

Packer M, Coats AJS, Fowler MD, et al for the COPERNICUS Study Group. Effect of carvedilol on the morbidity of patients with severe chronic heart failure. N Engl J Med 2001; 344: 1651-1658. Prior studies had confirmed mortality benefit with the use of Metoprolol (Merit-HF: Lancet 1999; 353: 2001-2007) and Bisoprolol (CIBIS II: Lancet 1999; 353: 9-13). The authors of COPERNICUS chose Carvedilol for its alpha-1, beta-1, and beta-2 suppression. They showed a 35% reduction in mortality over a mean follow-up of 10.4 months in class III-IV CHF patients (EF<25%). This provided further evidence that suppressing the neurohormonal axis could delay the progression of CHF and improve survival. It is important to realize that none of these studies enrolled patients who were in the midst of decompensated heart failure or an acute exacerbation. The role of these medications in the acute setting remains controversial. However, each patient with newly diagnosed CHF who can tolerate them should be discharged on one of these three beta blockers.

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Effect of Carvedilol on the Morbidity of Patients With Severe Chronic Heart Failure: Results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study

Milton Packer, Michael B. Fowler, Ellen B. Roecker, Andrew J.S. Coats, Hugo A. Katus, Henry Krum, Paul Mohacsi, Jean L. Rouleau, Michal Tendera, Christoph Staiger, Terry L. Holcslaw, Ildiko Amann-Zalan, David L. DeMets and for the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group

Circulation 2002;106:2194-2199; originally published online Oct 7, 2002;

DOI: 10.1161/01.CIR.0000035653.72855.BF

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

Copyright © 2002 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org/cgi/content/full/106/17/2194>

Data Supplement (unedited) at:

<http://circ.ahajournals.org/cgi/content/full/106/17/2194/DC2>

Subscriptions: Information about subscribing to *Circulation* is online at

<http://circ.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:

journalpermissions@lww.com

Reprints: Information about reprints can be found online at

<http://www.lww.com/reprints>

Effect of Carvedilol on the Morbidity of Patients With Severe Chronic Heart Failure

Results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study

Milton Packer, MD; Michael B. Fowler, MD; Ellen B. Roecker, PhD; Andrew J.S. Coats, MD; Hugo A. Katus, MD; Henry Krum, MB, BS, PhD; Paul Mohacsi, MD; Jean L. Rouleau, MD; Michal Tendera, MD; Christoph Staiger, MD; Terry L. Holcslaw, PhD; Ildiko Amann-Zalan, MD; David L. DeMets, PhD; for the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group

Background— β -Blocking agents improve functional status and reduce morbidity in mild-to-moderate heart failure, but it is not known whether they produce such benefits in severe heart failure.

Methods and Results—We randomly assigned 2289 patients with symptoms of heart failure at rest or on minimal exertion and with an ejection fraction $<25\%$ (but not volume-overloaded) to double-blind treatment with either placebo ($n=1133$) or carvedilol ($n=1156$) for an average of 10.4 months. Carvedilol reduced the combined risk of death or hospitalization for a cardiovascular reason by 27% ($P=0.00002$) and the combined risk of death or hospitalization for heart failure by 31% ($P=0.000004$). Patients in the carvedilol group also spent 27% fewer days in the hospital for any reason ($P=0.0005$) and 40% fewer days in the hospital for heart failure ($P<0.0001$). These differences were as a result of both a decrease in the number of hospitalizations and a shorter duration of each admission. More patients felt improved and fewer patients felt worse in the carvedilol group than in the placebo group after 6 months of maintenance therapy ($P=0.0009$). Carvedilol-treated patients were also less likely than placebo-treated patients to experience a serious adverse event ($P=0.002$), especially worsening heart failure, sudden death, cardiogenic shock, or ventricular tachycardia.

Conclusion—In euvoletic patients with symptoms at rest or on minimal exertion, the addition of carvedilol to conventional therapy ameliorates the severity of heart failure and reduces the risk of clinical deterioration, hospitalization, and other serious adverse clinical events. (*Circulation*. 2002;106:2194-2199.)

