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EFFECT OF CARVEDILOL ON SURVIVAL IN SEVERE CHRONIC HEART FAILURE

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ABSTRACT

Background Beta-blocking agents reduce the risk of hospitalization and death in patients with mild-to-moderate heart failure, but little is known about their effects in severe heart failure.

Methods We evaluated 2289 patients who had symptoms of heart failure at rest or on minimal exertion, who were clinically euvolemic, and who had an ejection fraction of less than 25 percent. In a double-blind fashion, we randomly assigned 1133 patients to placebo and 1156 patients to treatment with carvedilol for a mean period of 10.4 months, during which standard therapy for heart failure was continued. Patients who required intensive care, had marked fluid retention, or were receiving intravenous vasodilators or positive inotropic drugs were excluded.

Results There were 190 deaths in the placebo group and 130 deaths in the carvedilol group. This difference reflected a 35 percent decrease in the risk of death with carvedilol (95 percent confidence interval, 19 to 48 percent; P=0.0014, adjusted for interim analyses). A total of 507 patients died or were hospitalized in the placebo group, as compared with 425 in the carvedilol group. This difference reflected a 24 percent decrease in the combined risk of death or hospitalization with carvedilol. The favorable effects on both end points were seen consistently in all the subgroups we examined. Fewer patients in the carvedilol group than in the placebo group withdrew because of adverse effects or for other reasons (P=0.02).

Conclusions The previously reported benefits of carvedilol with regard to morbidity and mortality in patients with mild-to-moderate heart failure were also found in the patients with severe heart failure who were evaluated in this trial. (N Engl J Med 2001;344: 1651-8.)

BETA-BLOCKING agents have been shown to reduce the risk of hospitalization and death in patients with mild-to-moderate heart failure,[1-4] but little is known about the efficacy or safety of these agents in severe heart failure. Earlier large-scale studies with bisoprolol, carvedilol, and metoprolol enrolled primarily patients with New York Heart Association class II or III symptoms, and thus they did not provide meaningful information about the effects of these drugs in patients who have symptoms at rest or on minimal exertion. Only one large-scale study of beta-blockade (with bucindolol) focused on patients with severe heart failure; it did not demonstrate a favorable effect of treatment on survival and suggested that therapy might adversely affect patients who are at the highest risk.[5] The results of the bucindolol trial raised the possibility that the benefits of beta-blockade might diminish as the disease advances[6] and reinforced the long-held concern that beta-blockers may worsen heart failure, particularly in patients with the most advanced disease.[7,8]

We conducted a large-scale, prospective, randomized, double-blind, placebo-controlled trial of the effect of the beta-blocker carvedilol on the survival of patients with severe heart failure. Like bisoprolol and metoprolol, carvedilol has been shown to improve

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*The investigators and coordinators of the study group are listed in the Appendix.

symptoms and reduce the risk of disease progression in patients with mild-to-moderate heart failure.[1-3] However, unlike bisoprolol and metoprolol, which interact primarily with β_1-receptors, carvedilol blocks α_1-, β_1-, and β_2-receptors[9] and can interfere with the adverse effects of sympathetic activation through several nonadrenergic mechanisms.[10-14] These additional actions may be particularly important in patients with severe heart failure.[15,16]

METHODS

Conduct of the Study

The trial was designed, executed, and analyzed by a steering committee, an end-points committee, a biostatistics center, and a data and safety monitoring board, all of whom operated independently of the sponsors. The protocol was approved by the institutional review boards of all participating institutions, and written informed consent was obtained from all patients.

Study Patients

Patients with severe chronic heart failure as a result of ischemic or nonischemic cardiomyopathy were enrolled at 334 centers in 21 countries. Severe chronic heart failure was defined by the occurrence of dyspnea or fatigue at rest or on minimal exertion for at least two months and a left ventricular ejection fraction of less than 25 percent, despite appropriate conventional therapy. Such therapy was defined as treatment with diuretics (in doses adjusted to achieve clinical euvolemia) and an angiotensin-converting–enzyme inhibitor or an angiotensin II–receptor antagonist (unless such therapy was not tolerated). "Clinical euvolemia" was defined as the absence of rales and ascites and the presence of no more than minimal peripheral edema, unless these signs were considered to be due to noncardiac causes. Treatment with digitalis, nitrates, hydralazine, spironolactone, and amiodarone was allowed, but not required. Hospitalized patients could be enrolled, but only if they had no acute cardiac or noncardiac illness that required intensive care or continued inpatient care. Recent adjustments in medications (including the use of intravenous diuretics immediately before randomization) were allowed, but intravenous positive inotropic agents or intravenous vasodilators were not permitted within four days of screening.

