

A TRIAL OF THE BETA-BLOCKER BUCINDOLOL IN PATIENTS WITH ADVANCED CHRONIC HEART FAILURE

THE BETA-BLOCKER EVALUATION OF SURVIVAL TRIAL INVESTIGATORS*

ABSTRACT

Background Although beta-adrenergic-receptor antagonists reduce morbidity and mortality in patients with mild-to-moderate chronic heart failure, their effect on survival in patients with more advanced heart failure is unknown.

Methods A total of 2708 patients with heart failure designated as New York Heart Association (NYHA) functional class III (in 92 percent of the patients) or IV (in 8 percent) and a left ventricular ejection fraction of 35 percent or lower were randomly assigned to double-blind treatment with either bucindolol (1354 patients) or placebo (1354 patients) and followed for the primary end point of death from any cause.

Results The data and safety monitoring board recommended stopping the trial after the seventh interim analysis. At that time, there was no significant difference in mortality between the two groups (unadjusted $P=0.16$). The results presented here are based on complete follow-up at the time of study termination (average, 2.0 years). There were a total of 449 deaths in the placebo group (33 percent) and 411 deaths in the bucindolol group (30 percent, adjusted $P=0.13$). The risk of the secondary end point of death from cardiovascular causes was lower in the bucindolol group (hazard ratio, 0.86; 95 percent confidence interval, 0.74 to 0.99), as was the risk of heart transplantation or death. In a subgroup analysis, there was a survival benefit in nonblack patients.

Conclusions In a demographically diverse group of patients with NYHA class III and IV heart failure, bucindolol resulted in no significant overall survival benefit. (N Engl J Med 2001;344:1659-67.)

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BETA-BLOCKERS have emerged as an important treatment for chronic heart failure. Two recently completed trials, the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure¹ and the Cardiac Insufficiency Bisoprolol Study II,² demonstrated statistically significant and clinically relevant decreases in the rates of hospitalization and death with beta-adrenergic-receptor antagonists in patients with New York Heart Association (NYHA) class II, III, or IV heart failure. However, mortality in the placebo group in these trials was only 11 to 13 percent annually, suggesting that the proportion of high-risk, severely ill patients was low. Furthermore, both studies were performed in largely white European populations.

In heart failure, cardiac adrenergic drive and sys-

temic adrenergic drive are activated in proportion to the severity of symptoms and are strongly prognostic for outcome.³⁻⁶ Since beta-adrenergic-blocking agents initially depress myocardial function⁷ and may worsen symptoms with initial dosing and upward titration,⁸ it is not known whether these agents would be tolerated or whether they would improve survival among patients with advanced heart failure who are more dependent on beta-adrenergic support. In addition, it is important to explore the effect of beta-blockade in racial and other demographic groups that have not been studied extensively in previous trials.^{1,2} Blacks represent a substantial proportion of the patients with heart failure in the United States and have a higher rate of death from heart failure than non-blacks.^{9,10} The Beta-Blocker Evaluation of Survival Trial (BEST)⁸ was designed to determine whether bucindolol hydrochloride (Bextra, Incara Pharmaceuticals, Research Triangle Park, N.C.), a nonselective beta-adrenergic blocker and mild vasodilator, would reduce the rate of death from any cause among patients with advanced heart failure and to assess its effect in various subgroups defined by ethnic background and demographic criteria — specifically women and members of minority groups.

METHODS**Study Subjects**

The design of the trial has been described previously.¹¹ All patients had NYHA class III or IV heart failure that was due to primary or secondary dilated cardiomyopathy, as well as a left ventricular ejection fraction of 35 percent or lower. All patients were required to have received optimal medical therapy, including the use of angiotensin-converting-enzyme inhibitors (if tolerated), for at least one month. Before the publication of the results of the Digitalis Investigation Group trial,¹² digoxin therapy was required, but thereafter its use became discretionary. The racial and ethnic classification of the patients was self-reported. All patients were 18 years old or older and gave written informed consent. The protocol was approved by the institutional review board of each participating site.