Key Words: heart failure ■ adrenergic beta-antagonists ■ carvedilol

The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial was designed to evaluate the effects of the α -, β -adrenergic blocker carvedilol in patients with severe chronic heart failure. The primary objective of the trial was to evaluate the effects of the drug on survival, and a beneficial effect of treatment on this end point was described in an earlier publication.¹ In this article, we describe the effects of carvedilol on morbidity in the COPERNICUS

study, assessed subjectively by patients and objectively by the occurrence of major clinical events.

See p 2164

Methods

Patients were enrolled if they had dyspnea or fatigue at rest or on minimal exertion for ≥ 2 months and a left ventricular ejection

Received July 11, 2002; revision received August 9, 2002; accepted August 13, 2002.

From the College of Physicians and Surgeons, Columbia University (M.P.), New York, NY; Royal Brompton Hospital (A.J.S.C.), London, UK; Stanford University Medical Center (M.B.F.), Stanford, Calif; Universitaets Klinikum Luebeck (H.A.K.), Luebeck, Germany; Monash University (H.K.), Prahran Victoria, Australia; University Hospital (P.M.), Bern, Switzerland; University Health Network and Mt Sinai Hospital (J.L.R.), Toronto, Canada; Silesian School of Medicine (M.T.), Katowice, Poland; Roche Pharmaceuticals (C.S., I.A.-Z.), Basel, Switzerland; GlaxoSmithKline Ltd (T.L.H.), Philadelphia, Pa; and the University of Wisconsin (E.B.R., D.L.D.), Madison.

The COPERNICUS Study Investigators are listed in the online-only Appendix, which is available in the Data Supplement at <http://www.circulationaha.org>.

Drs Packer, Fowler, Coats, Katus, Krum, Mohacsi, Rouleau, Tendera, and DeMets have served as consultants. Dr Roecker's salary is supported by a research grant. Dr Amann-Zalan is a current employee and Dr Staiger is a former employee of Roche Pharmaceuticals. Dr Holcslaw is an employee of GlaxoSmithKline Ltd.

Correspondence to Dr Milton Packer, Division of Circulatory Physiology, Columbia University, College of Physicians and Surgeons, 630 W 168th St, New York, NY 10032. E-mail mp65@columbia.edu

© 2002 American Heart Association, Inc.

Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000035653.72855.BF

fraction <25% as a result of an ischemic or nonischemic cardiomyopathy. All patients received a diuretic (which was adjusted to minimize the degree of fluid retention) and either an angiotensin-converting enzyme inhibitor or an angiotensin II receptor antagonist (unless these were not tolerated). Treatment with digitalis, spironolactone, vasodilators, and amiodarone was allowed, but not required. Patients could be inpatients or outpatients, but they could not have an acute illness that required continued hospitalization. Unlike earlier survival trials,²⁻⁴ the study imposed no stability criteria with regard to the use of background medications. Patients received any clinically indicated treatments (including intravenous diuretics) before or after randomization, but they could not have been treated with an intravenous positive inotropic agent or vasodilator within 4 days. Criteria for exclusion from the trial have been previously described.¹

Study Design

Eligible patients were randomly assigned (double-blind) to receive either carvedilol or placebo (in a 1:1 ratio) in addition to their usual medications for heart failure. The starting dose was 3.125 mg of carvedilol or placebo twice daily, which was then increased (if tolerated) at 2-week intervals to 6.25 mg, 12.5 mg, and finally to a target dose of 25 mg twice daily or placebo. The rapidity of up-titration was slowed if deemed appropriate. Each patient then entered a maintenance phase, during which he or she was seen as an outpatient every 2 months until the end of the study. If warranted by clinical circumstances, the dose of carvedilol or placebo could be reduced or temporarily discontinued, the doses of all concomitant drugs could be adjusted, and the investigator could implement any new treatments, except for open-label treatment with a β -blocker.

