroups of patients had similar reductions in mortality in the present study.

Nonetheless, only 34 percent of patients were discharged with a prescription for beta-blockers. Low-risk patients were more likely to be treated with beta-blockade, but nevertheless only 41 percent of patients with normal ejection fractions received beta-blockers. This finding is consistent with the results of previous studies that have shown low rates of use of beta blockers for young, “ideal” candidates.<sup>5</sup> The most severely ill patients were even less likely to receive beta-blockers. If one assumes a mean reduction of 9.5 deaths per 100 patients with myocardial

**TABLE 2.** ADJUSTED RISK AND RELATIVE RISK OF DEATH AMONG PATIENTS WHO RECEIVED OR DID NOT RECEIVE BETA-BLOCKERS AT HOSPITAL DISCHARGE.\*

CHARACTERISTIC	RISK OF DEATH AT 2 Yr			RELATIVE RISK (95% CI)
	RECEIVING BETA-BLOCKER	NOT RECEIVING BETA-BLOCKER	DIFFERENCE IN RISK†	
	percent			
Patient without complications‡	14.4	23.9	-9.5	0.60 (0.57-0.63)
Age (yr)				
<70 yr	11.3	18.7	-7.4	0.60 (0.57-0.63)
70-79 yr	15.3	24.0	-8.7	0.64 (0.58-0.70)
≥80 yr	22.6	33.1	-10.5	0.68 (0.63-0.75)
Black race	16.5	23.0	-6.4	0.72 (0.66-0.79)
Prior COPD	16.8	27.8	-11.1	0.60 (0.57-0.63)
Asthma	11.9	19.7	-7.8	0.60 (0.57-0.63)
Diabetes mellitus	17.0	26.6	-9.6	0.64 (0.60-0.69)
Q-wave MI	14.2	23.6	-9.4	0.60 (0.57-0.63)
Non-Q-wave MI	14.4	23.9	-9.5	0.60 (0.57-0.63)
Prior CHF	17.4	28.9	-11.5	0.60 (0.57-0.63)
Prior MI	16.8	25.1	-8.4	0.67 (0.62-0.72)
Systolic blood pressure				
<100 mm Hg	16.9	28.1	-11.2	0.60 (0.57-0.63)
100-139 mm Hg	10.4	17.2	-6.8	0.60 (0.57-0.63)
≥140 mm Hg	9.8	14.8	-5.0	0.66 (0.61-0.71)
Ejection fraction				
<20%	23.5	34.5	-11.0	0.68 (0.58-0.80)
20-49%	15.3	25.4	-10.1	0.60 (0.57-0.63)
≥50%	11.6	19.3	-7.7	0.60 (0.57-0.63)
Missing data	12.3	20.4	-8.1	0.60 (0.57-0.63)
Serum creatinine				
<0.8 mg/dl	12.9	21.4	-8.5	0.60 (0.57-0.63)
0.8-1.4 mg/dl	13.9	23.1	-9.2	0.60 (0.57-0.63)
>1.4 mg/dl	19.4	29.9	-10.5	0.65 (0.61-0.69)
Heart rate				
<70/min	13.1	21.7	-8.6	0.60 (0.57-0.63)
70-99/min	14.9	24.8	-9.9	0.60 (0.57-0.63)
≥100/min	16.9	26.2	-9.3	0.65 (0.60-0.69)
Treatment during current hospitalization				
CABG	6.1	10.2	-4.0	0.60 (0.57-0.63)
PTCA	9.2	15.2	-6.0	0.60 (0.57-0.63)
Thrombolytic agents	11.8	19.6	-7.8	0.60 (0.57-0.63)
Calcium-channel blockers	16.4	23.6	-7.1	0.70 (0.65-0.75)
ACE inhibitors	14.4	23.9	-9.5	0.60 (0.57-0.63)
Aspirin	13.8	22.9	-9.1	0.60 (0.57-0.63)

\*CI denotes confidence interval, COPD chronic obstructive pulmonary disease, MI myocardial infarction, CHF congestive heart failure, CABG coronary-artery bypass graft, PTCA percutaneous transluminal coronary angioplasty, and ACE angiotensin-converting-enzyme. To convert values for creatinine to micromoles per liter, multiply by 88.4.

