

RACE AND THE RESPONSE TO ADRENERGIC BLOCKADE WITH CARVEDILOL IN PATIENTS WITH CHRONIC HEART FAILURE

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ABSTRACT

Background The benefits of angiotensin-converting-enzyme inhibitors and beta-blockers may be smaller in black patients than in patients of other races, but it is unknown whether race influences the response to carvedilol in patients with chronic heart failure.

Methods In the U.S. Carvedilol Heart Failure Trials Program, 217 black and 877 nonblack patients (in New York Heart Association class II, III, or IV and with a left ventricular ejection fraction of no more than 0.35) were randomly assigned to receive placebo or carvedilol (at doses of 6.25 to 50 mg twice daily) for up to 15 months. The effects of carvedilol on ejection fraction, clinical status, and major clinical events were retrospectively compared between black and nonblack patients.

Results As compared with placebo, carvedilol lowered the risk of death from any cause or hospitalization for any reason by 48 percent in black patients and by 30 percent in nonblack patients. Carvedilol reduced the risk of worsening heart failure (heart failure leading to death, hospitalization, or a sustained increase in medication) by 54 percent in black patients and by 51 percent in nonblack patients. The ratios of the relative risks associated with carvedilol for these two outcome variables in black as compared with nonblack patients were 0.74 (95 percent confidence interval, 0.42 to 1.34) and 0.94 (95 percent confidence interval, 0.43 to 2.05), respectively. Carvedilol also improved functional class, ejection fraction, and the patients' and physicians' global assessments in both the black patients and the nonblack patients. For all these measures of outcome and clinical status, carvedilol was superior to placebo within each racial cohort ($P < 0.05$ in all analyses), and there was no significant interaction between race and treatment ($P > 0.05$ in all analyses).

Conclusions The benefit of carvedilol was apparent and of similar magnitude in both black and nonblack patients with heart failure. (N Engl J Med 2001; 344:1358-65.)

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HEART failure is a substantial public health problem among black Americans. It is more common in the black population than in other populations in the United States, affecting approximately 3 percent of all black adults in this country.^{1,2} Symptoms of heart failure develop in blacks at an earlier age than they do in nonblacks,³⁻⁵ possibly because blacks are more likely to

have hypertension and diabetes and to have ventricular hypertrophy and vascular injury than nonblacks.⁵⁻⁸ Once diagnosed, heart failure progresses more rapidly in black patients than in white patients, as evidenced by the higher risk of initial and repeated hospitalization and of death in the former group.^{3-5,9,10} These risks cannot be explained by the presence of documented coronary artery disease, which is less common in blacks than in nonblacks with heart failure.^{3,8,10}

What factors may explain or contribute to the poor long-term outcome in black patients with heart failure? First, the greater susceptibility of black patients to sodium retention, myocardial hypertrophy, and vascular injury may accelerate the rate of progression of heart failure.^{6,7,11} Second, limited access to medical care among black patients may delay both the diagnosis of heart failure and the prescription and use of effective medications.^{12,13} Third, even if deficiencies in access to medical care are corrected, pharmacologic interventions may be less effective in preventing adverse clinical events in black patients than in white patients. With regard to both hypertension and heart failure, blacks appear to derive less benefit than nonblacks from the use of angiotensin-converting-enzyme inhibitors and beta-blockers.^{4,14-17} As a result, there is a need to identify drugs that can control the progression of heart failure in black patients.

We conducted a retrospective analysis of the influence of race on the response to carvedilol among patients with heart failure who were enrolled in the U.S. Carvedilol Heart Failure Trials Program.¹⁸ Unlike other beta-blockers, carvedilol also inhibits α_1 -adrenergic receptors and has antioxidant properties that may contribute to its actions in patients with heart failure.¹⁹

METHODS

Patients

The U.S. Carvedilol Heart Failure Trials Program was a prospectively designed, stratified set of four concurrently conducted

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trials that were monitored by a single ethics committee. Details of the study design and main results have been previously published.²⁰ Of the 1094 patients enrolled, 217 (20 percent) were black and 877 (80 percent) were of European, Asian, or Native American descent. All the patients had heart failure categorized as New York Heart Association (NYHA) class II, III, or IV and a left ventricular ejection fraction of no more than 0.35, despite conventional therapy with diuretics and usually with digoxin and an angiotensin-converting-enzyme inhibitor.