Patients were excluded from the study if they had heart failure that was caused by uncorrected primary valvular disease or a reversible form of cardiomyopathy; had received or were likely to receive a cardiac transplant; had severe primary pulmonary, renal, or hepatic disease; or had a contraindication to beta-blocker therapy. In addition, patients were excluded if, within the previous two months, they had undergone coronary revascularization or had had an acute myocardial or cerebral ischemic event or a sustained or hemodynamically destabilizing ventricular tachycardia or fibrillation. Patients who had received an alpha-adrenergic blocker, a calcium-channel blocker, or a class I antiarrhythmic drug within the previous four weeks or a beta-blocker within the previous two months were also excluded. Finally, patients were excluded if they had a systolic blood pressure lower than 85 mm Hg; a heart rate lower than 68 beats per minute; a serum creatinine concentration higher than 2.8 mg per deciliter (247.5 μmol per liter); a serum potassium concentration lower than 3.5 mmol per liter or higher than 5.2 mmol per liter; or an increase of more than 0.5 mg per deciliter (44.2 μmol per liter) in the serum creatinine concentration or a change in body weight of more than 1.5 kg during the screening period (3 to 14 days).

Study Design

Patients who fulfilled all the entry criteria were randomly assigned in a 1:1 ratio and in a double-blind fashion to receive either oral carvedilol or matching placebo in addition to their usual medications for heart failure. Patients received an initial dose of 3.125 mg of carvedilol or placebo twice daily for two weeks, which was then increased at two-week intervals (if tolerated), first to 6.25 mg, then to 12.5 mg, and finally to a target dose of 25 mg twice daily. During the period of upward titration, patients were instructed to report adverse effects or weight gain; the dose of other medications could be modified and the rapidity of upward titration of the dose of the study drug could be decreased, if such adjustments were clinically warranted. Patients were then evaluated every two months until the end of the study. During this maintenance period, carvedilol or placebo could be temporarily discontinued or the dose reduced, but investigators were encouraged to reinstitute treatment with partial or full doses at a later time. Doses of all concomitant drugs could be adjusted at the discretion of the investigator. If the patient's condition deteriorated during the study, the investigator could use any interventions that were clinically indicated; however, investigators were instructed not to institute open-label treatment with a beta-blocker.

Statistical Analysis

The primary end point of the study was death from any cause, and the combined risk of death or hospitalization for any reason was one of four prespecified secondary end points. Cumulative survival curves for both end points were constructed by the Kaplan–Meier method,[17] and differences between the curves were tested for significance with the use of the log-rank statistic. Cox proportional-hazards regression models were used to estimate the hazard ratios and 95 percent confidence intervals.[18] The analyses included all randomized patients, and all events were attributed to the patient's original randomly assigned treatment group (according to the intention-to-treat principle). Data for patients who underwent cardiac transplantation were censored at the time of transplantation, and hospitalizations of less than 24 hours, as well as those that were only for the purpose of providing housing for the patient, were not included.

The sample size was estimated on the basis of the following assumptions: the one-year mortality in the placebo group would be 28 percent[19]; the risk of death would be altered by 20 percent as a result of treatment with carvedilol; and the study would have 90 percent power (two-sided $\alpha = 0.05$) to detect a significant difference between the treatment groups. Since it was recognized that the estimate of the rate of events might be too high, the trial was designed to continue until 900 deaths had occurred.