Patients were excluded if they had a reversible cause of heart failure, uncorrected primary valvular disease, untreated thyroid disease, obstructive or hypertrophic cardiomyopathy, pericardial disease, amyloidosis, active myocarditis, a malfunctioning artificial heart valve, or a history of myocardial infarction within the previous six months. Patients were also excluded if they were candidates for

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*The study investigators are listed in the Appendix.

TABLE 1. BASE-LINE CLINICAL CHARACTERISTICS OF THE PATIENTS ACCORDING TO TREATMENT GROUP.*

CHARACTERISTIC	PLACEBO GROUP (N=1354)	BUCINDOLOL GROUP (N=1354)
Age — yr		
Mean	60±12.3	60±12.6
Range	19–90	21–93
Age group — no. of patients (%)		
≤59 yr	598 (44)	600 (44)
60–68 yr	361 (27)	369 (27)
69–74 yr	245 (18)	213 (16)
≥75 yr	150 (11)	172 (13)
Sex — no. of patients (%)		
Male	1047 (77)	1068 (79)
Female	307 (23)	286 (21)
Weight — lb	186±44.3	185±44.1
Height — in.	68±3.9	68±3.9
Body-mass index†	28±6.1	28±6.0
Duration of chronic heart failure — mo		
Median	37	36
Range	1–336	1–456
Smoking status — no. of patients (%)		
Current smoker	212 (16)	262 (19)‡
Ever smoked	958 (71)	994 (74)
Race or ethnic group — no. of patients (%)		
White, not Hispanic	951 (70)	945 (70)
Black, not Hispanic	305 (23)	322 (24)
Hispanic	79 (6)	64 (5)
Other	19 (1)	23 (2)
NYHA functional class — no. of patients (%)		
III	1242 (92)	1240 (92)
IV	112 (8)	114 (8)

*Plus-minus values are means ±SD. To convert values for weight to kilograms, multiply by 0.45; to convert values for height to meters, multiply by 0.0254. NYHA denotes New York Heart Association, and ACE angiotensin-converting enzyme.

†The body-mass index is defined as the weight in kilograms divided by the square of the height in meters.

‡P<0.05 for the comparison with the placebo group.

§More than one nonischemic cause of heart failure could be listed for each patient.

heart transplantation; if they had undergone a revascularization procedure (a percutaneous transluminal intervention or a coronary-artery bypass procedure) within the previous 60 days; if they had unstable angina (requiring treatment with more than six nitroglycerin tablets per week); if they had a heart rate slower than 50 beats per minute; if they were undergoing treatment with other investigational agents; if they had a life expectancy of less than 3 years; if they had active liver disease (indicated by a total serum bilirubin concentration of 3.0 mg per deciliter [51 μmol per liter] or higher); if they had renal disease (indicated by a serum creatinine level of 3.0 mg per deciliter [265 μmol per liter] or higher); or if they had hematologic, gastrointestinal, immunologic, endocrine, metabolic, or central nervous system disease that could adversely affect the safety or the efficacy of the study drug. Patients with decompensated heart failure (i.e., those with evidence of hypoperfusion, acute pulmonary edema, or hypotension with a systolic blood pressure of less than 80 mm Hg) were excluded, as were active abusers of alcohol (ingesting more than 100 g of ethanol per day) or illicit drugs. Patients were also excluded if they had taken any of the following: calcium-channel-blocking agents (including amlodipine), theophylline, tricyclic antidepressants, monoamine oxidase inhibitors, or beta-agonists within 1 week before the base-line evaluation; beta-adrenergic-blocking agents within 30 days before the base-line evaluation; flecainide, encainide, propafenone, or disopyramide within 2 weeks before randomization; or amiodarone within 8 weeks before the base-line evaluation.

Within 60 days before randomization, patients underwent a

gated radionuclide ventriculographic assessment of the left ventricular ejection fraction; within 14 days before randomization, they underwent electrocardiography, chest radiography for the measurement of the cardiothoracic ratio, and laboratory blood tests including measurement of plasma norepinephrine in a blood sample obtained when the patient was resting in a supine position. Patients were included only if their symptoms were considered to be NYHA class III or IV on the day of randomization after at least seven days of stability.