†Because of rounding, the difference in risk does not always equal the difference between the risks shown for patients receiving a beta-blocker and those not receiving a beta-blocker.

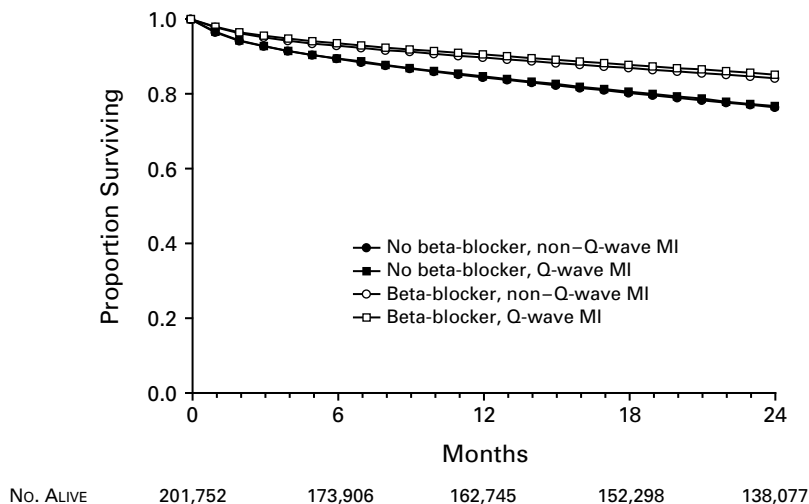
‡For patients without complications, all risk factors were set at the Cooperative Cardiovascular Project population means, with none of the factors that alter the effect of beta-blockers.

infarction in 24 months, more than 19,000 patients could have been kept alive had beta-blockers been more widely prescribed.

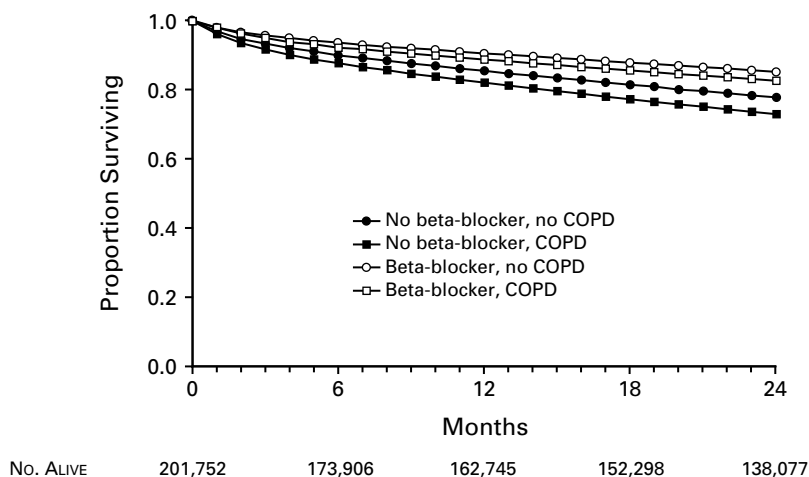
**Non-Q-Wave Infarction**

The relative risk of death in patients with non-Q-wave infarction who were prescribed beta-blockers was markedly decreased. This is important, because the use of beta-blockers in such patients has been questioned since the  $\beta$ -Blocker Heart Attack Trial found no improvement in survival among pa-

tients with nontransmural infarction who were given beta-blockers.<sup>11</sup> However, this study was a subgroup analysis performed at a time when the treatment of non-Q-wave infarction was substantially different from present practice. Indeed, the American College of Cardiology and American Heart Association joint guidelines for the management of acute myocardial infarction classify the evidence for the use of beta-blockade in this subgroup as conflicting and possibly unfavorable.<sup>12</sup> The overwhelming evidence from our study, however, suggests that beta-blockade should



**Figure 1.** Adjusted Probability of Survival among Patients with Q-Wave and Non-Q-Wave Myocardial Infarction (MI) Who Received or Did Not Receive Beta-Blockers. The patients with Q-wave infarction and those with non-Q-wave infarction had similar benefit with beta-blockade.