Study Design

Patients who tolerated open-label therapy with carvedilol (6.25 mg twice daily for two weeks) were randomly assigned to receive placebo or carvedilol (in a 1:1, 1:2, or 1:3 ratio, depending on the trial).²⁰⁻²³ The dose of study medication was to be increased (over a period of 4 to 6 weeks); therapy was then to be maintained at the highest tolerated dose of medication (6.25 to 50 mg of carvedilol or placebo twice daily), which was to be given in addition to conventional therapy, for up to 15 months. Doses of conventional medication were to remain constant during the double-blind treatment period.

During maintenance therapy, changes in the NYHA functional class and changes in the patients' and physicians' global assessments were recorded every month, and the left ventricular ejection fraction was measured by radionuclide ventriculography after 6 and 12 months (or at the end of the double-blind treatment period). All the patients were prospectively followed for the occurrence of death or hospitalization; these events were analyzed by a data and safety monitoring board, which combined the data from all four trials to monitor the safety of therapy. The study was stopped early by the data and safety monitoring board because of drug efficacy.

Statistical Analysis

Each of the four trials had different prespecified primary and secondary end points, as previously described.²⁰⁻²³ All the analyses in the current report included all the patients who underwent randomization, and all the analyses were stratified according to trial. All the events were assigned to the patient's original treatment group, whether or not the patient was receiving the study medication (according to the intention-to-treat principle). Data on deaths and hospitalizations were collected regardless of cause; hospitalizations were classified as for heart failure, for a cardiovascular reason (including heart failure), or for a noncardiovascular reason.

The risk of death and of hospitalization was assessed by analyzing the time to a first event, and the differences between treatment groups within each racial cohort were tested for significance with use of a stratified Cox proportional-hazards model. In the analysis of death, data from patients who underwent cardiac transplantation were censored at the time of transplantation. Analyses of hospitalization always included death as the worst possible outcome so as to avoid the problem of competing risks. The clinical progression of heart failure was prospectively defined as worsening heart failure leading to death, hospitalization, or a sustained increase in conventional medications for heart failure.²⁰ For each variable, treatment effects within each racial cohort and possible interactions between race and treatment were evaluated with the Cox model. All P values are two-sided.

Continuous data are summarized as means \pm SD. Differences between racial groups in prerandomization characteristics and in postrandomization measurements were evaluated for significance by means of a general linear model (for continuous variables) or by logistic regression (for categorical variables). The NYHA functional class and global assessments were classified as improved, unchanged, or worsened. In all the analyses, the last value obtained during the double-blind treatment period was used; patients for whom values at the planned time of assessment were missing because of death or withdrawal due to worsening heart failure were assigned the worst rank for the given variables. Possible interactions between race and treatment were evaluated by incorporating an interaction term in the Cox model.

RESULTS

Base-Line Characteristics

The 217 black patients were younger, on average, than the 877 nonblack patients ($P < 0.001$) and were more likely to have hypertension or a history of hypertension ($P < 0.001$), but they were less likely to have ischemic heart disease than the nonblacks ($P < 0.001$) (Table 1). These differences in base-line characteristics are consistent with those reported in other studies.³⁻⁵

Of the 217 black patients, 90 were randomly assigned to receive placebo and 127 to receive carvedilol; of the 877 nonblack patients, 308 were randomly assigned to receive placebo and 569 to receive carvedilol. The base-line characteristics of the placebo and carvedilol groups were similar in both the black and nonblack cohorts (Table 1). After randomization, the maintenance doses of carvedilol reached similar levels in the black and nonblack cohorts (23 ± 13 and 21 ± 13 mg twice daily, respectively; $P = 0.38$), and the duration of treatment was also similar (179 ± 91 days for the black patients and 189 ± 101 days for the nonblack patients, $P = 0.85$).

Hemodynamic Variables

After adjustment for the changes in the placebo groups, both the black patients and the nonblack patients had significant increases in left ventricular ejection fraction at the end of the double-blind treatment period ($P < 0.001$ in both cohorts) but minimal changes in systolic and diastolic blood pressure; the magnitude of these effects was similar in the two cohorts (Table 2). In contrast, the black patients had greater decreases in heart rate than the nonblack patients ($P = 0.03$). The magnitudes of the differences between the cohorts, after adjustment for the different racial distributions among the protocols (and expressed as the difference between the value in the black cohort and the value in the nonblack cohort), were as follows: ejection fraction, 0.02 (95 percent confidence interval, -0.01 to 0.05); systolic blood pressure, -0.34 mm Hg (95 percent confidence interval, -5.21 to 4.54); diastolic blood pressure, 0.54 mm Hg (95 percent confidence interval, -2.80 to 3.88); and heart rate, -4.27 beats per minute (95 percent confidence interval, -8.09 to -0.45).