Randomization

Patients were randomly assigned by a central coordinating center to bucindolol or a matched placebo. Randomization was stratified at each clinical site according to the underlying cause of heart failure (the presence or absence of coronary artery disease), the left ventricular ejection fraction (greater than 20 percent vs. 20 percent or lower), sex, and race (black vs. nonblack) and was balanced for each of these factors by means of an adaptive allocation scheme with a biased coin design.¹³

Treatment and Follow-up

On the day of randomization, patients were given an initial oral dose of 3 mg of the study medication (bucindolol or placebo), which was repeated twice daily for one week. Subsequently, doses were increased (as tolerated) on a weekly basis to 6.25 mg, 12.5 mg, 25 mg, 50 mg, and (for patients who weighed 75 kg or more)

TABLE 1. CONTINUED.

CHARACTERISTIC	PLACEBO GROUP (N=1354)	BUCINDOLOL GROUP (N=1354)
Cause of heart failure — no. of patients (%)		
Ischemic	791 (58)	796 (59)
Nonischemic§	563 (42)	558 (41)
Idiopathic	379 (28)	353 (26)
Hypertension-induced	143 (11)	149 (11)
Alcoholic cardiomyopathy	96 (7)	84 (6)
Viral	38 (3)	45 (3)
Mitral-valve disease	29 (2)	32 (2)
Aortic-valve disease	13 (1)	20 (1)
Familial	25 (2)	22 (2)
Drug-induced	18 (1)	15 (1)
Other	18 (1)	23 (2)
History of related illness — no. of patients (%)		
Hypertension	797 (59)	799 (59)
Hyperlipidemia	575 (42)	595 (44)
Diabetes mellitus	465 (34)	499 (37)
Insulin therapy	196 (14)	202 (15)
Diabetic end-organ disease	164 (12)	149 (11)
Hemodynamics and ventricular function		
Heart rate — beats/min	81±13.1	82±13.4
Blood pressure — mm Hg		
Systolic	117±17.8	117±18.2
Diastolic	71±11.0	71±11.4
Left ventricular ejection fraction — %	23±7.2	23±7.4
Right ventricular ejection fraction — %	35±13.6	35±13.5
Peak filling rate — end-diastolic volume/sec	1.2±0.7	1.2±0.8
Atrial fibrillation — no. of patients (%)	157 (12)	146 (11)
Plasma norepinephrine level — pg/ml		
Median	423	445
Mean	501±316	529±370
Routine medications — no. of patients (%)		
ACE inhibitor	1232 (91)	1238 (91)
Angiotensin-receptor blocker	94 (7)	80 (6)
Digitalis	1248 (92)	1253 (93)
Diuretic	1266 (94)	1271 (94)
Spironolactone	52 (4)	43 (3)
Vasodilator	646 (48)	625 (46)
Antiarrhythmic	28 (2)	45 (3)‡
Anticoagulant	622 (46)	593 (44)
Aspirin	615 (45)	600 (44)
Statin lipid-lowering agents	315 (23)	305 (23)

100 mg orally twice daily. These increases were slowed or stopped and the doses of diuretics and concomitant medications adjusted at the discretion of the investigator on the basis of the patient's response. Patients had follow-up visits at 3, 6, and 12 months after randomization, with regular follow-up visits every 6 months thereafter, for a planned average follow-up of 3 years. Gated radionuclide ventriculographic assessment of the left ventricular ejection fraction, measurement of the plasma norepinephrine concentration, laboratory blood tests, chest radiography, and electrocardiography were repeated 3 and 12 months after randomization.

End Points

The primary end point of the study was death from any cause. Secondary end points included death from cardiovascular causes (defined as death due to pump failure or an ischemic event or sudden death); hospitalization for any reason; hospitalization because of heart failure; a composite of death or heart transplantation; the left ventricular ejection fraction at 3 and 12 months; myocardial infarction; quality of life; and any change in the need for concomitant therapy. The cause of death was adjudicated by a central end-points committee whose members were blinded to the treatment-group assignments. The results with respect to quality

of life, myocardial infarction, and changes in the need for concomitant therapy are not reported here.