The primary end point of the study was all-cause mortality. The 4 prespecified secondary end points were the combined risk of death or hospitalization for any reason, the combined risk of death or hospitalization for a cardiovascular reason, the combined risk of death or hospitalization for heart failure, and the patient global assessment. The protocol specified the following definitions:

- A hospitalization for any reason was defined as an admission for medical therapy. Admissions only to provide housing for social reasons were excluded.
- A cardiovascular hospitalization was defined as an admission as a result of or associated with an atrial or ventricular tachyarrhythmia, symptomatic bradycardia or heart block, myocardial infarction or unstable angina, or worsening heart failure.
- A hospitalization for heart failure was defined as admission as a result of worsening heart failure (as the primary cause), as a result of another cause but associated with worsening heart failure at the time of admission, or as a result of another cause but complicated by worsening heart failure during its course. Admissions not requiring intravenous therapy for heart failure were excluded.
- The patient global assessment consisted of a judgment made by the patient at specified intervals as to whether his/her clinical status had markedly, moderately, or slightly improved, had remained unchanged, or had slightly, moderately, or markedly worsened since the start of the study.

The causes of hospitalization were adjudicated by an End Point Committee, which had no knowledge of the patient's drug assignment. As prespecified, those <24 hours in duration or ongoing at the time of randomization were excluded. The trial was monitored by an independent Data and Safety Monitoring Board, as previously described.¹

Statistical Analysis

Between-group differences in the Kaplan-Meier survival curves for morbidity end points were analyzed according to the intention-to-treat principle and were tested for significance by the log-rank statistic. Cox proportional hazards regression models were used to estimate hazard ratios and two-sided 95% confidence intervals (CIs). Patients who had a cardiac transplant or who withdrew consent were censored from the date of these events. For the patient global assessment, probability values for comparisons between treatment

groups after 6 months of maintenance therapy were derived with the use of a Mann-Whitney *U* test. Analyses of the patient global assessment were performed on all patients with available data, both with and without worst rank assignment, for the occurrence of a missing value as a result of death.

The effect of carvedilol on morbidity end points was assessed in specific subgroups defined by 6 prerandomization variables: age, sex, ejection fraction, cause of heart failure, location of the study center, and history of hospitalization for heart failure within one year, as previously described.¹ The first 4 analyses were prospectively planned in the original protocol. In addition, additional analyses were performed to determine if there were patients in the present trial who had heart failure too advanced to benefit from treatment. To do so, the effects of carvedilol were assessed in a very high-risk group consisting of 624 patients (316 on placebo and 308 on carvedilol) with recent or recurrent cardiac decompensation or very depressed cardiac function, characterized by one or more of the following: the presence of pulmonary rales, ascites, or edema at randomization; ≥ 3 hospitalizations for heart failure within the last year; hospitalization at the time of screening or randomization; need for intravenous positive inotropic agent or vasodilator drug within 14 days before randomization; or left ventricular ejection fraction $\leq 15\%$.¹ The baseline variables that defined this high-risk group were identified without knowledge of their influence on the treatment effect. This highest-risk group had an annual placebo mortality rate of 28.5% per patient-year of follow-up.

To assess whether the effect of carvedilol on the morbidity end points was simply the result of improved survival with the drug, hospitalizations were also analyzed alone (without the inclusion of deaths) with respect to the number of patients hospitalized (by χ^2 test) and the number and duration of hospitalizations (by Mann-Whitney *U* test). The frequencies of medical interventions during hospitalization, dose reductions, and permanent withdrawals were compared between the treatment groups with the use of a χ^2 test. By their very nature, these analyses ignore the competing risk of death and the effect that differences in survival between the treatment groups have on the length of time at risk for hospitalization or other nonfatal events. Thus—in view of the survival benefit of carvedilol¹—they are inherently biased in favor of placebo and underestimate the effect of carvedilol.

To complete the evaluation of morbidity, the safety of carvedilol was assessed primarily by reports of serious adverse events. An adverse event was defined in the study protocol as serious if it was fatal or life-threatening, required prolonged hospitalization, resulted in persistent or significant disability or incapacity, or resulted in a malignancy, congenital malformation, or anomaly. Differences between the treatment groups in the frequency of serious adverse events were tested for significance with the use of the χ^2 test. All reports of adverse events were included whether or not they were deemed relevant to treatment. All probability values are 2-sided and nominal.