Clinical Status

Patients assigned to receive carvedilol were more likely to have improvement and less likely to have deterioration in terms of NYHA functional class and their own and the physicians' global assessments than patients assigned to receive placebo, whether they were black ($P = 0.006$, $P = 0.002$, and $P < 0.001$, respectively) or nonblack ($P = 0.02$, $P < 0.001$, and $P < 0.001$, respectively) (Table 2). The ratios of the relative risks for these three symptom-related variables

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	BLACKS (N=217)		NONBLACKS (N=877)		P VALUE†
	PLACEBO (N=90)	CARVEDILOL (N=127)	PLACEBO (N=308)	CARVEDILOL (N=569)	
Age — yr	53±11	54±12	59±12	59±12	<0.001
Male sex — no. (%)	58 (64)	87 (69)	246 (80)	447 (79)	<0.001
NYHA class — no. (%)					0.30
II	46 (51)	54 (43)	162 (53)	320 (56)	
III	40 (44)	67 (53)	137 (44)	236 (41)	
IV	4 (4)	6 (5)	9 (3)	13 (2)	
Ischemia — no. (%)	33 (37)	36 (28)	156 (51)	296 (52)	<0.001
History of hypertension — no. (%)	50/80 (62)	71/104 (68)	95/214 (44)	211/418 (50)	<0.001
Prior myocardial infarction — no. (%)	12/42 (29)	25/95 (26)	81/211 (38)	190/468 (41)	0.01
Left ventricular ejection fraction	0.22±0.08	0.22±0.08	0.22±0.07	0.23±0.07	0.60
Systolic blood pressure — mm Hg	121±20	118±18	113±16	115±17	<0.001
Diastolic blood pressure — mm Hg	76±12	75±12	72±10	72±10	<0.001
Diastolic blood pressure >90 mm Hg — no. (%)	10 (11)	17 (13)	8 (3)	11 (2)	<0.001
Heart rate — beats/min	84±11	86±12	83±12	84±12	0.07

*Plus-minus values are means ±SD. Because of rounding, not all percentages total 100. NYHA denotes New York Heart Association.

†P values are for the comparison of the value in black patients (placebo and carvedilol groups combined) with the value in nonblack patients (placebo and carvedilol groups combined). None of the differences between the placebo and carvedilol groups within each racial cohort were significant.

TABLE 2. RESPONSE TO TREATMENT WITH PLACEBO OR CARVEDILOL IN THE BLACK AND NONBLACK PATIENTS.*

VARIABLE	BLACKS (N=217)			NONBLACKS (N=877)			P VALUE FOR INTERACTION†
	PLACEBO (N=90)	CARVEDILOL (N=127)	P VALUE‡	PLACEBO (N=308)	CARVEDILOL (N=569)	P VALUE‡	
NYHA functional class — no. (%)§			0.006			0.02	0.15
Improved	10 (12)	21 (18)		38 (13)	71 (13)		
Unchanged	43 (51)	73 (62)		163 (55)	348 (64)		
Worse	32 (38)	24 (20)		93 (32)	121 (22)		
Patient's global assessment — no. (%)¶			0.002			<0.001	0.18
Improved	44 (53)	85 (72)		136 (48)	318 (60)		
Unchanged	7 (8)	8 (7)		53 (19)	87 (16)		
Worse	32 (39)	25 (21)		96 (34)	128 (24)		
Physician's global assessment — no. (%)¶			<0.001			<0.001	0.06
Improved	35 (42)	83 (70)		123 (43)	307 (58)		
Unchanged	17 (20)	11 (9)		68 (24)	106 (20)		
Worse	31 (37)	24 (20)		94 (33)	120 (23)		
Change in left ventricular ejection fraction	0.02±0.08	0.10±0.12	<0.001	0.02±0.07	0.08±0.09	<0.001	0.16
Change in systolic blood pressure — mm Hg	1.9±14.9	1.2±18.0	0.46	0.5±15.1	-0.3±16.4	0.25	0.89
Change in diastolic blood pressure — mm Hg	-0.1±10.6	-0.9±11.8	0.38	0.2±10.9	-1.4±10.9	0.02	0.75
Change in heart rate — beats/min	1.4±12.3	-13.4±12.9	<0.001	-2.2±12.5	-13.0±12.6	<0.001	0.03

*Data are the final changes observed during the double-blind treatment period. Because of rounding, not all percentages total 100. Minus signs denote a decrease.

