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THE EFFECT OF CARVEDILOL ON MORBIDITY AND MORTALITY IN PATIENTS WITH CHRONIC HEART FAILURE

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Abstract *Background.* Controlled clinical trials have shown that beta-blockers can produce hemodynamic and symptomatic improvement in chronic heart failure, but the effect of these drugs on survival has not been determined.

Methods. We enrolled 1094 patients with chronic heart failure in a double-blind, placebo-controlled, stratified program, in which patients were assigned to one of four treatment protocols on the basis of their exercise capacity. Within each of the four protocols patients with mild, moderate, or severe heart failure with left ventricular ejection fractions ≤0.35 were randomly assigned to receive either placebo (n=398) or the beta-blocker carvedilol (n=696); background therapy with digoxin, diuretics, and an angiotensin-converting–enzyme inhibitor remained constant. Patients were observed for the occurrence of death or hospitalization for cardiovascular reasons during the following 6 months (12 months for the group with mild heart failure).

Results. The overall mortality rate was 7.8 percent in the placebo group and 3.2 percent in the carvedilol group; the reduction in risk attributable to carvedilol was 65 percent (95 percent confidence interval, 39 to 80 percent; $P<0.001$). This finding led the Data and Safety Monitoring Board to recommend termination of the study before its scheduled completion. In addition, as compared with placebo, carvedilol therapy was accompanied by a 27 percent reduction in the risk of hospitalization for cardiovascular causes (19.6 percent vs. 14.1 percent, $P=0.036$), as well as a 38 percent reduction in the combined risk of hospitalization or death (24.6 percent vs. 15.8 percent, $P<0.001$). Worsening heart failure as an adverse reaction during treatment was less frequent in the carvedilol group than in the placebo group.

Conclusions. Carvedilol reduces the risk of death as well as the risk of hospitalization for cardiovascular causes in patients with heart failure who are receiving treatment with digoxin, diuretics, and an angiotensin-converting–enzyme inhibitor. (N Engl J Med 1996;334:1349-55.)

ACTIVATION of the sympathetic nervous system is one of the cardinal pathophysiologic abnormalities in patients with chronic heart failure. Levels of circulating catecholamines increase in patients with heart failure in proportion to the severity of disease,[1] and those with the highest plasma levels of norepinephrine have the most unfavorable prognosis.[2] These observations have led to the hypothesis that sympathetic activation plays an important part in the progression of heart failure.[3,4] Norepinephrine can exert adverse effects on the circulation, both directly and indirectly,[5,6] and interference with its actions can retard the progression of heart failure in animal models of the disease.[7,8]

These findings have led investigators to propose that sympathetic antagonists (e.g., beta-blockers) might be useful in the management of heart failure. Such drugs were previously considered to be contraindicated in this disorder because of their short-term adverse effects,[9] but studies in Sweden in the 1970s raised the possibility that long-term therapy with these drugs might produce hemodynamic and clinical benefits.[10,11] Controlled trials of several different beta-blockers have shown that these drugs can reduce symptoms, improve left ventricular function, and increase functional capacity,[12-18] but recent large-scale studies[19,20] have not clarified the effects of beta-blockers on morbidity and mortality in patients with heart failure.

Hence, when a large clinical trial program with carvedilol in heart failure was being designed in 1992, we prospectively defined an overall objective of the program to be an evaluation of the effect of the drug on survival. Our principal goal was to assess the safety of

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carvedilol while recognizing its potential to prolong life, demonstrated by the results of experimental studies.[7,8,21] Carvedilol is a nonselective β-receptor antagonist that also blocks α_1-receptors and, unlike other beta-blockers, exerts antioxidant effects, which may contribute to its actions in heart failure.[22-24] This report summarizes the effects of carvedilol on survival and on hospitalization for cardiovascular causes.

METHODS

Study Patients

All patients in the study had had symptoms of heart failure for at least three months and had ejection fractions ≤0.35, despite at least two months of treatment with diuretics and an angiotensin-converting–enzyme inhibitor (if tolerated); treatment with digoxin, hydralazine, or nitrates was permitted but not required. Patients were excluded from the trial if they had had a major cardiovascular event or had undergone a major surgical procedure within three months of entry into the study, or if they had uncorrected, primary valvular disease; active myocarditis; sustained ventricular tachycardia or advanced heart block not controlled by antiarrhythmic intervention or a pacemaker; systolic blood pressure of more than 160 or less than 85 mm Hg or diastolic blood pressure of more than 100 mm Hg; a heart rate of less than 68 beats per minute; clinically important hepatic or renal disease; or any condition other than heart failure that could limit exercise or survival. Patients receiving calcium-channel blockers, α- or β-adrenergic agonists or antagonists, or class IC or III antiarrhythmic agents were also not enrolled. The protocol was approved by the institutional review boards of all 65 participating institutions; written informed consent was obtained from all patients.

