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 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.)

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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.\textsuperscript{1,4}
However, unlike bisoprolol and metoprolol, which interact primarily with $\beta_1$-receptors, carvedilol blocks $\alpha_1$, $\beta_1$, and $\beta_2$-receptors\textsuperscript{5} and can interfere with the adverse effects of sympathetic activation through several nonadrenergic mechanisms.\textsuperscript{10,14} These additional actions may be particularly important in patients with severe heart failure.\textsuperscript{15,16}

\section*{METHODS}

\subsection*{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.

\subsection*{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 euvoeola) and an angiotensin-converting–enzyme inhibitor or an angiotensin II–receptor antagonist (unless such therapy was not tolerated). “Clinical euvoeola” 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 inotrope 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 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 1 antiarrhythmic drug 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 $\mu$mol 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 $\mu$mol 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).

\subsection*{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.

\subsection*{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,\textsuperscript{15} 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.\textsuperscript{16} 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\textsuperscript{17}; 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 $a=0.05$) 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,\textsuperscript{18} computed with the use of the Lan–DeMets procedure.\textsuperscript{21}

The effect of carvedilol on survival and on the combined risk of death or hospitalization was assessed for subgroups defined by six baseline variables: age ($<65$ vs. $\geq65$ years); sex; left ventricular ejection fraction ($<20$ vs. $\geq20$ 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,\textsuperscript{19} 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=0.0013 \{unadjusted\} and P=0.0014 \{after adjustment for interim analyses\} \(\times\) 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

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Randomized Patients</th>
<th>Patients with Recent or Recurrent Decompensation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=1133)</td>
<td>Carvedilol (N=1156)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>63.4±11.5</td>
<td>63.2±11.4</td>
</tr>
<tr>
<td>Male sex (% of patients)</td>
<td>80</td>
<td>79</td>
</tr>
<tr>
<td>Ischemic cause of heart failure (% of patients)</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>19.8±4.0</td>
<td>19.9±4.0</td>
</tr>
<tr>
<td>Hospitalization for heart failure within previous year (% of patients)</td>
<td>65</td>
<td>66</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>123±19</td>
<td>123±19</td>
</tr>
<tr>
<td>Diastolic</td>
<td>76±11</td>
<td>76±11</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>83±13</td>
<td>83±12</td>
</tr>
<tr>
<td>Serum sodium (mmol/liter)</td>
<td>137±3</td>
<td>137±3</td>
</tr>
<tr>
<td>Serum creatinine (µmol/liter)</td>
<td>134±56</td>
<td>134±57</td>
</tr>
<tr>
<td>Concomitant medications (% of patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digitals</td>
<td>65</td>
<td>67</td>
</tr>
<tr>
<td>Diuretics</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>ACE inhibitor or angiotensin II antag-</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>onist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>17</td>
<td>18</td>
</tr>
</tbody>
</table>

*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.
The New England Journal of Medicine

The 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 euvoletic and were not receiving...
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 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. 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. 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. Previous work has raised important questions about both the efficacy and the safety of beta-blockade in such severe degrees of heart failure, 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; if so, sympathetic antagonism might be ineffective or might lead to rapid clinical deterioration. Therefore, instead of prescribing carvedilol for such patients in the midst of their acute illness, it would be prudent first to take
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 $\beta_1$-receptors, but not all drugs that block $\beta_1$-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 $\beta_2$-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-

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.

<table>
<thead>
<tr>
<th></th>
<th>Favors carvedilol</th>
<th>Favors placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr old</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\geq$65 yr old</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North or South America</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other continents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF &lt;0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF $\geq$0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td></td>
<td></td>
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<tr>
<td>Nonischemic</td>
<td></td>
<td></td>
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<tr>
<td>No recent hospitalization</td>
<td></td>
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<tr>
<td>Recent hospitalization</td>
<td></td>
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<tr>
<td>All patients</td>
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</tbody>
</table>

Hazard Ratio

0.0 1.5

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; $P=0.02$).
EFFECT OF CARVEDILOL ON SURVIVAL IN SEVERE CHRONIC HEART FAILURE

Carvedilol has additional properties (e.g., alpha-adrenergic blockade, antioxidant activity, and antiendothelin effects) that may enhance its ability to attenuate the adverse effects of the sympathetic nervous system on the circulation.11,13,14,50,51 These additional actions may be particularly important in severe heart failure.15,26 Regardless of the mechanisms involved, the differences observed between the effects of carvedilol and those of bucindol 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.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

We are indebted to Diethelm Messinger, M.S., and Ilidko Amanu-Zalan, M.D., of Roche Pharmaceuticals and to Terry Holc- slaw, Ph.D., of GlaxoSmithKline for their invaluable contributions to this study.

APPENDIX


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REFERENCES


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