†P values for interaction are for the comparison between the changes produced by carvedilol after adjustment for the effects of placebo in the black patients and the changes in the nonblack patients.

‡P values are for the comparison between the values in the placebo and carvedilol groups within each racial cohort.

§Data were available for 85 of the blacks who received placebo and 118 of the blacks who received carvedilol and for 294 of the nonblacks who received placebo and 541 of the nonblacks who received carvedilol.

¶Data were available for 83 of the blacks who received placebo and 118 of the blacks who received carvedilol and for 285 of the nonblacks who received placebo and 533 of the nonblacks who received carvedilol.

in black as compared with nonblack patients were 0.64 (95 percent confidence interval, 0.34 to 1.18), 0.56 (95 percent confidence interval, 0.30 to 1.04), and 0.65 (95 percent confidence interval, 0.35 to 1.22), respectively. None of the P values for the interaction between treatment and race with respect to these variables were significant (P=0.15, P=0.18, and P=0.06, respectively).

Risk of Death or Hospitalization

Black patients receiving placebo were more likely to die from any cause than nonblack patients (mortality, 8.9 percent vs. 7.5 percent); they were also more likely to be hospitalized for any reason than nonblack patients (31.1 percent vs. 25.3 percent). However, carvedilol reduced the risk of death from any cause and the combined risk of death from any cause or hospitalization to a similar degree in the two racial cohorts (Table 3). Specifically, carvedilol lowered the risk of death from any cause by 56 percent in blacks and 68 percent in nonblacks; decreased the risk of death from any cause or hospitalization for any reason by 48 percent in blacks and by 30 percent in nonblacks (Fig. 1); reduced the risk of death from any cause or hospitalization for a cardiovascular reason by 32 percent in blacks and by 35 percent in nonblacks; lowered the risk of death from any cause or hospitalization for heart failure by 43 percent in blacks and by 49 percent in nonblacks; and decreased the risk of progression of heart failure

by 54 percent in blacks and by 51 percent in nonblacks (Fig. 2). The ratios of the relative risks of these five outcome variables in black as compared with nonblack patients were 1.38 (95 percent confidence interval, 0.39 to 4.67), 0.74 (95 percent confidence interval, 0.42 to 1.34), 1.05 (95 percent confidence interval, 0.54 to 2.04), 1.12 (95 percent confidence interval, 0.47 to 2.72), and 0.94 (95 percent confidence interval, 0.43 to 2.05), respectively. None of the P values for the interaction between treatment and race for these five outcome variables were significant (P=0.63, P=0.33, P=0.89, P=0.78, and P=0.88, respectively).

For the two outcome variables associated with the highest event rates in the placebo group, the effect of carvedilol was statistically significant, even when the analysis was confined to black patients. Specifically, among black patients, carvedilol as compared with placebo reduced the combined risk of death from any cause or hospitalization for any reason by 48 percent (P=0.01) and lowered the risk of progression of heart failure by 54 percent (P=0.03).

Safety

During the two weeks of open-label therapy with carvedilol, the rates of withdrawal due to death or adverse reactions were similar among the black patients and the nonblack patients (5.1 percent and 6.8 percent, respectively). After randomization, the frequency of specific adverse events in the carvedilol

TABLE 3. RISK OF MAJOR CLINICAL EVENTS ACCORDING TO TREATMENT GROUP.

EVENT	PLACEBO (N=398)	CARVEDILOL (N=696)	RELATIVE RISK (95% CI)*	P VALUE†	P VALUE FOR INTERACTION‡
	no./total no. (%)				
Death from any cause					0.63
Blacks	8/90 (8.9)	6/127 (4.7)	0.44 (0.15–1.28)	0.13	
Nonblacks	23/308 (7.5)	16/569 (2.8)	0.32 (0.17–0.62)	<0.001	
Death from any cause or hospitalization for any reason					0.33
Blacks	33/90 (36.7)	26/127 (20.5)	0.52 (0.31–0.88)	0.01	
Nonblacks	90/308 (29.2)	119/569 (20.9)	0.70 (0.53–0.92)	0.01	
Death from any cause or hospitalization for a cardiovascular reason					0.89
Blacks	22/90 (24.4)	22/127 (17.3)	0.68 (0.37–1.23)	0.20	
Nonblacks	76/308 (24.7)	95/569 (16.7)	0.65 (0.48–0.88)	0.005	
Death from any cause or hospitalization for heart failure					0.78
Blacks	14/90 (15.6)	12/127 (9.4)	0.57 (0.26–1.25)	0.16	
Nonblacks	46/308 (14.9)	46/569 (8.1)	0.51 (0.33–0.77)	0.001	
Clinical progression of heart failure					0.88
Blacks	23/90 (25.6)	17/127 (13.4)	0.46 (0.23–0.94)	0.03	
Nonblacks	92/308 (29.9)	100/569 (17.6)	0.49 (0.35–0.69)	<0.001	

*The relative risk is the risk in the carvedilol group relative to that in the placebo group. CI denotes confidence interval.