An independent data and safety monitoring board was prospectively constituted at the start of the study; this board periodically reviewed the unblinded results and was empowered to recommend early termination of the study if it observed a treatment effect on survival that exceeded the prespecified boundaries. To protect against increasing the false positive error rate with repeated interim analyses, we used a truncated O'Brien–Fleming-type boundary,[20] computed with the use of the Lan–DeMets procedure.[21]

The effect of carvedilol on survival and on the combined risk of death or hospitalization was assessed for subgroups defined by six base-line variables: age (<65 vs. ≥ 65 years); sex; left ventricular ejection fraction (<20 vs. ≥ 20 percent); cause of heart failure (ischemic vs. nonischemic cardiomyopathy); location of the study center (North or South America vs. Europe, Asia, Africa, or Australia); and history or lack of history of hospitalization for heart failure within one year before enrollment in the study. The first four subgroup analyses were specified in the original protocol. In addition, because earlier studies had suggested that the patients at the highest risk might respond poorly to beta-blockade,[5,6] further analyses were conducted to determine whether there were patients in the present trial who had heart failure too advanced to benefit from treatment. These analyses consisted of assessments of the effects of carvedilol in a subgroup of patients at very high risk, defined as those with recent or recurrent cardiac decompensation or severely depressed cardiac function that was characterized by one or more of the following: the presence of pulmonary rales, ascites, or edema at randomization; three or more hospitalizations for heart failure within the previous year; hospitalization at the

time of screening or randomization; the need for an intravenous positive inotropic agent or an intravenous vasodilator drug within 14 days before randomization; or a left ventricular ejection fraction of 15 percent or lower. The base-line variables that defined this high-risk group were identified without knowledge of their influence on the effect of treatment.

RESULTS

Randomization began on October 28, 1997, and was stopped early (on March 20, 2000) on the recommendation of the data and safety monitoring board. This recommendation was based on the finding of a significant beneficial effect of carvedilol on survival that exceeded the prespecified interim monitoring boundaries.

At the time of the early termination of the trial, 2289 patients had been assigned to treatment groups — 1133 to the placebo group and 1156 to the carvedilol group. The two treatment groups were similar with respect to all base-line characteristics (Table 1). After four months, 78.2 percent of the surviving patients in the placebo group and 65.1 percent of those in the carvedilol group were receiving the target doses of their assigned medications (mean doses, 41 mg of placebo daily and 37 mg of carvedilol daily), and these doses were generally maintained until the end of the study. The mean duration of follow-up was 10.4 months. During this time, no patient was lost to follow-up with regard to mortality, and fewer than 5 percent of the patients received open-label treatment with a beta-blocker.

Effect of Carvedilol on Survival

According to the intention-to-treat analysis, 190 patients in the placebo group died and 130 patients in the carvedilol group died; this difference reflected a 35 percent decrease in the risk of death with carvedilol (95 percent confidence interval, 19 to 48 percent; $P=0.00013$ [unadjusted] and $P=0.0014$ [after adjustment for interim analyses]) (Fig. 1). According to the Kaplan–Meier analysis, the cumulative risk of death at one year was 18.5 percent in the placebo group and 11.4 percent in the carvedilol group.

A total of 12 patients (6 in each group) underwent cardiac transplantation, after which 3 died (2 in the carvedilol group and 1 in the placebo group). The results with respect to mortality were essentially the same when the data for the patients who received transplants were not censored and when deaths after transplantation were included in the analysis.

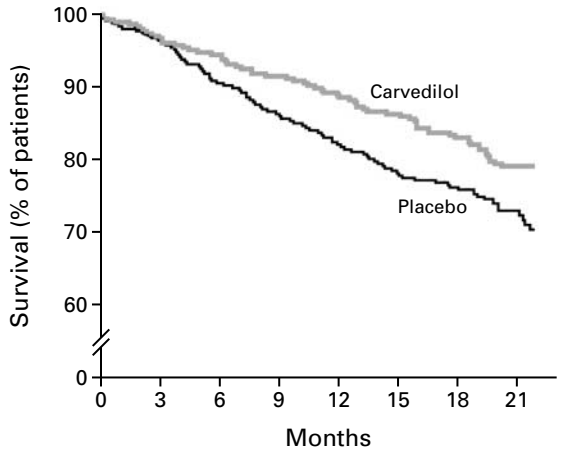
Effect of Carvedilol on the Combined Risk of Death or Hospitalization

According to the intention-to-treat analysis, there were 507 patients who died or were hospitalized in the placebo group and 425 such patients in the carvedilol group; this difference reflected a risk of the