Results

Of the 2289 patients who were enrolled in the trial, 1133 were randomized to the placebo group and 1156 to the carvedilol group. The 2 treatment groups were similar with regard to all baseline characteristics.¹

Most patients were successfully titrated to and maintained on target doses of the study medication. Excluding patients who did not have the opportunity for full up-titration (either because they died or because the study was terminated while they were being up-titrated), 77.6% and 66.0% of the placebo and carvedilol groups, respectively, were receiving the target dose of the study drug at 12 weeks, and 70.5% and 60.0%, respectively, were maintained at the target dose at the end of the study. When compared with the placebo group, patients in the carvedilol group were more likely to require a reduction in dose (38.3% versus 33.2%, respectively, $P=0.010$) but

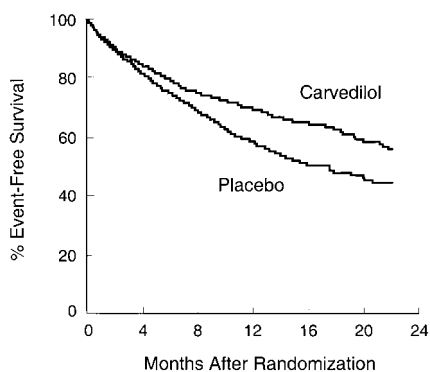


Figure 1. Kaplan-Meier analysis of time to death or hospitalization for a protocol-specified cardiovascular reason in all patients randomized to placebo or carvedilol. The 27% lower risk in the carvedilol group was highly significant ($P=0.00002$).

were less likely to require permanent withdrawal of the study drug (12.6% versus 15.9%, respectively, $P=0.026$). The 3 primary reasons for permanent withdrawal of the study medication (adverse events, withdrawal of consent, and noncompliance with study procedures) were all more common in the placebo group than in the carvedilol group.

As previously reported,¹ the annual mortality rate in the placebo group was 19.7% per patient-year of follow-up, which was reduced to 12.8% by treatment with carvedilol, reflecting a 35% reduction in the risk of death ($P=0.00013$). In addition, carvedilol reduced the risk of death or any hospitalization by 24% ($P=0.00004$). These differences led the Data and Safety Monitoring Board to recommend early termination of the study.¹ The mean and maximum durations of follow-up were 10.4 and 28.7 months, respectively.

Effect of Carvedilol on Combined Risk of Death or Hospitalization

By intention-to-treat, there were 395 patients who died or who were hospitalized for a cardiovascular reason in the placebo group and 314 such patients in the carvedilol group, corresponding to Kaplan-Meier 1-year cumulative risks of 41.6% and 30.2%, respectively. These differences reflected a 27% lower risk as a result of treatment with carvedilol (95% CI, 16% to 37%), $P=0.00002$ (Figure 1). By intention-to-treat, there were 357 patients who died or who were hospitalized for heart failure in the placebo group and 271 such patients in the carvedilol group, corresponding to Kaplan-Meier 1-year cumulative risks of 37.9% and 25.5%, respectively. These differences reflected a 31% lower risk in the carvedilol group (95% CI, 19% to 41%), $P=0.000004$ (Figure 2).

The reduction in the combined risk of death or hospitalization for a cardiovascular reason or for heart failure with carvedilol was similar in direction and magnitude across the prespecified and post hoc subgroups (Figure 3). The favorable effects of carvedilol were apparent even in patients at highest risk (ie, those with recent or recurrent cardiac decompensation or very depressed cardiac function), who had a 33% decrease in the combined risk of death or hospitalization for a cardiovascular reason (95% CI, 14% to 48%, $P=0.002$) and a 33% decrease in the combined risk of death or hospitaliza-