†P values are for the comparison between the values in the placebo and carvedilol groups within each racial cohort.

‡P values for interaction are for the comparison between the effect of carvedilol in the black patients and the effect in the nonblack patients.

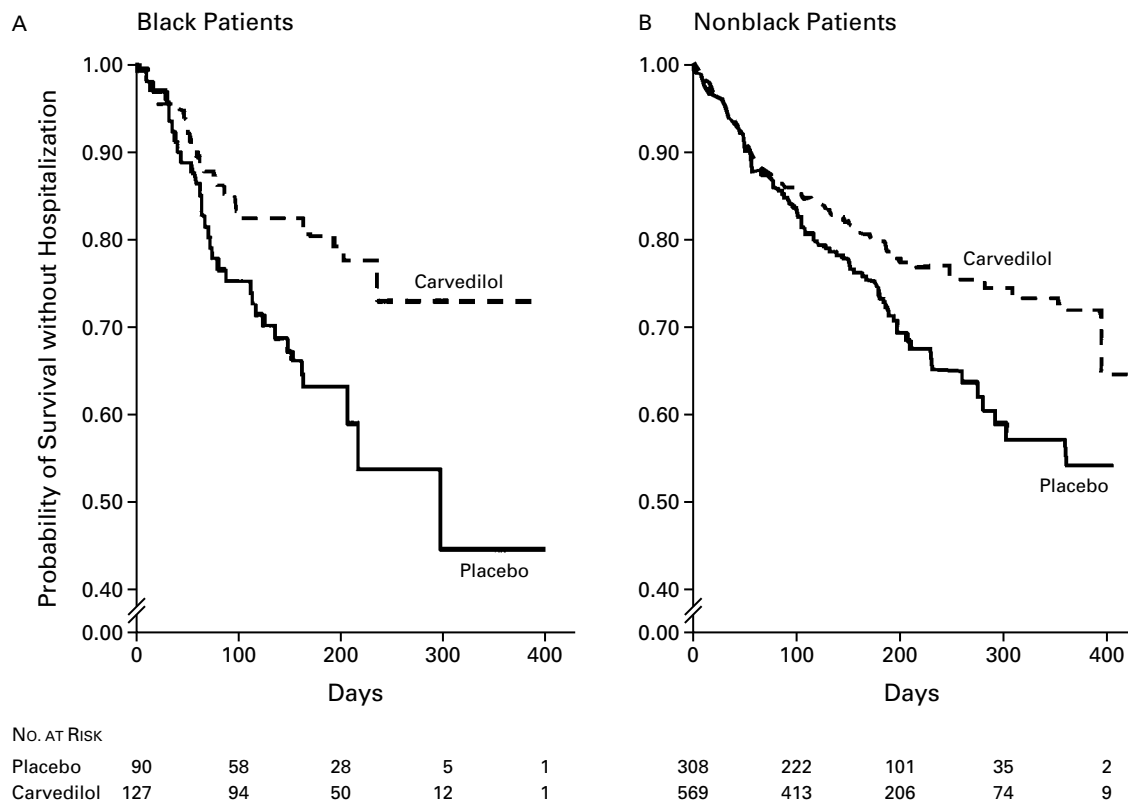


Figure 1. Kaplan–Meier Analysis of Cumulative Rates of Survival without Hospitalization among the Black Patients (Panel A) and among the Nonblack Patients (Panel B).