TABLE 1. PRETREATMENT CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	ALL RANDOMIZED PATIENTS		PATIENTS WITH RECENT OR RECURRENT DECOMPENSATION	
	PLACEBO (N=1133)	CARVEDILOL (N=1156)	PLACEBO (N=316)	CARVEDILOL (N=308)
Age (yr)	63.4±11.5	63.2±11.4	62.6±11.5	64.9±11.1
Male sex (% of patients)	80	79	81	79
Ischemic cause of heart failure (% of patients)	67	67	66	69
Left ventricular ejection fraction (%)	19.8±4.0	19.9±4.0	16.1±4.8	16.3±4.7
Hospitalization for heart failure within previous year (% of patients)	65	66	74	72
Blood pressure (mm Hg)				
Systolic	123±19	123±19	119±18	118±19
Diastolic	76±11	76±11	75±11	74±11
Heart rate (beats/min)	83±13	83±12	83±13	84±12
Serum sodium (mmol/liter)	137±3	137±3	137±3	137±3
Serum creatinine (μmol/liter)	134±36	134±37	140±42	139±41
Concomitant medications (% of patients)				
Digitalis	65	67	72	76
Diuretics	99	99	99	99
ACE inhibitor or angiotensin II antagonist	97	97	96	97
Spironolactone	20	19	23	26
Amiodarone	17	18	22	22

*All continuous data are expressed as means ±SD. ACE denotes angiotensin-converting enzyme. To convert the values for creatinine to milligrams per deciliter, divide by 88.4.

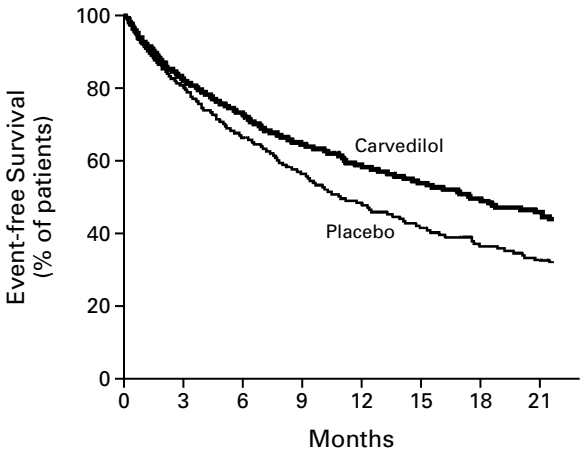


NO. OF PATIENTS AT RISK

Placebo	1133	937	703	580	446	286	183	114
Carvedilol	1156	947	733	620	479	321	208	142

Figure 1. Kaplan–Meier Analysis of Time to Death in the Placebo Group and the Carvedilol Group.

The 35 percent lower risk in the carvedilol group was significant: P=0.00013 (unadjusted) and P=0.0014 (adjusted).



NO. OF PATIENTS AT RISK

Placebo	1133	767	513	377	262	154	88	55
Carvedilol	1156	789	559	431	318	208	122	81

Figure 2. Kaplan–Meier Analysis of Time to Death or First Hospitalization for Any Reason in the Placebo Group and the Carvedilol Group.

The 24 percent lower risk in the carvedilol group was significant (P<0.001).

combined end point that was 24 percent lower as a result of treatment with carvedilol (95 percent confidence interval, 13 to 33 percent; P<0.001) (Fig. 2).

Effect of Carvedilol in Subgroups

The reduction in mortality and in the combined risk of death or hospitalization with carvedilol was similar in direction and in magnitude in subgroups defined according to age, sex, left ventricular ejection fraction, cause of heart failure, location of the study center, and history with respect to hospitalization for heart failure within the previous year (Fig. 3 and 4).

The favorable effects of carvedilol on both end points were apparent even in the patients at the highest risk — namely, those with recent or recurrent cardiac decompensation or severely depressed cardiac function — for whom the cumulative risk of death within one year was 24.0 percent in the placebo group, according to the Kaplan–Meier analysis. In this high-risk cohort, carvedilol reduced the risk of death by 39 percent (95 percent confidence interval, 11 to 59 percent; P=0.009) and decreased the combined risk of death or hospitalization by 29 percent (95 percent confidence interval, 11 to 44 percent; P=0.003).