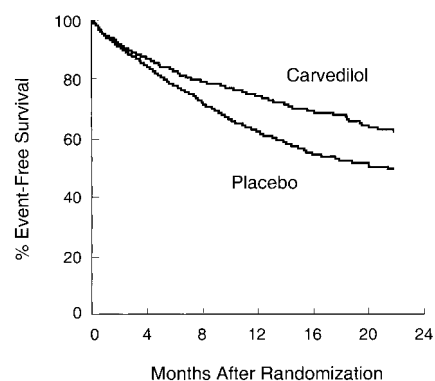


Figure 2. Kaplan-Meier analysis of time to death or hospitalization for heart failure in all patients randomized to placebo or carvedilol. The 31% lower risk in the carvedilol group was highly significant ($P=0.000004$).

tion for heart failure (95% CI, 13% to 49%, $P=0.002$) when treated with carvedilol, Figure 4.

Effect of Carvedilol on Hospitalizations (Analyzed Without Inclusion of Death)

Fewer patients in the carvedilol group than in the placebo group were hospitalized for heart failure (17.1% versus 23.7%, $P=0.0001$), for a cardiovascular reason (21.3% versus 27.7%, $P=0.0003$) or for any reason (32.2% versus 38.1%, $P=0.003$) (Table 1). Patients treated with carvedilol were not only less likely to be hospitalized at least once but were less likely to be hospitalized multiple times (13.1% versus 16.6%, $P=0.021$).

When all (including repeat) hospitalizations were considered, the carvedilol group had 20% fewer hospitalizations for any reason ($P=0.002$), 28% fewer hospitalizations for a cardiovascular reason ($P=0.0002$), and 33% fewer admissions for heart failure ($P<0.0001$) (Table 1). Among the

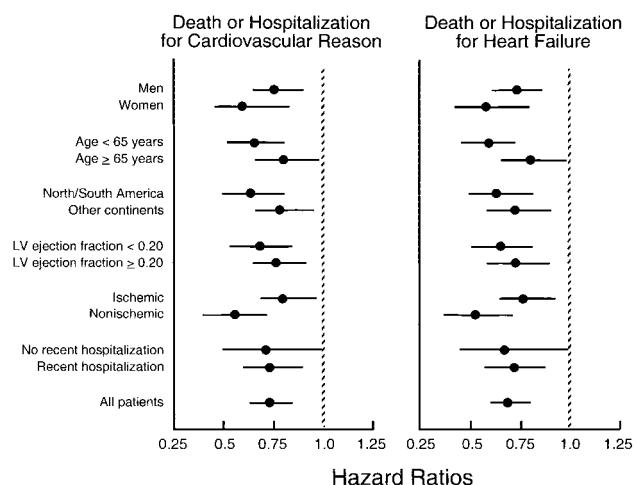


Figure 3. Hazard ratios (circles) and 95% confidence intervals (horizontal lines) in subgroups defined by baseline characteristics. Shown on the left are the effects on all cause mortality or hospitalization for a cardiovascular reason; shown on the right are the effects on all cause mortality or hospitalization for heart failure. Recent hospitalization refers to hospitalization for heart failure within the prior year. Hazard ratios <1.0 indicate a favorable effect of carvedilol.

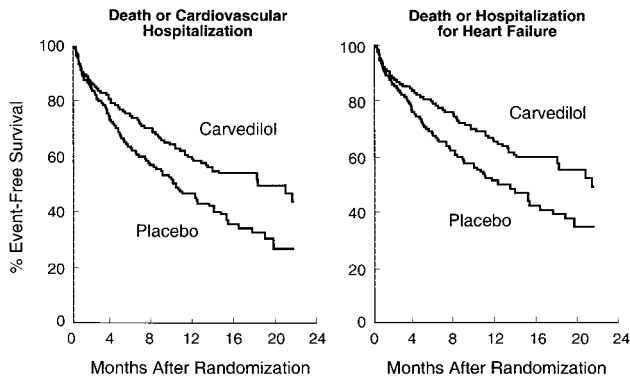


Figure 4. Kaplan-Meier analysis of time to death or cardiovascular hospitalization (left panel) or death or hospitalization for heart failure (right panel) in the 624 patients randomized to placebo or carvedilol who had recent or recurrent decompensation or a very depressed ejection fraction ($\leq 15\%$). In both analyses, carvedilol reduced the risk of a major clinical event by 33% (both $P=0.002$).

protocol-specified cardiovascular hospitalizations other than for heart failure, carvedilol-treated patients had fewer hospitalizations for arrhythmias and myocardial ischemia but more for bradycardia and heart block (Table 1).