Study Procedures

The patients' eligibility was assessed during a three-week screening period, during which exercise capacity was measured by a six-minute corridor-walk test. Enrollment was stratified into one of four treatment protocols on the basis of the patients' performance on the exercise test. According to the original design, patients able to walk between 426 and 550 m when tested were assigned to the mild-heart-failure protocol; those able to walk between 150 and 425 m were assigned either to the moderate-heart-failure protocol or to a dose-ranging protocol, depending on the location of the study center; and those able to walk only less than 150 m were assigned to the severe-heart-failure protocol.

After a base-line evaluation, all patients received 6.25 mg of carvedilol twice daily for two weeks (the open-label portion of the study); if this dose was not tolerated, it could be temporarily reduced to 3.125 mg twice daily and then later increased. Patients who could tolerate 6.25 mg twice daily were randomly assigned to receive carvedilol or placebo on a double-blind basis, in addition to their usual medication. The allocation ratio (of patients given carvedilol to patients given placebo) was one-to-one in the moderate-heart-failure protocol and two-to-one in the mild- and severe-heart-failure protocols; for these patients, the dose of medication was initially 12.5 mg twice daily and was increased, if tolerated, to 25 to 50 mg twice daily. Patients assigned to the dose-ranging protocol were randomly assigned to one of four parallel treatment groups (placebo or 6.25 mg, 12.5 mg, or 25 mg of carvedilol, twice daily). For all four protocols, the dose was gradually adjusted upward to the target level over a period of 2 to 10 weeks, after which double-blind therapy was maintained for an additional 6 months (except in the mild-heart-failure protocol, in which patients were treated for an additional 12 months). During this time, the patients' other drug therapies for heart failure were kept constant, unless side effects occurred that were thought to be related either to these other medications or to the study drug itself.

Study Objectives and Monitoring

Because of concern that new drugs for heart failure might increase the risk of death, the sponsors of the program agreed with the Food and Drug Administration in July 1992 to enroll a sufficient number of patients in placebo-controlled trials of carvedilol to rule out (with 95 percent confidence) the risk of a 33 percent increase in mortality with active therapy, assuming an annual mortality rate of 12 percent in the placebo group. As a result of these discussions, an evaluation of mortality was prospectively defined for the present stratified trial program, primarily for reasons of safety, with the intent to enroll 1101 patients. However, since it was anticipated (on the basis of earlier studies) that carvedilol could reduce mortality, all statistical analyses were two-sided. All deaths were classified by investigators who had no knowledge of the patients' treatment assignments. In addition, a major secondary objective of each of the component protocols was to evaluate the effect of carvedilol on cardiovascular morbidity, defined as hospitalization for heart failure or other cardiovascular causes.

A data and safety monitoring board was constituted before recruitment began, met periodically to review the unblinded results, and was empowered to recommend early termination of the program if its members observed a clinically important treatment effect. No formal rules for stopping the trial were adopted before the initiation of enrollment.

Statistical Analysis

The base-line characteristics of the two treatment groups were compared with use of the t-test and the chi-square statistic. Cumulative survival curves were constructed as time-to-first-event plots by Kaplan–Meier survivorship methods,[25] and differences between the curves were tested for significance by the log-rank statistic with use of a Cox proportional-hazards regression model (which included the protocol as a covariate).[26] The analyses included all randomized patients, and all events were assigned to the patients' original treatment group (on the intention-to-treat principle). In the analysis of mortality, data on patients were censored at the time of cardiac transplantation. Differences between treatment groups in post-randomization measures or events were evaluated by analysis of variance and with the chi-square statistic. All data are reported as means ±SD.

RESULTS

Randomization began on April 29, 1993, and the study was stopped early on the recommendation of the Data and Safety Monitoring Board on February 3, 1995. This decision was based on the finding of a significant effect of carvedilol on survival — an effect that exceeded all conventional boundaries used to stop clinical trials.[27,28]

At the time of the study's early termination, 1197 patients had entered the open-label, run-in period. Of these, 5.6 percent failed to complete this period because of adverse events (e.g., worsening heart failure in 1.4 percent and death in 0.6 percent); another 3.0 percent failed to do so because of violations of the protocol or for other administrative reasons. Accordingly, 1094 patients were randomly assigned to double-blind treatment: 398 with placebo and 696 with carvedilol.