Safety

Fewer patients in the carvedilol group than in the placebo group required the permanent discontinuation of treatment because of adverse effects or for reasons other than death (P=0.02) (Fig. 5). According to the Kaplan–Meier analysis, the cumulative withdrawal rates at one year for the total cohort were 18.5 percent in the placebo group and 14.8 percent in the carvedilol group. The withdrawal rates for the patients with recent or recurrent cardiac decompensation or severely depressed cardiac function were 24.2 percent in the placebo group and 17.5 percent in the carvedilol group.

DISCUSSION

The results of this study demonstrate that long-term treatment with carvedilol has substantial benefit in patients with severe chronic heart failure. The addition of carvedilol to conventional therapy for a mean of 10.4 months decreased the rate of death by 35 percent and the rate of death or hospitalization by 24 percent. These benefits were apparent regardless of age, sex, cause of heart failure, left ventricular ejection fraction, or recent history with respect to hospitalization and were seen even in patients with a history of recent or recurrent cardiac decompensation or severely depressed cardiac function. Finally, treatment with carvedilol was well tolerated; fewer patients in the carvedilol group than in the placebo group required permanent discontinuation of treatment because of adverse effects or for other reasons. These benefits were observed in a group of patients who were clinically euvolemic and were not receiving

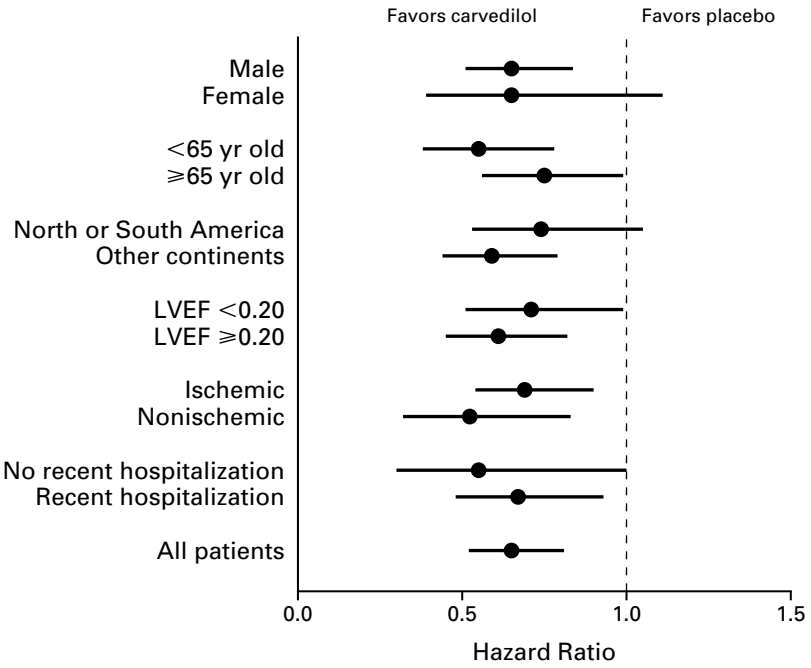


Figure 3. Hazard Ratios (and 95 Percent Confidence Intervals) for Death from Any Cause in Subgroups Defined According to Base-Line Characteristics.

LVEF denotes left ventricular ejection fraction. Recent hospitalization refers to hospitalization for heart failure within the year before enrollment.

intravenous positive inotropic agents or intravenous vasodilator drugs for the treatment of heart failure.