Compared with the placebo group, patients in the carvedilol group spent 27% fewer days in the hospital for any reason (6.2 versus 8.5 days per patient, $P=0.0005$) and 40% fewer days in the hospital for heart failure (2.9 versus 4.9

days per patient, $P<0.0001$) (Table 2). These differences were as a result of both a decrease in the number of hospitalizations and a shorter duration of each hospitalization. Carvedilol reduced the average duration of each admission for heart failure by 2.3 days ($P=0.005$) and of each admission for any reason by 1.1 days ($P=0.015$). In addition, while in the hospital, carvedilol-treated patients required fewer intravenous treatments for heart failure (ie, intravenous diuretics and positive inotropic agents, both $P<0.001$) and underwent fewer evaluations of ventricular function (by echocardiography, $P=0.004$, or by pulmonary arterial catheterization, $P=0.035$) (Table 2).

Effect of Carvedilol on the Patient Global Assessment

More patients considered themselves improved and fewer patients considered themselves worse in the carvedilol group than in the placebo group after 6 months of maintenance therapy. Specifically, carvedilol-treated patients were more likely than placebo-treated patients to show marked (21.1% versus 16.1%) or moderate (28.5% versus 23.9%) improvement and were less likely to show moderate (1.2% versus 2.5%) or marked (0.3% versus 1.7%) worsening. The differences in favor of carvedilol were significant, whether or not patients who had missing values because of death were assigned worst rank ($P<0.0001$ and $P=0.0009$, respectively). The direction and magnitude of the carvedilol effect was virtually identical when the analysis was confined to patients

TABLE 1. Causes and Characteristics of Hospitalizations in the Treatment Groups

	Placebo (n=1133)	Carvedilol (n=1156)	P
No. of randomized patients who were hospitalized (%)			
For worsening heart failure	268 (23.7)	198 (17.1)	0.0001
For cardiovascular reason	314 (27.7)	246 (21.3)	0.0003
For any reason	432 (38.1)	372 (32.2)	0.003
More than once	188 (16.6)	152 (13.1)	0.021
No. of hospitalizations*			
For worsening heart failure	441	302	...
For worsening heart failure per randomized patient	0.389	0.261	<0.0001
For cardiovascular reason (specified in protocol)	528	386	...
For cardiovascular reason per randomized patient	0.466	0.334	0.0002
For atrial tachyarrhythmia	52	29	...
For ventricular tachyarrhythmia	23	22	...
For symptomatic bradycardia	9	18	...
For symptomatic heart block	2	5	...
For myocardial infarction	13	6	...
For unstable angina	49	35	...
For cardiovascular reasons not specified in protocol	116	106	...
For noncardiovascular reasons	238	221	...
For any reason	827	674	...
For any reason per randomized patient	0.730	0.583	0.002

These analyses do not account for the risk of death as a competing factor. Data include multiple categorizations for a single hospitalization.

*Results per patient and per admission are mean values; remaining results are sums across all patients.