The placebo and carvedilol groups were similar in all pretreatment characteristics (Table 1). After randomization and the adjustment of dosage, patients received a mean total daily dose of 45±27 mg of carvedilol or 60±24 mg of placebo; these doses were maintained at similar levels throughout the study period. Eighty percent of the patients received target doses of the study drugs. The duration of therapy ranged from 1 day to 15.1 months (median, 6.5 months). No patient was lost to follow-up with respect to mortality.

Effect of Carvedilol on Survival

In the intention-to-treat analysis, there were 31 deaths (7.8 percent) in the placebo group and 22 deaths (3.2

Table 1. Pretreatment Characteristics of Patients in the Study.*

Characteristic	Placebo (N = 398)	Carvedilol (N = 696)
Age (yr)	58.1±12.3	57.9±12.2
Sex (M/F)	304/94	534/162
New York Heart Association class		
II	208	374
III	177	303
IV	13	19
Cause of heart failure†		
Coronary artery disease	189	332
Nonischemic dilated cardiomyopathy	208	362
Left ventricular ejection fraction	0.22±0.07	0.23±0.07
Six-minute walk (m)	386±96	390±90
Systolic blood pressure (mm Hg)	115±17	116±17
Diastolic blood pressure (mm Hg)	73±11	72±10
Heart rate (beats/min)	83±12	84±12
Medication (% of patients)		
Digitalis	90	91
Loop diuretic	95	95
ACE inhibitor	95	95
Direct-acting vasodilator	32	32

*Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme.

†The cause of heart failure was not recorded for one patient in the placebo group and two in the carvedilol group.

percent) in the carvedilol group; this difference represents a 65 percent decrease in the risk of death (95 percent confidence interval, 39 to 80 percent; $P<0.001$) in patients assigned to carvedilol (Fig. 1). Treatment with the drug was associated with a large decrease in the risk of dying of progressive heart failure and in the risk of sudden death (Table 2). The reduction in mortality due to carvedilol was similar regardless of age, sex, the cause of heart failure, ejection fraction, exercise tolerance, systolic blood pressure, heart rate, or protocol assignment (Table 3).

Effect of Carvedilol on Cardiovascular Morbidity

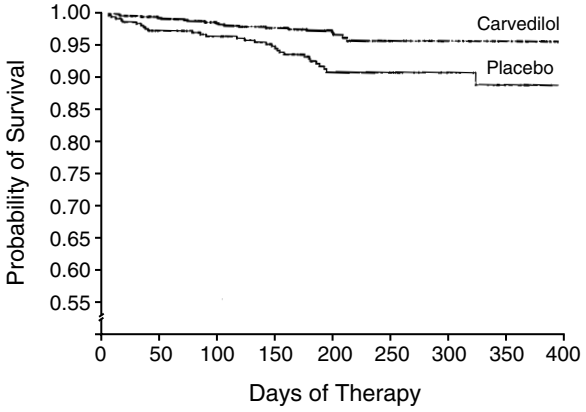
During double-blind therapy, 98 patients (14.1 percent) in the carvedilol group and 78 patients (19.6 percent) in the placebo group had at least one hospitalization for cardiovascular causes; this difference represents a 27 percent reduction in the risk of hospitalization (95 percent confidence interval, 3 to 45 percent; $P=0.036$). To avoid the analytic problem of competing risks (since patients who have died cannot be hospitalized), the effect of carvedilol on the combined risk of death or hospitalization for cardiovascular causes was evaluated with the use of a time-to-first-event analysis. As tested for significance with use of the log-rank test, the combined risk of either dying or being hospitalized for cardiovascular reasons was reduced from 24.6 percent in the placebo group to 15.8 percent in the carvedilol group, a 38 percent reduction (95 percent confidence interval, 18 to 53 percent; $P<0.001$) (Fig. 2).

Safety

At the end of double-blind therapy, the mean heart rate decreased significantly more in the carvedilol group than in the placebo group (by 12.6±12.8 beats per minute vs. 1.4±12.2, $P<0.001$), although neither group had significant changes in systolic or diastolic blood pressure. Frequently reported adverse reactions are listed in Table 4; those necessitating discontinuation of the study drug are shown in Table 5. The most common side effect of carvedilol was dizziness, which occurred during the initiation of therapy or during the dose-adjustment period but which subsided either spontaneously or after the adjustment of concomitant medications; it did not generally lead to the withdrawal of treatment with the study drug. The most common reason for the discontinuation of double-blind treatment was worsening heart failure, which occurred more frequently in the placebo group. Overall, 7.8 percent of the placebo group and 5.7 percent of the carvedilol group discontinued the study medication because of adverse reactions; 1.5 percent and 1.1 percent, respectively, were withdrawn from the study medication after cardiac transplantation. When the program was terminated, more patients were receiving or had completed double-blind treatment in the carvedilol group than in the placebo group (89 percent vs. 83 percent, $P=0.002$).