**Figure 2.** Adjusted Probability of Survival among Patients with or without a History of Chronic Obstructive Pulmonary Disease (COPD) Who Received or Did Not Receive Beta-Blockers. Patients with chronic obstructive pulmonary disease had a larger absolute benefit with beta-blockade.

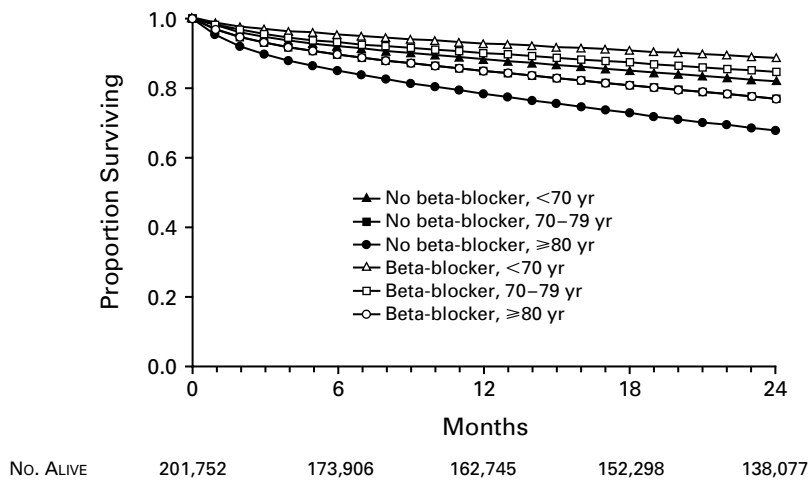
be part of the treatment of patients with non-Q-wave infarction.

**Older Age**

The present study demonstrates that older patients have a greater absolute benefit when treated with beta-blockade. Indeed, even among those 80 years of age or older, mortality was 32 percent lower when beta-blockers were prescribed. It is thus unfortunate that the elderly often receive less treatment after a myocardial infarction than younger patients.<sup>13</sup> The present study found that only 27 percent of those over 84 years of age received beta-blockers. In

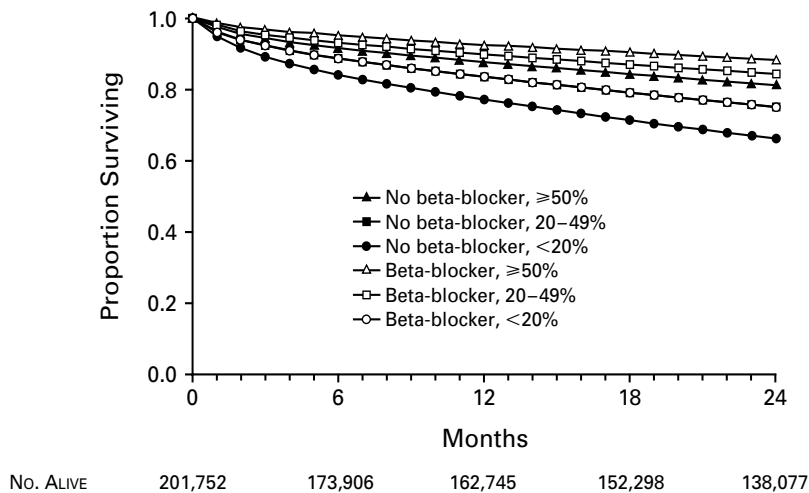
a previous study of elderly patients admitted to a nursing home with evidence of a prior myocardial infarction, only 8 percent were receiving beta-blockade. Interestingly, in that study 37 percent of the patients were receiving calcium-channel blockers, which have not been shown to improve survival and may actually increase mortality.<sup>14</sup>

There are few studies of older patients, which might explain the reluctance on the part of many physicians to use these agents. Previous studies, even of elderly patients, have generally limited analysis to patients less than 69 or 75 years of age.<sup>15</sup> Nevertheless, the results of our study are consistent with those



**Figure 3.** Adjusted Probability of Survival According to Age among Patients Who Received or Did Not Receive Beta-Blockers.