TABLE 2. Utilization of Healthcare Resources During Hospitalization

	Placebo (n=1133)	Carvedilol (n=1156)	<i>P</i>
No. of randomized patients who required treatments during hospitalization* (%)			
Intravenous diuretics	259 (22.9)	198 (17.1)	0.0006
Intravenous positive inotropic agent	153 (13.5)	105 (9.1)	0.0008
Intravenous vasodilators	81 (7.1)	64 (5.5)	0.11
No. of randomized patients who required treatments during hospitalization* (%)			
Echocardiography	179 (15.8)	135 (11.7)	0.004
Pulmonary artery catheterization	40 (3.5)	24 (2.1)	0.035
Left heart catheterization	37 (3.3)	26 (2.2)	0.14
Direct current cardioversion or defibrillation	31 (2.7)	24 (2.1)	0.30
Days spent in the hospital for any reason*			
Per randomized patient	9603	7124	...
Per patient hospitalized	8.5	6.2	0.0005
Per admission for each randomized patient	22.2	19.2	0.014
Per admission for each hospitalized patient	4.8	3.7	0.0005
Per admission for each hospitalized patient	12.5	11.4	0.015
Days spent in the hospital for heart failure†			
Per randomized patient	5549	3374	...
Per patient hospitalized	4.9	2.9	<0.0001
Per admission for each randomized patient	12.8	9.1	0.0003
Per admission for each hospitalized patient	3.2	1.9	<0.0001
Per admission for each hospitalized patient	13.5	11.2	0.005

These analyses do not account for the risk of death as a competing factor.

*Only procedures used in >2% of patients or intravenous drugs used for treatment of heart failure are listed.

†Results per patient and per admission are mean values; remaining results are sums across all patients.

with recent or recurrent cardiac decompensation or very depressed cardiac function ($P=0.0002$ and $P=0.039$ with and without worst rank assignment for death, respectively).

Serious Adverse Events

A total of 516 patients (45.5%) in the placebo group and 451 patients (39.0%) in the carvedilol group experienced a serious adverse event ($P=0.002$). All serious adverse events with a frequency >1% are listed in Table 3. Reports of worsening heart failure, sudden death, cardiogenic shock, and ventricular tachycardia were less frequent in the carvedilol group than in the placebo group (all $P<0.05$) as were reports of myocardial infarction or unstable angina, abnormal renal function, and atrial and ventricular fibrillation (all $0.05<P<0.10$). There was little difference between the two groups in the frequency of serious adverse events commonly ascribed to α - or β -adrenergic blockade (eg, bradycardia, hypotension, or syncope).

Discussion

The findings of the present study indicate that, in addition to prolonging survival, carvedilol ameliorates the morbidity of patients with severe chronic heart failure when assessed by both patients and physicians. During long-term treatment, carvedilol-treated patients were more likely to feel better and less likely to feel worse than patients in the placebo group. This symptomatic benefit was apparent even though all patients had had symptoms at the start of the study that had been refractory to conventional therapy for heart failure. At the same time, carvedilol markedly reduced the risk of

clinical deterioration, as reflected by physician reports of the occurrence of hospitalization or a serious adverse event. Carvedilol reduced the combined risk of death or hospitalization for heart failure by 31%, of death or cardiovascular hospitalization by 27%, and of death or hospitalization for any reason by 24%. Fewer patients in the carvedilol group

TABLE 3. Serious Adverse Events With an Overall Frequency >1%

	Placebo (n=1133)	Carvedilol (n=1156)	<i>P</i>
Heart failure	273 (24.1)	192 (16.6)	<0.0001
Sudden death	69 (6.1)	45 (3.9)	0.016
Myocardial infarction/unstable angina	50 (4.4)	35 (3.0)	0.080
Angina pectoris/chest pain	46 (4.1)	38 (3.3)	0.33
Abnormal renal function	35 (3.1)	22 (1.9)	0.069
Pneumonia	32 (2.8)	23 (2.0)	0.19
Dyspnea	26 (2.3)	19 (1.6)	0.26
Ventricular tachycardia	26 (2.3)	12 (1.0)	0.019
Acute cerebrovascular disorder	26 (2.3)	17 (1.5)	0.15
Ventricular fibrillation	23 (2.0)	12 (1.0)	0.053
Atrial fibrillation	22 (1.9)	12 (1.0)	0.074
Cardiogenic shock	19 (1.7)	5 (0.4)	0.003
Hypotension	18 (1.6)	22 (1.9)	0.57
Bronchitis	17 (1.5)	15 (1.3)	0.68
Syncope	17 (1.5)	19 (1.6)	0.78
Bradycardia	14 (1.2)	17 (1.5)	0.63

Values are given as n (%).

than in the placebo group were hospitalized for heart failure (17.1% versus 23.7%), for a cardiovascular reason (21.3% versus 27.7%), or for any reason (32.2% versus 38.1%). Thus, differences in the risk of the combined end points were not simply the result of improved survival with carvedilol.