We observed favorable effects of carvedilol in patients whose heart failure was more advanced than that of patients enrolled in earlier large-scale trials of beta-blockers. Whereas earlier studies focused primarily on patients with mild-to-moderate symptoms, our study enrolled patients who had symptoms at rest or on minimal exertion. Consequently, the 18.5 percent risk of death within one year in our placebo group (or the annual mortality rate of 19.7 percent per patient-year of follow-up) was higher than the corresponding rates, ranging from 11.0 percent to 16.6 percent, in trials of metoprolol, bisoprolol, and bucindolol[2,3,5] but was similar to the annual mortality rate of 20.7 percent among the patients in these studies who had New York Heart Association class IV symptoms and who were assigned to placebo.[22] The pretreatment values for the ejection fraction in our trial were also lower than those in previous studies of patients with severe heart failure, despite similar systolic blood pressures and heart rates before treatment.[19,23,24] Finally, many patients in our trial had evidence of recent or recurrent cardiac decompensation, and in this subgroup, the risk of death at one year in the placebo group was 24.0 percent (or an annual mortality rate of 28.5 percent per patient-year of follow-up) — a risk that was similar to the rates among the patients with the most advanced degrees of heart failure in other studies.[2-5,19,24] Previous work has raised important questions about both the efficacy and the safety of beta-blockade in such severe degrees of heart failure,[5-8] yet carvedilol was effective and well tolerated both in our patients overall and in those at the highest risk.

Although all the patients in our study had severe heart failure, not all patients with severe heart failure were allowed to participate in the trial. Patients who required intensive care, had marked fluid retention, or were receiving intravenous vasodilators or intravenous positive inotropic agents were not enrolled. We also excluded patients with symptomatic hypotension or severe renal dysfunction. Thus, physicians should not assume that such patients would have favorable responses to treatment with carvedilol. It is possible that activation of the sympathetic nervous system in such critically ill patients is essential to the maintenance of circulatory homeostasis[25]; if so, sympathetic antagonism might be ineffective or might lead to rapid clinical deterioration.[7,25] Therefore, instead of prescribing carvedilol for such patients in the midst of their acute illness, it would be prudent first to take

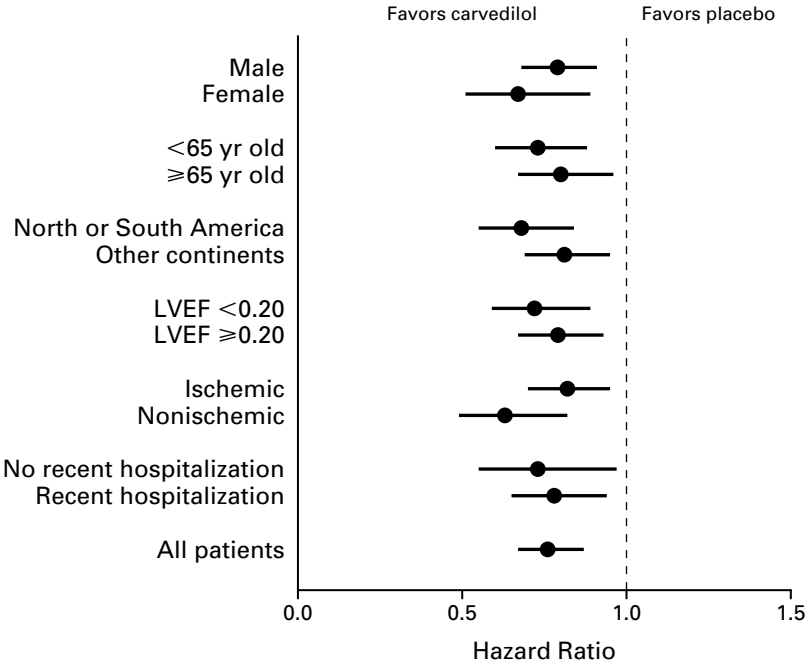


Figure 4. Hazard Ratios (and 95 Percent Confidence Intervals) for the Combined Risk of Death or Hospitalization for Any Reason in Subgroups Defined According to Base-Line Characteristics.

LVEF denotes left ventricular ejection fraction. Recent hospitalization refers to hospitalization for heart failure within the year before enrollment.

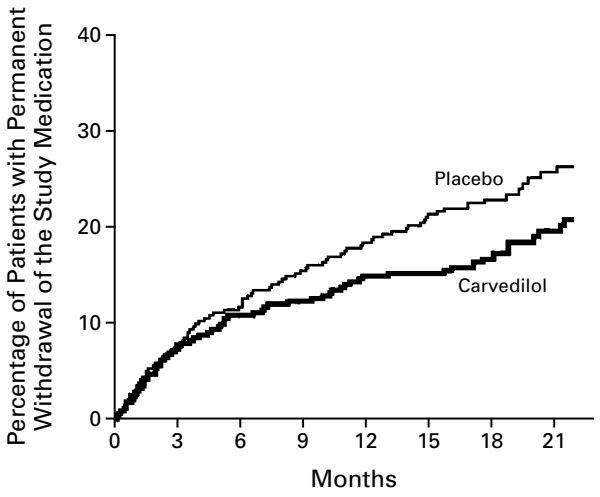


Figure 5. Kaplan–Meier Analysis of the Time to Permanent Withdrawal of the Study Medication because of Adverse Reactions or for Reasons Other Than Death in the Placebo Group and the Carvedilol Group.