Statistical Analysis

We estimated that a sample of 2800 patients would be required for the study to detect a 25 percent reduction in annual mortality (from an estimated 15 percent) with bucindolol therapy with a statistical power of 85 percent with use of the log-rank test and a significance level of 5 percent.^{14,15} The design of the trial called for an enrollment period of 3 years, a minimum follow-up of 18 months, and a maximum follow-up of 4.5 years. The trial was monitored by an independent data and safety monitoring board. The group sequential method of Lan and DeMets,¹⁶⁻¹⁸ with a linear alpha spending function,¹⁶ was used for monitoring the interim data analyses. After the fifth interim analysis, the data and safety monitoring board changed the stopping rule to a nominal 0.05 level, and this rule was used during the sixth and seventh interim analyses.

Continuous variables are reported as means ±SD, and reported P values are for comparisons between treatment groups by the t-test or the Wilcoxon rank-sum test, unless otherwise noted. Categorical variables are reported as proportions, and the reported P values are for comparisons between the treatment groups by

the chi-square or Fisher's exact test. Cumulative survival curves were constructed by means of Kaplan–Meier methods,^{19,20} and differences between the treatment groups were evaluated with the use of the log-rank test. The Cox proportional-hazards regression model was used to examine the effect of treatment in the presence of prespecified covariates.^{21–24} All analyses were conducted in accordance with the intention-to-treat principle.

Because of the change in monitoring boundaries during the trial, it is difficult to calculate an adjusted P value to reflect the eight analyses of the study results. However, to attempt to adjust for the multiple examinations of the data, we used as an adjusted P value the null probability of exceeding one of the seven interim stopping boundaries or, if no interim boundaries were exceeded, of obtaining a final result at least as extreme as the observed result. We report unadjusted estimates and confidence intervals for the primary end point, but we report both the unadjusted and adjusted P values. The reported P values for the secondary study end points have not been formally adjusted for the number of multiple secondary end points, but they have been interpreted in view of the multiple tests conducted. All reported P values are two-sided.

RESULTS

Characteristics of the Patients

Between May 31, 1995, and December 31, 1998, a total of 2708 patients underwent randomization at 90 clinical sites in the United States and Canada. The base-line characteristics of the patients are given in Table 1. No significant differences between groups were observed except for slightly higher rates in the bucindolol group of current smoking and of the use of antiarrhythmic drugs other than amiodarone.

Follow-up

We report data collected through July 26, 1999. On that day, the data and safety monitoring board recommended the early termination of the trial after the seventh interim analysis, citing the “totality of evidence regarding the usefulness of β -blocker treatment derived from BEST and other studies.” The board's recommendation was influenced by information that had been accruing from other studies of beta-blockers in chronic heart failure and by a concern about the equipoise of the trial. At the time of this recommendation, there was no significant difference in mortality between the two treatment groups (unadjusted $P=0.16$). On July 29, 1999, the trial was terminated by the study's sponsors (the National Heart, Lung, and Blood Institute and the Department of Veterans Affairs). The mean duration of follow-up reported to the time the study was terminated was 2.0 years.

A total of eight patients (less than 1 percent) — three in the placebo group and five in the bucindolol group — either withdrew consent or were lost to follow-up. The average degree of compliance with treatment during the trial, as assessed by pill counts, was 81 percent in both groups. For patients who were receiving treatment at the time the study was terminated, the mean dose was 76 mg twice daily for the patients in the bucindolol group and 79 mg twice daily for the patients in the placebo group. During the trial, 25 percent of the patients in the placebo

group and 23 percent of those in the bucindolol group permanently discontinued the study medication ($P=0.16$); the rate of use of open-label beta-blockers differed between the groups (10 percent in the placebo group, as compared with 6 percent in the bucindolol group; $P<0.001$) and was higher than had been anticipated.

Survival

A total of 449 patients in the placebo group (33 percent) died, as did 411 in the bucindolol group (30 percent; hazard ratio, 0.90; 95 percent confidence interval, 0.78 to 1.02; unadjusted $P=0.10$; adjusted $P=0.13$) (Table 2 and Fig. 1) — a nonsignificant trend. This resulted in annual mortality of 17 percent in the placebo group as compared with 15 percent in the bucindolol group.