Discussion

The present report indicates that the addition of carvedilol to conventional therapy is associated with a decrease in mortality among patients with chronic heart failure. Patients treated with carvedilol had a 65 percent lower risk of death than those given placebo during follow-up that averaged 6.5 months and extended to 15 months. The beneficial effect of carvedilol on survival was consistent in all evaluated subgroups and was reflected in a decrease in the risk of death from progressive heart failure as well as in the risk of sudden death.



No. at Risk

Placebo	398	353	329	305	163	71	55	43	3
Carvedilol	696	637	581	546	314	131	106	83	11

Figure 1. Kaplan–Meier Analysis of Survival among Patients with Chronic Heart Failure in the Placebo and Carvedilol Groups.

Patients in the carvedilol group had a 65 percent lower risk of death than patients in the placebo group ($P<0.001$).

In addition, carvedilol therapy was associated with a 26 percent reduction in hospitalization for cardiovascular causes, a 38 percent decrease in the risk of death or hospitalization, and a lower rate of withdrawal from the trial due to worsening heart failure.

Previous controlled studies have shown that beta-blockade can improve cardiac function, reduce the symptoms of heart failure, improve functional capacity, and enhance exercise tolerance.[12-20] Most of these trials were too small to evaluate the effects of beta-blockers on morbidity or mortality, but one single-center study with carvedilol[18] and two multicenter studies with the β_1-selective agents metoprolol and bisoprolol[19,20] suggested that long-term beta-blockade may have favorable effects on the course of heart failure. In the single-center study,[18] treatment with carvedilol for four months reduced the risk of cardiovascular events. In the two multicenter studies,[19,20] treatment with metoprolol for 12 to 18 months or with bisoprolol for 4 to 44 months was associated with fewer hospitalizations for worsening heart failure and a reduced risk of clinical deterioration requiring cardiac transplantation. The decrease in hospitalizations for cardiovascular causes seen with carvedilol in our study reaffirms these earlier observations.

Yet previous trials in heart failure have not demonstrated a reduction in mortality during beta-blockade. In the two multicenter studies,[19,20] treatment with metoprolol or bisoprolol did not significantly decrease the risk of death. One of the trials retrospectively noted a reduction in mortality only among patients with nonischemic dilated cardiomyopathy.[20] In contrast, in our study, carvedilol therapy was associated with a decrease in mortality, and the benefits of the drug were apparent in all the subgroups we examined, including patients with underlying ischemic heart disease. The fact that two earlier multicenter studies did not find an effect on survival may have been related to the sample sizes, to the study designs, or to chance. Alternatively, the effects of carvedilol on survival may differ from those of other beta-blockers. Unlike metoprolol and bisoprolol, carvedilol blocks both α_1- and β_2-adrenergic receptors, reduces cardiac norepinephrine levels, and does not elicit up-regulation of cardiac β-receptors.[29-31] Furthermore, unlike other beta-blockers, carvedilol has potent antioxidant effects,[24] which may protect against the continuing loss of cardiac myocytes that characterizes the progression of heart failure.[21,32]

Table 2. Cause of Death in the Patients in the Study.

Cause of Death	Placebo (N = 398)	Carvedilol (N = 696)
	no. (%)	
Progressive heart failure	13 (3.3)	5 (0.7)
Sudden death	15 (3.8)	12 (1.7)
Myocardial ischemia	2 (0.5)	1 (0.1)
Other cardiovascular causes	1 (0.3)	2 (0.3)
Noncardiovascular causes	0	2 (0.3)

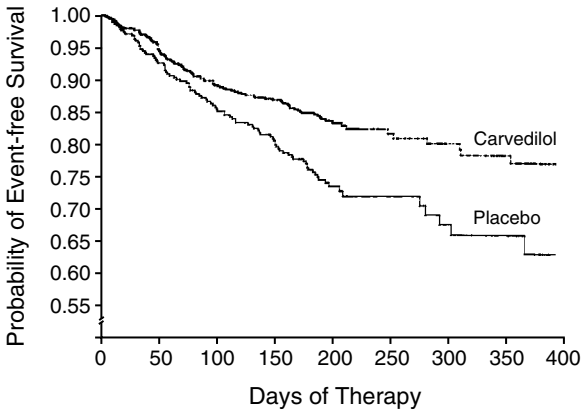
Table 3. Effect of Placebo and Carvedilol Treatment on Mortality in Patient Subgroups.

