Effects of Initiating Carvedilol in Patients With Severe Chronic Heart Failure
Results From the COPERNICUS Study

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Context β-Blockers remain underused despite their established utility for improving outcome in heart failure. Concerns that initiation of treatment produces few immediate benefits and may have important risks may be deterring widespread use.

Objective To evaluate the early effects of the β-blocker carvedilol in patients with severe heart failure.

Design, Setting, and Patients Randomized, double-blind, placebo-controlled trial conducted from October 28, 1997, to March 20, 2000, at 334 hospital centers in 21 countries among 2289 patients with symptoms of heart failure at rest or with minimal exertion who were clinically euvoletic and had a left ventricular ejection fraction of less than 25%.

Intervention Patients were randomly assigned to receive carvedilol, with start dosage of at 3.125 mg twice daily with uptitration to a target dosage of 25 mg twice daily (n=1156), or placebo (n=1133), in addition to their usual medications for heart failure.

Main Outcome Measures Death, hospitalization, or permanent withdrawal from study drug, as well as adverse events during the first 8 weeks of treatment.

Results The carvedilol group experienced no increase in cardiovascular risk but instead had fewer patients who died (19 vs 25; hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.41-1.35); who died or were hospitalized (134 vs 153; HR, 0.85; 95% CI, 0.67-1.07); or who died, were hospitalized, or were permanently withdrawn from treatment (162 vs 188; HR, 0.83; 95% CI, 0.68-1.03). These effects were similar in direction and magnitude to those observed during the entire study, and were apparent particularly in the 624 patients with recent or recurrent decompensation or a very depressed left ventricular ejection fraction. Differences in favor of carvedilol became apparent as early as 14 to 21 days following initiation of treatment. Worsening heart failure was the only serious adverse event with a frequency greater than 2% and was reported with similar frequency in the placebo and carvedilol groups (6.4% vs 5.1%).

Conclusions These data suggest that, in clinically euvoletic patients, the relation of benefit to risk during initiation of treatment with carvedilol is similar to that seen during long-term therapy with the drug. Our findings should provide the reassurance needed to encourage the high levels of use that are warranted by the results of long-term clinical trials.

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initiation of β-blocker therapy carries important risks and few immediate benefits has contributed to the underutilization of these drugs in the management of heart failure.\textsuperscript{7}

Most of the information we have about the responses to β-blocker therapy have been derived from uncontrolled studies,\textsuperscript{9,13,15} and thus, it has been difficult to determine if the effects reported were related to treatment or to underlying disease. To date, only 2 controlled trials (with metoprolol and bucindolol) have described in detail the clinical events occurring following the initiation of therapy.\textsuperscript{16-18} In these studies, initiation of β-adrenergic blockade appeared to be well-tolerated in patients with mild heart failure but was associated with an early increase in risk of worsening heart failure and drug withdrawal in patients with severe heart failure.

We describe the initiation of treatment with the α, β-adrenergic blocker carvedilol in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study.\textsuperscript{19} The primary objective of the COPERNICUS trial was to evaluate the long-term effects of carvedilol on the survival of patients with severe heart failure. In the overall study (mean follow-up, 10.4 months), carvedilol reduced the risk of death by 35% compared with placebo. The COPERNICUS study provides an ideal setting in which to evaluate the early benefits and risks of treatment, since this trial focused on patients with severe heart failure who might be expected to have the greatest difficulty starting treatment with a β-blocker.\textsuperscript{9,13}

**METHODS**

**Study Participants**

COPERNICUS study patients were enrolled from 334 hospital centers and 21 countries between October 28, 1997, and March 20, 2000. Patients were eligible if they had dyspnea or fatigue at rest or on minimal exertion for at least 2 months and a left ventricular ejection fraction less than 25% due to ischemic or nonischemic cardiomyopathy. All patients were treated with a diuretic (which was adjusted to minimize the degree of volume retention) and treated with an angiotensin-converting enzyme inhibitor or an angiotensin II receptor antagonist (unless these were not tolerated). Treatment with digitalis, spironolactone, vasodilators, and amiodarone were allowed, but not required.

Patients were excluded if they had a reversible or correctable cause of heart failure; had severe primary pulmonary, renal, or hepatic disease; had a contra-indication to β-blocker therapy; or had an acute illness that required continued hospitalization. In addition, patients were not allowed to have had within the past 2 months cardiac surgery or angioplasty, a myocardial or cerebral ischemic event, or sustained or hemodynamically destabilizing ventricular tachyarrhythmia. Patients also were excluded if they had received an α-blocker, calcium channel blocker, or class I antiarrhythmic drug within 4 weeks; a β-blocker within 2 months; or an intravenous positive inotropic agent or vasodilator within 4 days of screening. Other exclusion criteria included systolic blood pressure less than 85 mm Hg, heart rate less than 68/min, serum creatinine level greater than 2.8 mg/dL (213.5 μmol/L), or a serum potassium level less than 3.5 mEq/L or greater than 5.2 mEq/L.

**Study Design**

Details of the study design have been previously published.\textsuperscript{19} In this double-blind trial, eligible patients were randomly assigned to receive either carvedilol or placebo (in a 1:1 ratio provided as capsules identical in size and shape), in addition to their usual medications for heart failure. Study medication was labeled with sequential randomization numbers linked up to a block randomization scheme; at the randomization visit, each patient was assigned the lowest number available at each site. The starting dosage was 3.125 mg of carvedilol or placebo twice daily, which if tolerated then was increased to 6.25 mg twice daily after 2 weeks, to 12.5 mg twice daily after 4 weeks, and finally to a target dosage of 25 mg twice daily or placebo after 6 weeks. At each visit, patients were asked about the occurrence of any clinical event or adverse effect, vital signs and body weight were measured, the dose of the study drug was recorded, and patients were administered the next level of the study drug if they were tolerating the drug at a dosage less than 25 mg twice daily and had not received a higher dose. The intent of the up-titration phase was to identify the highest dose of carvedilol that each patient could tolerate, and patients were considered to have completed the up-titration phase when they were able to tolerate this dose for 2 weeks. Thus, the duration of the up-titration period was expected to be 8 weeks, although the rapidity of up-titration could be slowed if deemed appropriate.