The risk of withdrawal was 23 percent lower in the carvedilol group (95 percent confidence interval, 4 to 38 percent; P=0.02).

measures to stabilize their clinical condition (particularly with respect to volume status) and then to initiate treatment with carvedilol. Consultation with a physician who has expertise in the care of patients with advanced heart failure may also be warranted. Such precautions would mirror precisely the procedures that were followed before the enrollment of patients in the present study.

The mechanisms by which carvedilol reduces mortality among patients with heart failure remain unclear. Like other beta-blockers, carvedilol antagonizes β_1-receptors, but not all drugs that block β_1-receptors have a favorable effect on mortality or on the combined risk of death or hospitalization when administered to patients with advanced heart failure.[4,5,26] Like bucindolol, carvedilol blocks β_2-receptors,[9] but unlike bucindolol, carvedilol prolongs life in patients with severe symptoms.[5] How can this difference be explained? On the one hand, bucindolol may exert additional actions (e.g., intrinsic sympathomimetic activity)[27,28] that may have deleterious effects in patients with severe heart failure.[26] Direct studies of cardiac tissue, however, have raised doubts as to whether bucindolol has intrinsic sympathomimetic activity in failing human hearts.[29] On the other hand, carve-

dilol has additional properties (e.g., alpha-adrenergic blockade, antioxidant activity, and antiendothelin effects[9,10,12]) that may enhance its ability to attenuate the adverse effects of the sympathetic nervous system on the circulation.[11,13,14,30,31] These additional actions may be particularly important in severe heart failure.[15,16] Regardless of the mechanisms involved, the differences observed between the effects of carvedilol and those of bucindolol in large-scale trials suggest that a drug should not be assumed to be effective in patients with severe heart failure simply because it has the ability to block beta-adrenergic receptors.

To place the findings of the present study in context, if physicians treated 1000 patients with severe heart failure similar to that found in the patients in our trial with carvedilol for one year, approximately 70 premature deaths would be prevented. This effect compares favorably with the approximately 20 to 40 deaths that would be prevented if angiotensin-converting–enzyme inhibitors or beta-blockers were administered for one year to 1000 patients with mild-to-moderate symptoms[2,3,32] and with the approximately 50 deaths that would be prevented if an aldosterone antagonist were prescribed for one year to 1000 patients with severe symptoms.[24]

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APPENDIX

The members of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group were as follows: *Steering Committee:* M. Packer (chair), A. Castaigne, A. Coats, M. Fowler, H. Katus, H. Krum, P. Mohacsi, J.-L. Rouleau, M. Tendera; *Data and Safety Monitoring Board:* K. Swedberg (chair), C. Angermann, R. Campbell (deceased), J. Cohn, A. Maseri, S. Pocock; *End Point Committee:* P. Carson (chair), V. Bernstein, C. O'Connor, M. Haass, V. Mareev, A. Miller, S. Perrone, B. Rauch, G. Sutton; *Operations Committee:* C. Staiger (cochair), E. Curtin (cochair), I. Amann-Zalan, M. Harsch, T. Holcslaw, E. Kroener-Bentel, D. Messinger. *Investigators: Argentina* — F. Diez, E. Kuschnir; *Australia* — P. Garrahy, J. Horowitz, I. Jeffery, J. Karrasch, P. McDonald, J. Waites; *Austria* — B. Eber, F. Schmalzl, J. Slany, R. Spinka, W. Weihs; *Canada* — P. Alain, M. Arnold, R. Baigrie, M. Bentley-Taylor, J. Bonet, J. Champagne, P. Costi, T. Cuddy, D. Dion, D. Fell, D. Gossard, M. 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