Variable*	Placebo	Carvedilol	Hazard Ratio (95% CI)†
	no. of deaths/total no.		
Protocol			
Mild heart failure	5/134	2/232	0.22 (0.04–1.14)
Moderate heart failure	11/145	6/133	0.57 (0.21–1.54)
Dose-ranging	13/84	12/261	0.27 (0.12–0.60)
Severe heart failure	2/35	2/70	0.53 (0.07–3.76)
Age (yr)			
<59	11/190	7/350	0.30 (0.11–0.80)
≥59	20/208	15/346	0.38 (0.19–0.77)
Sex			
Male	22/304	17/534	0.41 (0.22–0.80)
Female	9/94	5/162	0.23 (0.07–0.69)
Left ventricular ejection fraction			
<0.23	20/209	10/334	0.25 (0.11–0.56)
≥0.23	11/189	12/360	0.49 (0.21–1.14)
Six-minute walk (m)			
<396	20/202	17/345	0.49 (0.25–0.93)
≥396	11/196	5/351	0.25 (0.09–0.71)
Cause of heart failure			
Ischemic	17/189	13/332	0.35 (0.16–0.73)
Nonischemic	14/208	9/362	0.35 (0.15–0.83)
Systolic blood pressure (mm Hg)			
<115	19/210	13/337	0.34 (0.17–0.70)
≥115	12/188	9/359	0.38 (0.15–0.95)
Heart rate (beats/min)			
<82	10/186	11/354	0.61 (0.25–1.49)
≥82	21/212	11/342	0.26 (0.12–0.55)

*For continuous variables, medians were used to define the subgroups. The type of heart failure was not recorded for one patient in the placebo group and two in the carvedilol group. The ejection fraction was not recorded for two patients in the carvedilol group.

†CI denotes confidence interval.

The initiation of therapy with carvedilol in our study produced side effects consistent with its antiadrenergic actions, but most of these reactions disappeared — either spontaneously or after the adjustment of concomitant medications — and did not require the discontinuation of double-blind treatment. Thus, most patients were able to tolerate target doses of carvedilol. The most feared side effect of beta-blockade — worsening heart failure during the initiation of therapy — was not an important limitation of treatment; 5.9 percent of the patients had this side effect during the open-label period, and an additional 5.1 percent in the carvedilol group and 4.1 percent in the placebo group had this reaction after increases in dose during the early phases of double-blind therapy. It must be emphasized, however, that carvedilol therapy was initiated in the study with extreme care by physicians experienced in the management of heart failure, who followed specific guidelines that encouraged changes in concomitant medications to ensure the safety of the patient. Furthermore, our program recruited few patients with New York Heart Association class IV heart failure,[33] and patients who required hospitalization for intravenous drug support were not enrolled. Hence, our study does not allow any conclusions to be drawn about the



No. at Risk

Placebo	398	336	292	260	134	63	45	35	2
Carvedilol	696	607	529	491	270	117	92	70	9

Figure 2. Kaplan–Meier Analysis of Survival without Hospitalization for Cardiovascular Reasons (Event-free Survival) in the Placebo and Carvedilol Groups.

Patients in the carvedilol group had a 38 percent lower risk of death or hospitalization for cardiovascular disease than patients in the placebo group ($P<0.001$).

safety of carvedilol when it is administered without rigorous supervision or in bedridden patients with advanced heart failure.

To enhance the safety of patients, therapy with carvedilol was initiated in small doses that were gradually increased over a period of several weeks. This cautious approach has been followed in studies of other beta-blockers[12-20,34] and is designed to minimize the adverse effects that may occur after the abrupt withdrawal of the homeostatic support provided by the sympathetic nervous system. Despite such care, however, the frequency of early side effects was expected to be high enough potentially to unblind both the patient and the investigator as to the treatment-group assignment. To avoid this difficulty, we required patients to complete a two-week, open-label period before randomly assigning them to double-blind therapy; this design feature has been part of many trials studying survival in heart failure[19,35,36] and of all previous controlled trials with carvedilol. The use of an open-label period not only allows drug-related side effects to subside before randomization (thus maintaining the blindedness of the study) but also enhances the study's power, since a trial is less likely to detect a true effect on survival if patients are randomly assigned to treatment that cannot be maintained for the planned length of the study. Although deaths may occur during the open-label period, they cannot be validly assigned to either the treatment or the placebo group, since they may be related either to the natural history of heart failure or to carvedilol. Fortunately, the mortality rate during the two-week, open-label period was low (0.6 percent) and was similar to — if not less than — the rate in the preceding three weeks (1.7 percent), during which patients were being screened for the program but were receiving only their usual medications for heart failure.