Secondary End Points

The rate of death from cardiovascular causes was significantly lower with bucindolol ($P=0.04$), and the rates of death due to pump failure and sudden death were somewhat lower; these results are consistent with the overall effect on death from cardiovascular causes (Table 2). Bucindolol significantly reduced the proportion of patients who had to be hospitalized for illnesses related to heart failure, as determined by each local investigator (hazard ratio, 0.78; 95 percent confidence interval, 0.69 to 0.88; $P<0.001$), and there was a nonsignificant difference in favor of bucindolol in the proportion of patients who were hospitalized for any reason (hazard ratio, 0.92; 95 percent confidence interval, 0.84 to 1.01; $P=0.08$). Bucindolol reduced the average number of hospitalizations and the average number of inpatient days per patient. The combined end point of death or heart transplantation during the trial occurred in 32 percent of the patients in the bucindolol group and 35 percent of those in the placebo group (hazard ratio, 0.87; 95 percent confidence interval, 0.77 to 0.99; $P=0.04$). The left ventricular ejection fraction showed greater improvement with bucindolol therapy than with placebo at 3 months (5.5 ± 7.8 ejection-fraction units, vs. 2.1 ± 6.9 in the placebo group; $P<0.001$) and at 12 months (7.3 ± 10.0 ejection-fraction units, vs. 3.3 ± 8.7 in the placebo group; $P<0.001$).

Other Analyses

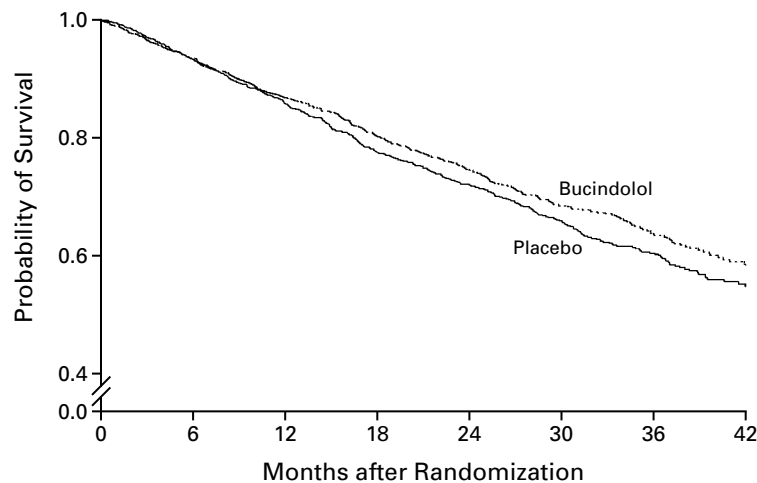
With bucindolol therapy, the heart rate was lowered significantly at 3 months (decrease from base line, 9.4 ± 13.0 beats per minute, vs. a decrease of 1.3 ± 12.9 in the placebo group; $P<0.001$) and at 12 months (a decrease of 8.6 ± 13.9 beats per minute, vs. a decrease of 2.1 ± 13.4 in the placebo group; $P<0.001$), and the plasma norepinephrine levels were reduced at 3 months (decrease from base line, 72 ± 345 pg per milliliter, vs. an increase of 27 ± 300 in the placebo group; $P<0.001$) and at 12 months (a decrease of