Within the cohort of black patients, those randomly assigned to carvedilol had a 48 percent lower risk of death from any cause or hospitalization for any reason than those assigned to placebo ($P=0.01$); among the nonblack patients, the risk reduction was 30 percent ($P=0.01$). There was no significant difference in the magnitude of the drug's effect between the two racial cohorts ($P=0.33$).

group (after adjustment for the frequency of events in the placebo group) was also similar among the black patients and the nonblack patients, except that carvedilol produced hypotension (but not dizziness) more frequently in nonblacks than in blacks ($P=0.02$ for the interaction between race and treatment), possibly because of the lower base-line blood pressures in nonblack patients (Table 1). Most of the adverse events were mild or moderate in severity and resolved either spontaneously or after a reduction in the dose of the study medication. The proportion of patients who discontinued treatment because of an adverse event was lower in the carvedilol group than in the placebo group, whether patients were black (7 percent vs. 14 percent, $P=0.06$) or nonblack (8 percent vs. 12 percent, $P=0.02$). In addition, there was no difference in these proportions between the two racial cohorts.

DISCUSSION

Previous studies have suggested that black patients with heart failure may derive less benefit than non-

black patients from drugs that prolong life and reduce the risk of hospitalization or that they may even have a detrimental response to such drugs.^{4,16,17} In the present retrospective analysis, however, race did not influence the response to carvedilol in patients with heart failure. Long-term treatment with carvedilol improved cardiac function, lessened symptoms, and reduced the risk of death and hospitalization to a similar degree in black patients and nonblack patients. Furthermore, the favorable effect of carvedilol on clinical status, NYHA functional class, left ventricular ejection fraction, the risk of the combined end point of death or hospitalization, and the progression of heart failure in black patients was significant in its own right. These findings suggest that the appropriate use of carvedilol may help to lessen the public health effects of heart failure in the black community.

The results of our analysis of the effects of carvedilol differ from those observed in previous studies of neurohormonal antagonists in patients with heart failure. In the Studies of Left Ventricular Dysfunction (SOLVD)¹⁶ and in the second Vasodilator–Heart

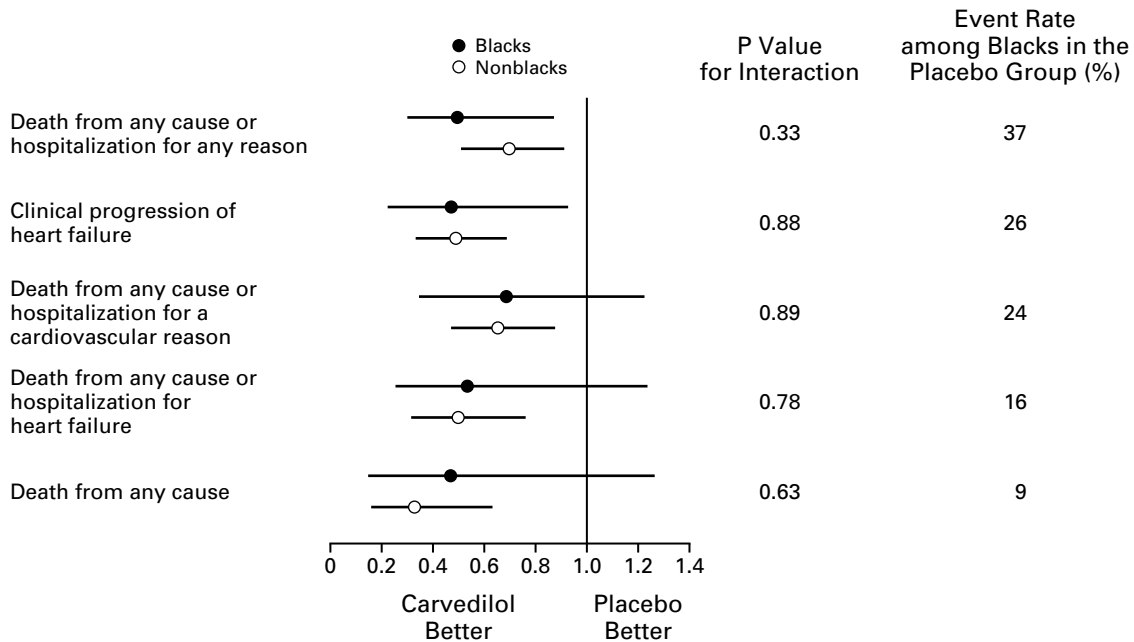


Figure 2. Effects of Carvedilol in Black Patients and Nonblack Patients, Expressed as Relative Risks (Carvedilol vs. Placebo) of Five Outcome Variables.

Point estimates to the left of the vertical line (the line of unity) indicate a favorable effect of carvedilol. P values for interaction are for the comparison of the effects of carvedilol (after adjustment for the effects of placebo) in the two racial cohorts. The outcome variables are listed in order according to the rate of events among black patients in the placebo group. The horizontal lines indicate 95 percent confidence intervals.