Treatment with carvedilol not only reduced the likelihood of being hospitalized but also lessened the severity of illness at the time of admission among those who were hospitalized. Specifically, carvedilol reduced the number of hospitalizations for heart failure (from 441 to 302 admissions) and also decreased the average duration of each admission (from 13.5 to 11.2 days). As a result, carvedilol-treated patients spent 40% fewer days in the hospital for heart failure and 27% fewer days in the hospital for any reason—in spite of improved survival. In addition, while in the hospital, when compared with placebo-treated patients, carvedilol-treated patients required fewer intravenous treatments for heart failure (diuretics and positive inotropic agents) and had fewer evaluations of ventricular function (by echocardiography or by pulmonary arterial catheterization). These observations, taken together, suggest that hospitalization represented a less severe event in the patients assigned to carvedilol than in those assigned to placebo. A similar benefit of carvedilol has been previously reported in patients with mild-to-moderate symptoms.⁵

Serious adverse events contribute importantly to the morbidity of patients with heart failure, and the proportion of patients who experienced a serious adverse event was lower in the carvedilol group than in the placebo group. These differences were primarily a result of a lower frequency of reports of worsening heart failure, sudden death, cardiogenic shock, and ventricular tachycardia in patients treated with the drug. No serious adverse event occurred with a significantly higher frequency in the carvedilol group. In contrast, placebo-treated patients were more likely to experience a major adverse cardiac event that reflected worsening of the underlying cardiac disease and had a higher rate of permanent discontinuation. Similar results were seen in an earlier study of carvedilol in mild-to-moderate heart failure.¹

The most feared serious adverse event associated with the use of β -blockers in heart failure (ie, worsening heart failure) was reported less frequently in the carvedilol group than in the placebo group (16.6% versus 24.1%). In addition, time-

to-event analyses of the combined risk of morbidity and mortality (Figures 1 to 4) revealed no early increase in the risk of hospitalization for heart failure (or other serious adverse cardiovascular events) in patients assigned to carvedilol, even though patients in the study had advanced disease. Despite these findings, carvedilol should not be administered to patients who require intensive care, have marked fluid retention, or who are receiving intravenous vasodilators or positive inotropic agents. Such patients were not enrolled in the COPERNICUS study and may not respond favorably to the initiation of treatment with any β -blocker.

In conclusion, the addition of carvedilol to conventional therapy not only prolongs survival, but also ameliorates the severity of heart failure and reduces the risk of clinical deterioration, hospitalization, and serious adverse clinical events in patients with symptoms at rest or on minimal exertion. The findings of the COPERNICUS trial extends the benefits previously reported with carvedilol in patients with mild-to-moderate heart failure to those with severe symptoms.^{1,6,7}

Acknowledgments

We thank Diethelm Messinger, MS, of Roche Pharmaceuticals; Ellen L. Curtin, MD, and Neil Shusterman, MD, of GlaxoSmithKline Ltd; and Melissa K. Schultz, MS, of the University of Wisconsin, for their invaluable contributions to the study. This study was supported by grants from Roche Pharmaceuticals and GlaxoSmithKline Ltd.

References

1. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344:1651–1658.
2. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med*. 1996;334:1349–1355.
3. CIBIS II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study (CIBIS II): a randomized trial. *Lancet*. 1999;353:9–13.
4. Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) Study Group. Effect of metoprolol CR/XL in chronic heart failure. *Lancet*. 1999;353:2001–2007.
5. Fowler MB, Vera-Llonch M, Oster G, et al. Influence of carvedilol on hospitalizations in heart failure: incidence, resource utilization and costs. *J Am Coll Cardiol*. 2001;37:1692–1699.
6. Packer M, Colucci WS, Sackner-Bernstein JD, et al. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. *Circulation*. 1996;94:2793–2799.
7. Colucci WS, Packer M, Bristow MR, et al. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. *Circulation*. 1996;94:2800–2806.