Our findings should be interpreted with the knowledge that the trial program had several unusual characteristics for a study of the effect of a drug on survival. Most such trials are designed as long-term studies in which nonfatal events are considered to be secondary end points. In our program, however, the individual protocols were designed first to evaluate nonfatal end points as components of a single stratified trial program, and then mortality was specified a priori to assess safety and potential benefit. As a result, the duration of follow-up was short and fixed. Although several trials examining mortality in heart failure have also used a fixed follow-up period,[19,37] such a design necessarily reduces the number of events that can be observed. This explains why, although the annual mortality in our placebo group (14 to 15 percent) was similar to that in many studies,[35,38] we recorded only 53 deaths (since the average follow-up was only 6.5 months). This limited experience restricts our ability to reach conclusions about the true magnitude or persistence of any effect on survival. Yet it should be noted that the number of events during follow-up in our trial was not small if morbidity and mortality are combined; 25 percent of the placebo group died or were hospitalized for cardiovascular reasons, and this combined rate was substantially lower in the carvedilol group. Furthermore, a long follow-up period may not be possible if the finding of a large treatment effect leads the Data and Safety Monitoring Board to recommend early termination of a study, as occurred in this case; the mean duration of follow-up in the present program was similar to that in

Table 4. Most Frequent Adverse Reactions.*

Reaction	Placebo (N = 398)	Carvedilol (N = 696)
	no. (%)	
Dizziness	80 (20)	233 (33)
Fatigue	93 (23)	177 (25)
Dyspnea	101 (25)	150 (22)
Upper respiratory tract infection	74 (19)	133 (19)
Heart failure	84 (21)	111 (16)
Chest pain	61 (15)	104 (15)
Hyperglycemia	34 (9)	88 (13)
Diarrhea	24 (6)	83 (12)
Increase in weight	30 (8)	71 (10)
Cough	40 (10)	58 (8)
Pain	33 (8)	62 (9)
Headache	30 (8)	57 (8)
Nausea	18 (5)	60 (9)
Hypotension	15 (4)	60 (9)
Asthenia	27 (7)	49 (7)
Bradycardia	4 (1)	65 (9)
Worsening renal function	20 (5)	46 (7)
Vomiting	18 (5)	46 (7)

*Patients may have had more than one adverse reaction.

Table 5. Most Frequent Adverse Reactions Leading to Discontinuation of Double-Blind Treatment.*

Reaction	Placebo (N = 398)	Carvedilol (N = 696)
	no. (%)	
Heart failure	9 (2.3)	11 (1.6)
Fatigue	3 (0.8)	5 (0.7)
Myocardial infarction	4 (1.0)	3 (0.4)
Bradycardia	0	6 (0.9)
Dyspnea	4 (1.0)	2 (0.3)
Dizziness	0	3 (0.4)
Hypotension	1 (0.3)	2 (0.3)
Syncope	1 (0.3)	2 (0.3)
Nausea	0	3 (0.4)
Abnormal liver function	1 (0.3)	2 (0.3)
Worsening renal function	1 (0.3)	2 (0.3)
Depression	1 (0.3)	2 (0.3)

*Patients may have had more than one adverse reaction leading to withdrawal of placebo or carvedilol.

other trials that have been terminated early.[36,39,40] Fortunately, long-term data on carvedilol have recently become available from a trial of 415 patients with mild-to-moderate heart failure due to ischemic heart disease who were treated for 18 to 24 months. In that study, carvedilol reduced the combined risk of death or hospitalization by 26 percent (Sharpe N: personal communication) — a finding similar to the 38 percent reduction in mortality and hospitalization we observed.

Our finding that carvedilol reduces morbidity and mortality supports the hypothesis that a beta-blocker can favorably influence the course of disease in patients with heart failure. However, because carvedilol exerts pharmacologic effects atypical of and in addition to its action on adrenergic receptors,[22-24] experience with this drug does not allow us to conclude that all beta-blockers will favorably alter the natural history of this disorder. The question of whether other beta-blockers (such as metoprolol, bisoprolol, and bucindolol) prolong survival in heart failure is being addressed in ongoing trials.