TABLE 2. PRIMARY AND SECONDARY END POINTS.*

END POINT	PLACEBO GROUP (N=1354)	BUCINDOLOL GROUP (N=1354)	HAZARD RATIO (95% CI)	P VALUE†
Primary end point				
Death from any cause — no. (%)	449 (33)	411 (30)	0.90 (0.78–1.02)	0.10
Secondary end points				
Death — no. (%)				
Cardiovascular causes	389 (29)	342 (25)	0.86 (0.74–0.99)	0.04
Sudden death	203 (15)	182 (13)	0.88 (0.72–1.07)	0.21
Pump failure	140 (10)	122 (9)	0.85 (0.67–1.08)	0.19
Myocardial infarction	13 (1)	10 (1)	0.75 (0.33–1.72)	0.50
Other	33 (2)	28 (2)	0.83 (0.50–1.37)	0.46
Noncardiovascular causes	42 (3)	51 (4)	1.19 (0.79–1.78)	0.41
Unknown causes	18 (1)	18 (1)	0.97 (0.50–1.86)	0.92
Hospitalization				
Any admission — no. (%)	875 (65)	829 (61)	0.92 (0.84–1.01)	0.08
Admission due to chronic heart failure — no. (%)	569 (42)	476 (35)	0.78 (0.69–0.88)	<0.001
No. of admissions per patient	2.0±2.0	1.8±2.6		0.02
No. of inpatient days per patient	16.3±30.5	13.5±24.0		0.004
Heart transplantation — no. (%)	41 (3)	29 (2)	0.69 (0.43–1.10)	0.12
Death or transplantation — no. (%)	480 (35)	431 (32)	0.87 (0.77–0.99)	0.04

*Plus-minus values are means ±SD. CI denotes confidence interval.

†The reported P values are unadjusted.



NO. AT RISK		0	6	12	18	24	30	36	42
Placebo	1354	1261	1046	822	671	481	294	123	
Bucindolol	1354	1265	1058	855	697	492	304	126	

Figure 1. Survival According to Treatment Group.

There were a total of 860 deaths, 449 in the placebo group and 411 in the bucindolol group (log-rank statistic=1.63; unadjusted P=0.10).

22±300 pg per milliliter, as compared with an increase of 45±309 in the placebo group; P<0.001).

Subgroup Analysis

The hazard ratios and 95 percent confidence intervals for the main effects, as estimated with the Cox

proportional-hazards model, are presented in Figure 2 for the subgroups that were prespecified in the protocol. A nominally significant interaction effect was found only for race (black vs. nonblack) and treatment ($\chi^2=5.06$, P=0.02). With any reasonable adjustment for multiple comparisons, this finding could be ex-

plained as due to chance. The apparent interaction effect for race and treatment reflects the lack of benefit observed in blacks (hazard ratio for death with bucindolol vs. placebo, 1.17; 95 percent confidence interval, 0.89 to 1.53; $P=0.27$), but there was a significant survival benefit in nonblack patients (hazard ratio, 0.82; 95 percent confidence interval, 0.70 to 0.96; $P=0.01$).

We also found a trend toward improved survival with bucindolol among patients with less advanced heart failure: for patients with NYHA class III heart failure, the hazard ratio for death was 0.87 (95 percent confidence interval, 0.75 to 1.01; $P=0.06$); for those with a left ventricular ejection fraction greater than 20 percent, the hazard ratio was 0.83 (95 percent confidence interval, 0.69 to 1.00; $P=0.05$). Similar trends were seen in patients with and without coronary artery disease. Given the small number of patients in our study with NYHA class IV heart failure, firm conclusions cannot be reached about the effect of bucindolol on mortality in this subgroup.

Adverse Events

The incidence of selected adverse events is presented in Table 3. As expected, the incidence of angina, tachycardia, and palpitations was significantly reduced with bucindolol therapy. The incidence of

bradycardia, intermittent claudication, diarrhea, dizziness, and hyperglycemia was increased with bucindolol therapy. The incidence of insomnia and depression was reduced with beta-blockade, and reports of impotence were no more frequent than in the placebo group.

DISCUSSION

We found no significant improvement in overall survival in patients assigned to receive the beta-blocker bucindolol. The rates of the secondary end points of death from cardiovascular causes and hospitalization because of heart failure were significantly reduced by treatment with bucindolol. The reason for the difference between the reduction in mortality in our study and those found in other recently reported trials of beta-blockers^{1,2} is not clear. One possibility is that the patient populations studied were different. This hypothesis is supported by the observation that bucindolol had a beneficial effect on the rate of death in nonblack patients and a nonsignificant benefit in patients with NYHA class III heart failure that was not dissimilar from the effects found in previous trials of beta-blockers conducted in similar patient populations, primarily in Europe.^{1,2} Alternatively, different pharmacologic properties of the various beta-blocking agents used in the studies could