Failure Trial (V-HeFT II),⁴ angiotensin-converting–enzyme inhibitors reduced the risk of death or hospitalization in white patients but not black patients. In the Beta-Blocker Evaluation of Survival Trial,¹⁷ the beta-blocker bucindolol reduced the risk of death or hospitalization among nonblack patients but was associated with a nonsignificant increase in the risk of a serious clinical event in black patients. In all three of these studies, a statistically significant or nearly significant interaction between treatment and race was observed. This pattern of response in patients with heart failure is strikingly similar to that seen in patients with hypertension — that is, the antihypertensive efficacy of both angiotensin-converting–enzyme inhibitors and beta-blockers is lower in black patients than in white patients.^{14,15} This racial difference has been attributed to the fact that neurohormonal systems may have a smaller role in the control of blood pressure in blacks than in whites.^{24–26}

What might explain the favorable responses to carvedilol in the black patients evaluated in the present analyses? Unlike metoprolol and bisoprolol, carvedilol inhibits both β_2 - and α_1 -adrenergic receptors.¹⁹ Such actions are noteworthy, since blacks have greater responses to cardiac β_2 -adrenergic stimuli and periph-

eral α_1 -adrenergic stimuli than whites,^{27–30} particularly in states of potassium depletion.³¹ As a result, both β_2 - and α_1 -adrenergic blockade may be especially important in black patients, particularly those with heart failure, whose potassium balance may be disturbed by the concomitant use of diuretics. This hypothesis is supported by the observation in the present study that carvedilol was associated with a greater reduction in the heart rate in black patients than in nonblack patients and by the previous finding that the resistance of hypertension to beta-blockade in black patients can be overcome by the use of a beta-blocker with alpha-blocking properties.³² Combined alpha- and beta-blockade may also minimize the adverse effects of beta-blockade alone on blood lipids and insulin sensitivity,^{33,34} two important cofactors in the evolution of cardiovascular disease in black patients.^{6,35}

Long-term therapy with carvedilol was well tolerated by the black patients in this study. The most worrisome adverse effect of beta-blockade in patients with heart failure — worsening heart failure — occurred with a similar frequency in the two racial cohorts. This finding may be surprising, since beta-blockers cause worsening heart failure primarily by reducing renal blood flow and sodium excretion,^{36,37} and since

blacks are more likely to have impaired renal blood flow and to retain sodium than nonblacks.^{38,39} However, in the present study, black patients (like nonblack patients) who received carvedilol had a lower risk of progression of heart failure during treatment than those who received placebo. The finding that black patients were not at increased risk of heart failure may be related to the alpha-blocking actions of carvedilol.

The present analyses were not based on a prospectively designed trial in black patients, and randomization in the trials that were the source of the analyzed data was not stratified according to race; thus, it is possible that our findings are due to idiosyncrasies in our patient population or to chance. However, the black patients in our study differed from their nonblack counterparts in precisely the manner that would be predicted from earlier studies: they were younger (indicating an earlier onset of heart failure), were more likely to have hypertension, were less likely to have ischemic heart disease, and had higher rates of hospitalization than the nonblack patients.³⁻⁸ Nevertheless, our results differed from the results of earlier trials of angiotensin-converting-enzyme inhibitors and beta-blockers.^{3,4,17} In contrast to those trials, in which the benefits of treatment were found to be largely confined to the nonblack population, our study found the effects of carvedilol on the risk of major clinical events in black patients to be uniformly favorable. These analyses suggest that the effects of carvedilol in black patients may differ meaningfully from those of other beta-blockers — a hypothesis that requires confirmation by further prospective study.