The oldest patients had a smaller relative benefit (32 percent reduction in the risk of death) but a larger absolute benefit than younger patients. The curve for the patients not receiving beta-blockers who were 70 to 79 years old overlaps that for the patients receiving beta-blockers who were  $\geq 80$  years old.



**Figure 4.** Adjusted Probability of Survival According to Left Ventricular Ejection Fraction among Patients Who Received or Did Not Receive Beta-Blockers.

Patients with ejection fractions under 20 percent had a smaller relative benefit but a larger absolute benefit than patients with normal ejection fractions. The curve for the patients not receiving beta-blockers who had left ejection fractions of 20 through 49 percent overlaps that for the patients receiving beta-blockers who had left ejection fractions below 20 percent.

of an analysis of 5332 Medicare patients without relative contraindications to beta-blockade.<sup>16</sup>

**Diabetes Mellitus**

Diabetic patients treated with beta-blockers had a 36 percent reduction in mortality. The present study supports previous work demonstrating that patients with diabetes have a worse outcome after myocardial infarction than those without diabetes.<sup>17,18</sup> However, physicians have been reluctant to treat diabetic pa-

tients with beta-blockers because of the risk of worsening the diabetes or of masking hypoglycemic symptoms. Although it is true that blood glucose concentrations may increase with the use of some beta-blockers,<sup>19</sup> our study confirms previous studies that have documented the benefit of beta-blockade in patients with diabetes mellitus.<sup>20,21</sup> Because of the high mortality rate among diabetic patients after myocardial infarction, the absolute survival benefit is particularly large in this group of patients.

### Pulmonary Disease

Patients with a history of chronic obstructive pulmonary disease had a high mortality rate but had a risk reduction of 40 percent with beta-blockade. Even patients with a history of asthma had lower mortality with beta-blockers, although these might be the patients under observation who tolerated the drug.

Many physicians withhold beta-blockers from patients with pulmonary disease because of concern about bronchoconstriction. It is true that beta-blockers cause bronchoconstriction in patients with asthma,<sup>22</sup> and bronchial hyperresponsiveness has even been reported in patients with chronic obstructive pulmonary disease.<sup>23</sup> Indeed, such patients have generally not been evaluated in studies of beta-blockers because of concern about bronchial hyperresponsiveness. However, the stimuli to hyperresponsiveness in patients with chronic obstructive pulmonary disease may be different from those in patients with asthma, and beta-blockade may not cause bronchoconstriction in patients with chronic obstructive pulmonary disease.<sup>23</sup> This may be the reason that in a study of 50 patients with chronic obstructive pulmonary disease who were given esmolol, there was no change in pulmonary function.<sup>24</sup>

It appears clear that beta-blockers should be tried in patients with chronic obstructive pulmonary disease who have had myocardial infarction. It may be necessary in a very few patients to discontinue the drug because of bronchoconstriction, but the potential benefit appears large enough to warrant this small risk. We did not compare  $\beta_1$ -selective and non-selective drugs. It is possible that they may have different effects on mortality because  $\beta_1$ -selective drugs have less pulmonary effect.<sup>25</sup>

### Congestive Heart Failure

Whether beta-blockers should be given to patients with both congestive heart failure and myocardial infarction remains controversial. Despite initial concern that the negative inotropic effects of beta-blockade would be detrimental in patients with heart failure, recent studies have suggested that the long-term effects of beta-blockade are beneficial.<sup>26-28</sup> However, patients with ischemic cardiomyopathy may not fare as well,<sup>29</sup> and many studies of heart failure have evaluated patients with nonischemic cardiomyopathy.

There are no randomized studies evaluating the effects of beta-blockers in patients with recent myocardial infarction and poor cardiac function. In one retrospective analysis, propranolol was effective in patients with a history of congestive heart failure,<sup>30</sup> but the sickest patients have traditionally been excluded from studies.