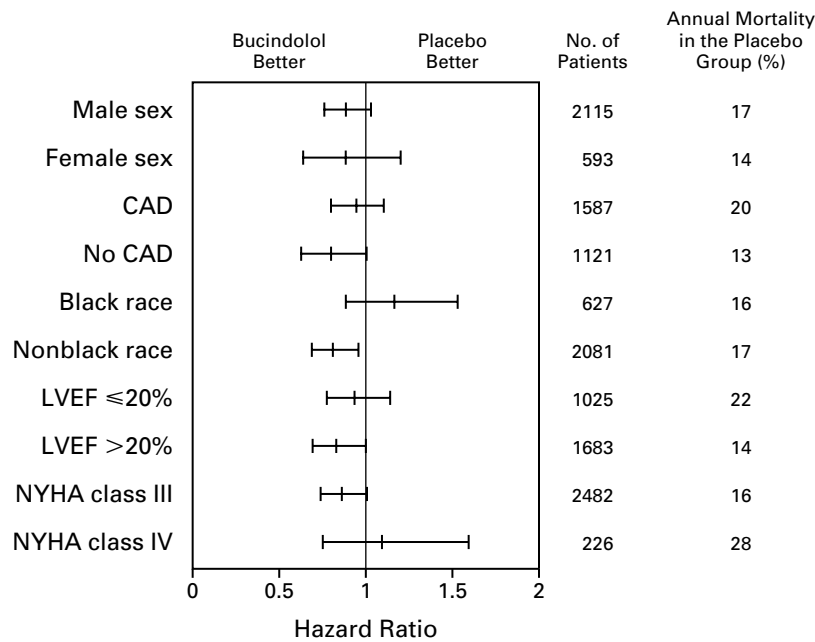


Figure 2. Hazard Ratios for Death in Prespecified Subgroups of Patients.

Hazard ratios are shown with 95 percent confidence intervals. Hazard ratios with upper confidence limits that are less than 1 represent a survival benefit with bucindolol. Confidence intervals have not been corrected for multiple comparisons. CAD denotes coronary artery disease, LVEF left ventricular ejection fraction, and NYHA New York Heart Association.

TABLE 3. INCIDENCE OF SELECTED ADVERSE EVENTS ACCORDING TO TREATMENT GROUP.

EVENT	PLACEBO GROUP	BUCINDOLOL GROUP	P VALUE
	(N=1354)	(N=1354)	
	no. (%)		
Fatigue	733 (54)	756 (56)	0.37
Dizziness	524 (39)	583 (43)	0.02
Weight gain	429 (32)	471 (35)	0.09
Edema	384 (28)	359 (27)	0.28
Nausea	347 (26)	316 (23)	0.17
Angina	304 (22)	259 (19)	0.03
Hypotension	272 (20)	279 (21)	0.74
Diarrhea	261 (19)	332 (25)	0.001
Tachycardia	240 (18)	136 (10)	<0.001
Headache	229 (17)	204 (15)	0.19
Abdominal pain	219 (16)	226 (17)	0.72
Insomnia	207 (15)	163 (12)	0.01
Anorexia	202 (15)	205 (15)	0.87
Vomiting	201 (15)	184 (14)	0.35
Hyperglycemia	196 (14)	243 (18)	0.01
Depression	158 (12)	117 (9)	0.009
Palpitations	156 (12)	115 (8)	0.009
Syncope	137 (10)	131 (10)	0.70
Postural hypotension	127 (9)	142 (10)	0.34
Atrial fibrillation	111 (8)	78 (6)	0.01
Bradycardia	68 (5)	156 (12)	<0.001
Cerebrovascular accident	43 (3)	45 (3)	0.83
Impotence	42 (3)	41 (3)	0.91
Transient ischemic attack	22 (2)	24 (2)	0.77
Intermittent claudication	14 (1)	34 (3)	0.004

explain the smaller effect in our study. The absence of an early separation between the survival curves for the two groups is probably related to the same factors that caused the study results to be neutral.