Appendix

The following centers and principal investigators composed the U.S. Carvedilol Heart Failure Study Group: 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.S. Colucci and 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 State University Hospital, R.J. Cody; Dallas — University of Texas Southwestern Medical Center, C.W. Yancy; and Veterans Affairs Medical Center (VAMC), E. Eichhorn; Denver — University of Colorado, M.R. Bristow; 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; University of Texas Medical School, G. Schroth and S.E. El Hafi; Jackson — University of Mississippi Medical Center, J. O'Connell; Jacksonville — University of Florida, A. Miller; Las Vegas — Heart Institute of Nevada, J.A. Bowers; Lincoln — Nebraska Heart Institute, S. Krueger; Los Angeles — University of Southern California School of Medicine, V. DeQuattro; Madison — University of Wisconsin School of Medicine, P.S. Rahko; Memphis — University of Tennessee School of Medicine, K.B. Ramanathan; Miami — University of Miami, E. deMarchena; Mineola, N.Y. — Cardiovascular Medical Associates, M. Goodman; and Winthrop University Hospital, R. Steingart; Minneapolis — University of Minnesota Medical School, S. Kubo and J.N. Cohn; 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, G. W. Neuberg, and M. Packer; Mount Sinai Medical Center, M. Kukin; and St. Luke's–Roosevelt Medical Center, M. Klapholz; Northport, N.Y. — VAMC, G. Mallis; Oklahoma City — University of Oklahoma and VAMC, U. Thadani; Park Ridge, Ill. — Lutheran General Hospital, R.P. Sorkin; Philadelphia — Temple University Hospital, I. Pina; Phoenix, Ariz. — Carl T. Hayden VAMC, J.V. Felicetta; Pittsburgh — Presbyterian University Hospital, B. Uretsky and S. Murali; and Western Pennsylvania Hospital, A. Gradman; Portland — Oregon Health Sciences Center, R. Hershberger; Richmond — 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; Salt Lake City — University of Utah, E.M. Gilbert; 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 VAMC, 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; Stanford, Calif. — Stanford University School of Medicine, M.B. Fowler; Summit, N.J. — Overlook Hospital, J.J. Gregory; Torrance, Calif. — Harbor–UCLA Medical Center, K.A. Narahara; Tucson — University of Arizona Medical Center, S. Butman; Washington, D.C. — Georgetown University Hospital, D. Pearle; Winston-Salem, N.C. — Bowman Gray School of Medicine, F. Kahl; and Worcester — 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. Holcslaw, and L.G. Parchman.

References

1. Thomas JA, Marks BH. Plasma norepinephrine in congestive heart failure. Am J Cardiol 1978;41:233-43.
2. Cohn JN, Levine TB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984;311:819-23.
3. Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. J Am Coll Cardiol 1992;20:248-54.
4. Bristow MR. Pathophysiologic and pharmacologic rationales for clinical management of chronic heart failure with beta-blocking agents. Am J Cardiol 1993;71:12C-22C.
5. Yates JC, Beamish RE, Dhalla NS. Ventricular dysfunction and necrosis produced by adrenochrome metabolite of epinephrine: relation to pathogenesis of catecholamine cardiomyopathy. Am Heart J 1981;102:210-21.
6. Mann DL, Kent RL, Parsons B, Cooper G IV. Adrenergic effects on the biology of the adult mammalian cardiocyte. Circulation 1992;85:790-804.
7. ver Donck L, Wouters L, Olbrich HG, Mutschler E, Borgers M. Nebivolol increases survival in cardiomyopathic hamsters with congestive heart failure. J Cardiovasc Pharmacol 1991;18:1-3.
8. Sabbah HN, Shimoyama H, Kono T, et al. Effects of long-term monotherapy with enalapril, metoprolol, and digoxin on the progression of left ventricular dysfunction and dilation in dogs with reduced ejection fraction. Circulation 1994;89:2852-9.