The present analysis suggests that patients with the poorest cardiac function benefit as much as patients with better function. Patients with congestive heart failure had a 40 percent reduction in mortality

when they received beta-blockers. The relative risk of death decreased by 40 percent in patients with an ejection fraction between 20 percent and 49 percent and by 32 percent in patients with an ejection fraction below 20 percent. However, since patients with the lowest ejection fractions have the highest mortality rate, the absolute benefit for these patients is actually greater than for those with higher ejection fractions. The estimates of ejection fraction are obtained by various methods and should not be considered precise. They do show, however, that patients can benefit from beta-blockade regardless of their ejection fraction.

### Low-Risk Patients

The risks of a drug could conceivably be greater than the benefits in relatively healthy patients. Indeed, the recommendations of the American Heart Association for the treatment of myocardial infarction state that "there is continued debate about whether low-risk subjects . . . should be treated with  $\beta$ -adrenoceptor blockers because their long-term prognosis is extremely favorable irrespective of such therapy."<sup>12</sup> In the present study, however, the lowest-risk subgroups had a decrease in mortality of 40 percent with beta-blockade. These subgroups included patients with normal ejection fractions, patients with low serum creatinine concentrations, and those who had undergone revascularization or thrombolysis.

Randomized studies of beta-blocker therapy were performed in the prethrombolytic era, raising the question of whether beta-blockers are beneficial in patients who have undergone reperfusion.<sup>31</sup> Previous smaller analyses of patients receiving thrombolytic agents have not clearly shown a long-term effect on mortality. For example, immediate use of beta-blockers did not improve long-term survival in the II-B substudy of the Thrombolysis in Myocardial Infarction trial.<sup>32</sup> We found a decrease in mortality of 40 percent with the use of beta-blockers in this low-risk subgroup.

Because of their lower mortality rates, the absolute benefit is not as great in members of low-risk subgroups, but beta-blockers substantially improved survival in these patients. The question posed by the American College of Cardiology and American Heart Association guidelines for the treatment of patients with acute myocardial infarction appears to have been answered, at least with respect to the predominantly elderly patients analyzed in the present study.

### Race

Black patients with hypertension do not respond as well as whites to treatment with beta-adrenergic blockers.<sup>33,34</sup> The reasons are unknown, but they may be related to differences in beta-adrenoceptor sensitivity.<sup>35</sup> This difference has aroused concern

that blacks may not benefit from beta-blockade after myocardial infarction. In contrast to the  $\beta$ -Blocker Heart Attack Trial, which found similar benefits in whites and blacks,<sup>36</sup> the benefit in blacks appeared to be lower in the present study. This could be due to differences in the sympathetic nervous system, differences in the use of the drugs, or other factors. Nevertheless, it should be noted that both blacks and whites had decreased mortality rates when given beta-blockers.

### Limitations

Our study was not a randomized, controlled trial, and its conclusions must be viewed with important reservations. We could not control for characteristics that may influence a physician's decision to prescribe beta-blockers or the patient's decision to comply with a physician's choice of therapy. It is possible that patients who received beta-blockers were healthier than patients who did not or that they differed in some other way that caused them to have lower mortality. They could have had better physicians or have received different medications after discharge. Nevertheless, we attempted to control for or study the interactive effects of most of the known risk factors.

It is also possible that there were a substantial number of crossovers between the groups. The data reflect beta-blocker use at hospital discharge; some patients may have started treatment later, and some may have discontinued it. Such an effect, however, would be expected to decrease the power of the study.

The consistency among groups suggests that the results of the present analysis reflect the benefit of the intervention. The present analysis also confirms previous studies, but it extends the evidence of the benefit of beta-blockade to groups not previously evaluated. In contrast to other studies, however, our analysis of a large number of patients did not exclude patients at highest risk.

This analysis strongly indicates that beta-blockade is an underused therapy for patients who have had a myocardial infarction. Despite a decrease in mortality of between 28 and 40 percent, patients in many subgroups are not being prescribed these drugs. In addition to otherwise healthy patients, those with nontransmural infarction, heart failure, pulmonary disease, and older age are likely to benefit when given beta-blockers after a myocardial infarction.

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