Among the patients in our study with NYHA functional class III heart failure, the annual mortality rate was 16 percent in the placebo group, as compared with 12 percent in the Cardiac Insufficiency Bisoprolol Study II and 13 percent in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure. For patients with NYHA class IV heart failure, the annual mortality rate in the placebo group was 28 percent, as compared with 20 percent in the Cardiac Insufficiency Bisoprolol Study II. These data suggest that within each NYHA class, we enrolled more patients with advanced heart failure or coexisting conditions than did the other two trials. If the severity of the heart failure modulates the effect of treatment with beta-blocking agents, the loss of adrenergic support that results from the initiation of beta-blocker therapy may not be as well tolerated in patients with more advanced disease. Also, the my-

ocardium may have less capacity to respond to treatment, perhaps because there is less viable myocardium.

We enrolled a substantial number of women, and the results did not demonstrate a sex-related effect of bucindolol. However, the data did suggest the possibility that bucindolol may be beneficial in nonblack but not in black patients. Although these results may represent a chance finding, the observed interaction raises the possibility of differences between racial groups in the response to beta-blockers in patients with chronic heart failure. Other studies of hypertensive patients^{25,26} and patients with heart failure^{10,27,28} have also suggested the possibility of a difference between racial groups in the response to treatment with angiotensin-converting-enzyme inhibitors and beta-blockers. Two studies of beta-blocking agents in patients with heart failure have reported similar results in blacks and in nonblacks; one of these studies, however, was conducted in a population with mild-to-moderate heart failure and reported a total of only 14 deaths in black patients treated with placebo or carvedilol,²⁹ and the other study was extremely small, with a cohort of only 54 patients.³⁰

Although it is likely that the differences in the observed effect on mortality in black and nonblack populations have many determinants (including, as described above, the possibility that the difference is a chance finding), blacks may have race-specific responses to pharmacologic therapy for cardiovascular disease. The genetic or other reasons for heterogeneous responses to such therapy in different racial groups are currently unknown but may include differences in the renin-angiotensin system^{31,32} or the beta-adrenergic pathway.³³ Chance and more advanced ventricular dysfunction cannot be excluded as possible reasons for the differential effect.

Another possible explanation for the apparent difference between the results of our study and those of other studies of beta-blockers and mortality may derive from the unique pharmacologic properties of bucindolol. Bucindolol is a nonselective beta-blocking agent³⁴ without intrinsic sympathomimetic activity in the human heart³⁴⁻³⁷; because of its mild vasodilator effect³⁶ and low inverse agonist properties (the ability of an antagonist to inactivate active-state receptors),³⁸ bucindolol is well tolerated in patients with advanced heart failure. Strong β_2 -adrenergic blockade and only weak α_1 -blocking properties³⁹ make bucindolol uniquely sympatholytic among beta-blocking agents that have been evaluated in trials in patients with heart failure.^{40,41} In fact, in our study, the 19 percent reduction in systemic norepinephrine levels (as compared with the change in placebo group) at three months was similar to the 23 percent reduction that was associated with treatment with the centrally acting sympatholytic agent moxonidine in the Effect of Sustained-Release Moxonidine on Mortality and Morbidity in Patients with Congestive Heart Failure trial

(unpublished data). In that study, moxonidine increased mortality by more than 50 percent, which led to the premature termination of the trial.⁴² Unlike receptor blockade, sympatholysis produces an irreversible loss of adrenergic support to the failing heart, which may be deleterious early in the course of therapy in patients with advanced heart failure. This property could also have had a mitigating effect on the mortality-lowering aspects of beta-receptor blockade in our study.

There is no longer any doubt that beta-blockers have a role in the treatment of mild-to-moderate (NYHA class II to III) chronic heart failure. Our findings raise questions about the efficacy of these agents in blacks and in patients with more advanced heart failure, as well as about the equivalency of beta-blockers. In doing so, it makes clear the need for studies that examine the mechanism of the heterogeneity of response to beta-blockers and for clinical trials that directly evaluate beta-blockers in blacks and in patients with NYHA class IV heart failure.

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APPENDIX

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