9. Epstein SE, Braunwald E. The effect of beta adrenergic blockade on patterns of urinary sodium excretion: studies in normal subjects and in patients with heart disease. Ann Intern Med 1966;65:20-7.
10. Waagstein F, Hjalmarson A, Varnauskas E, Wallentin I. Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy. Br Heart J 1975;37:1022-36.
11. Swedberg K, Hjalmarson A, Waagstein F, Wallentin I. Prolongation of survival in congestive cardiomyopathy by beta-receptor blockade. Lancet 1979;1:1374-6.
12. Eichhorn EJ, Heesch CM, Barnett JH, et al. Effect of metoprolol on myocardial function and energetics in patients with nonischemic dilated cardiomyopathy: a randomized, double-blind, placebo-controlled study. J Am Coll Cardiol 1994;24:1310-20.
13. Fisher ML, Gottlieb SS, Plotnick GD, et al. Beneficial effects of metoprolol in heart failure associated with coronary artery disease: a randomized trial. J Am Coll Cardiol 1994;23:943-50.
14. Woodley SL, Gilbert EM, Anderson JL, et al. Beta-blockade with bucindolol in heart failure caused by ischemic versus idiopathic dilated cardiomyopathy. Circulation 1991;84:2426-41.
15. Bristow MR, O'Connell JB, Gilbert EM, et al. Dose-response of chronic β-blocker treatment in heart failure from either idiopathic dilated or ischemic cardiomyopathy. Circulation 1994;89:1632-42.
16. Olsen SL, Gilbert EM, Renlund DG, Taylor DO, Yanowitz FD, Bristow MR. Carvedilol improves left ventricular function and symptoms in chronic heart failure: a double-blind randomized study. J Am Coll Cardiol 1995;25:1225-31.
17. Metra M, Nardi M, Giubbini R, Cas LD. Effects of short- and long-term carvedilol administration on rest and exercise hemodynamic variables, exercise capacity and clinical conditions in patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol 1994;24:1678-87.
18. Krum H, Sackner-Bernstein JD, Goldsmith RL, et al. Double-blind, placebo-controlled study of the long-term efficacy of carvedilol in patients with severe chronic heart failure. Circulation 1995;92:1499-506.
19. Waagstein F, Bristow MR, Swedberg K, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Lancet 1993;342:1441-6.
20. CIBIS Investigators and Committees. A randomized trial of β-blockade in heart failure: the Cardiac Insufficiency Bisoprolol Study (CIBIS). Circulation 1994;90:1765-73.
21. Bril A, Slivjak M, DiMartino MJ, et al. Cardioprotective effects of carvedilol, a novel beta adrenoceptor antagonist with vasodilating properties, in anaesthetized minipigs: comparison with propranolol. Cardiovasc Res 1992;26:518-25.
22. Ruffolo RR Jr, Gellai M, Heible JP, Willette RN, Nicholas AJ. The pharmacology of carvedilol. Eur J Clin Pharmacol 1990;38:Suppl 2:S82-S88.
23. Yoshikawa T, Port JD, Asano K, et al. Cardiac adrenergic effects of carvedilol. Eur Heart J (in press).
24. Yue T-L, Cheng H-Y, Lysko PG, et al. Carvedilol, a new vasodilator and beta adrenoceptor antagonist, is an antioxidant and free radical scavenger. J Pharmacol Exp Ther 1992;263:92-8.
25. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
26. Cox DR. Regression models and life-tables. J R Stat Soc [B] 1972;34:187-202.
27. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.
28. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. Br J Cancer 1976;34:585-612.
29. Gilbert EM, Olsen SL, Renlund DG, Bristow MR. Beta-adrenergic receptor regulation and left ventricular function in idiopathic dilated cardiomyopathy. Am J Cardiol 1993;71:23C-29C.
30. Newton GE, Parker JD. β_1 vs nonselective β-blockade in human congestive heart failure: acute effects on cardiac sympathetic activity. Circulation 1995;92:Suppl I:I-395. abstract.
31. Bristow MR, Olsen S, Gilbert EM, et al. β-blockade with carvedilol selectively lowers cardiac adrenergic drive in the failing human heart. J Am Coll Cardiol 1992;19:146A. abstract.
32. Dhalla AK, Singh N, Singal PK. Antioxidant therapy associated with the reversal of oxidative stress delays the pathogenesis of heart failure. Circulation 1994;90:I-491. abstract.
33. Sackner-Bernstein J, Krum H, Goldsmith RL, et al. Should worsening heart failure early after initiation of beta-blocker therapy for chronic heart failure preclude long-term treatment? Circulation 1995;92:Suppl I:I-395. abstract.
34. Waagstein F, Caidahl K, Wallentin I, Bergh CH, Hjalmarson A. Long-term β-blockade in dilated cardiomyopathy: effects of short- and long-term metoprolol treatment followed by withdrawal and readministration of metoprolol. Circulation 1989;80:551-63.
35. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.
36. Packer M, Rouleau J, Swedberg K, et al. Effect of flosequinan on survival in chronic heart failure: preliminary results of the PROFILE Study. Circulation 1993;88:Suppl I:I-301. abstract.
37. Feldman AM, Bristow MR, Parmley WW, et al. Effects of vesnarinone on morbidity and mortality in patients with heart failure. N Engl J Med 1993; 329:149-55.
38. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. N Engl J Med 1986;314:1547-52.
39. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316: 1429-35.
40. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. N Engl J Med 1991;325:1468-75.