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APPENDIX

The other principal investigators of the U.S. Carvedilol Heart Failure Study Group were as follows: *Albuquerque, N.M.* — Lovelace Scientific Resources: L. Kuo; *Baltimore* — Johns Hopkins University Hospital: E. Kasper and A.M. Feldman; Union Memorial Hospital: H. Meilman and D. Goldscher; and University of Maryland: S.S. Gottlieb; *Beverly Hills, Calif.* — Cardiovascular Research Institute of Southern California: R. Karlsburg; *Boston* — Boston City Hospital: R.H. Falk; Brigham and Women's Hospital: W. Carlson; Massachusetts General Hospital: G.W. Dec; and New England Medical Center: J.E. Udelson; *Bronx, N.Y.* — Albert Einstein College of Medicine: T.H. LeJemtel; *Chapel Hill, N.C.* — University of North Carolina: K. Adams; *Cleveland* — Cleveland Clinic: R. Hobbs; *Columbus, Ohio* — Ohio State University Hospital: R.J. Cody; *Dallas* — Veterans Affairs Medical Center: E. Eichhorn; *East Meadow, N.Y.* — Nassau County Medical Center: E. Brown and I. Freeman; *Elmhurst, N.Y.* — Elmhurst Hospital Center: N. Kantrowitz; *Falls Church, Va.* — Inova Health System: J. Kiernan, J. O'Brien, and P. Carson; *Grosse Pointe, Mich.* — Henry Ford Health System and Pierson Clinic: V. Kinhal; *Houston* — Baylor College of Medicine: J. Young; and University of Texas Medical School: G. Schroth and S.E. El Hafi; *Jackson, Miss.* — University of Mississippi Medical Center: J. O'Connell; *Jacksonville, Fla.* — University of Florida: A. Miller; *Las Vegas*

— Heart Institute of Nevada: J.A. Bowers; *Lincoln, Nebr.* — Nebraska Heart Institute: S. Krueger; *Los Angeles* — University of Southern California School of Medicine: V. DeQuattro; *Madison, Wis.* — University of Wisconsin School of Medicine: P.S. Rahko; *Memphis, Tenn.* — University of Tennessee School of Medicine: K.B. Ramanathan; *Miami* — University of Miami: E. deMarchena; *Mincola, N.Y.* — Cardiovascular Medical Associates: M. Goodman; and Winthrop University Hospital: R. Steingart; *Minneapolis* — University of Minnesota Medical School: S. Kubo; *Nashville* — Vanderbilt University Medical Center: J.R. Wilson and T.K. Yeoh; *New Haven, Conn.* — Yale University School of Medicine: F. Lee; *New York* — Columbia–Presbyterian Medical Center: J. Sackner-Bernstein and G.W. Neuberger; Mount Sinai Medical Center: M. Kukin; and St. Luke's–Roosevelt Medical Center: M. Klapholz; *Northport, N.Y.* — Veterans Affairs Medical Center: G. Mallis; *Oklahoma City* — University of Oklahoma and Veterans Affairs Medical Center: U. Thadani; *Park Ridge, Ill.* — Lutheran General Hospital: R.P. Sorokin; *Philadelphia* — Temple University Hospital: I. Pina; *Phoenix, Ariz.* — Carl T. Hayden Veterans Affairs Medical Center: J.V. Felicetta; *Pittsburgh* — Presbyterian University Hospital: B. Uretsky and S. Murali; and Western Pennsylvania Hospital: A. Gradman; *Portland, Oreg.* — Oregon Health Sciences Center: R. Hershberger; *Richmond, Va.* — Medical College of Virginia: G.W. Vetrovec; *Rochester, Minn.* — Mayo Medical School: L.J. Olson; *Rochester, N.Y.* — University of Rochester Medical Center: C.S. Liang; *San Diego, Calif.* — Cardiology Associates Medical Group of East San Diego: L. Yellen; and Sharp Rees-Stealy Medical Center: H. Ingersoll; *San Francisco* — California Pacific Medical Center: S. Woodley; and Veterans Affairs Medical Center: B.M. Massie; *Sellersville, Pa.* — Buxmont Cardiology Associates: M. Greenspan; *St. Louis* — St. Louis University Medical Center: L.W. Miller, S.H. Jennison, A.J. Lonigro, and H. Stratman; *Summit, N.J.* — Overlook Hospital: J.J. Gregory; *Torrance, Calif.* — Harbor–UCLA Medical Center: K.A. Narahara; *Tucson, Ariz.* — University of Arizona Medical Center: S. Butman; *Washington, D.C.* — Georgetown University Hospital: D. Pearl; *Winston-Salem, N.C.* — Bowman Gray School of Medicine: F. Kahl; and *Worcester, Mass.* — University of Massachusetts Medical Center: L. Heller. Committee members were as follows: *Executive Committee* — M. Packer, M.R. Bristow, J.N. Cohn, W.S. Colucci, M.B. Fowler, and E.M. Gilbert; *Data and Safety Monitoring Board* — A.M. Katz (chair), T. Bashore, C.E. Davis, and P. Kowey; *Biostatistics* — J. Hosking and S.T. Young; and *Study Operations and Monitoring* — N.H. Shusterman, M.A. Lukas, A. Flagg, T. Holclaw, and L.G. Parchman.

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