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. Following completion of the up-titration phase, patients entered the maintenance phase and continued in the double-blind therapy until the entire trial ended. The COPERNICUS trial was stopped on March 20, 2000, when the finding of a marked beneficial effect of carvedilol on survival led to a recommendation by the trial’s data and safety monitoring board for early termination.\textsuperscript{19}
Statistical Analysis

A major clinical event was defined as death, hospitalization, or permanent withdrawal of the study medication for any reason. Cumulative incidence curves for the occurrence of these events were constructed by the Kaplan-Meier method, using a time-to-first-event approach. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). The analyses of major outcome variables included all randomly assigned patients according to the intention-to-treat principle. Since the present report focused on the effects of treatment during initiation and up-titration, the period of principal interest was 8 weeks, which corresponded to the expected duration of the up-titration period. These specific outcomes and the 8-week period also were the focus of an earlier analysis of the up-titration period in the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure Study Group. Because earlier studies had raised concerns that patients at highest risk might respond poorly to β-adrenergic blockade, the effects of carvedilol were assessed in a very high risk subgroup consisting of patients with recent or recurrent cardiac decompensation or very depressed cardiac function. These high-risk patients were characterized by 1 or more of the following: the presence of pulmonary rales, ascites, or edema at randomization; 3 or more 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 of 15% or less. The baseline variables that defined this high-risk group were identified a priori without knowledge of their influence on the treatment effect.

The safety of carvedilol was assessed by changes in vital signs (summarized as a mean [SE] change from baseline) and by reports of adverse events with onset within 8 weeks of randomization. All reports of adverse events were included whether or not they were deemed by the investigator to be related to treatment. Adverse events with a frequency of at least 2% among all randomly assigned patients in either treatment group, and differences between treatment groups of at least 2% in the frequencies of the event were considered clinically significant. An adverse event was defined in the study protocol as serious if it was fatal or life-threatening, required or prolonged hospitalization, or resulted in persistent or significant disability or incapacity. Statistical analyses were performed using SAS (versions 6.12 and 8.0; SAS Institute, Cary, NC).

RESULTS

Of the 2289 patients who were enrolled into the trial, 1133 were randomly assigned to the placebo group and 1156 to the carvedilol group (Figure 1). Of these, 624 (27.3%) patients fulfilled the criteria for recent or recurrent cardiac decompensation or very depressed cardiac function, of whom 316 were randomly assigned to placebo and 308 to carvedilol. As reported previously, the 2 treatment groups were similar with respect to all baseline characteristics. En-
rolled patients had a mean age of 63.3 years, a median left ventricular ejection fraction of 20%; 79.7% were male and 67.2% had ischemic heart disease.

The majority of patients were successfully titrated to the target doses of the study medication specified for each visit. At 2 weeks, 97.2% of placebo patients and 97.1% of carvedilol patients were receiving at least 3.125 mg twice daily. At 4 weeks, 87.6% of placebo patients and 84.0% of carvedilol patients were receiving at least 6.25 mg twice daily. At 6 weeks, 79.1% of placebo patients and 71.7% of carvedilol patients were receiving at least 12.5 mg twice daily. At 8 weeks, 70.9% of placebo patients and 58.6% of carvedilol patients were receiving 25 mg twice daily. The mean dosages of placebo at 2, 4, 6, and 8 weeks were 3.5, 6.7, 12.5, and 19.8 mg twice daily, respectively; the mean dosages of carvedilol at 2, 4, 6, and 8 weeks were 3.5, 6.5, 11.6, and 17.8 mg twice daily, respectively.

Death, Hospitalization, or Permanent Withdrawal During First 8 Weeks

During the first 8 weeks, the carvedilol group, compared with the placebo group, had fewer patients with a major clinical event and had fewer patients who died, who died or were hospitalized, or who died, were hospitalized, or were permanently withdrawn from double-blind treatment (FIGURE 2). The direction and magnitude of these effects during the first 8 weeks were similar to those observed during the entire study.

Similar effects were observed for all 3 end points when the analyses were confined to patients at highest risk, that is, those patients with recent or recurrent decompensation or a very depressed left ventricular ejection fraction (Figure 2). The carvedilol group, when compared with the placebo group, had a lower risk of death, of death or hospitalization, and of death, hospitalization, or withdrawal of double-blind treatment. Again, the direction and magnitude of these effects seen in this cohort during the first 8 weeks were similar to those observed during the entire study.

Kaplan-Meier curves suggest that the differences between the carvedilol and placebo groups begin to appear as early as 14 to 21 days following initiation of treatment for both all-cause mortality and for the combined end point of death, hospitalization, or withdrawal, in the analysis of all randomly assigned patients and in the analysis of patients at highest risk (FIGURE 3).

Changes in Vital Signs During the First 8 Weeks

There were small changes in mean (SE) systolic blood pressure (placebo group, −2.0 [0.5] mm Hg and carvedilol group, −3.6 [0.5] mm Hg) and in diastolic blood pressure (placebo group, −1.8 [0.3] mm Hg and carvedilol group, −2.7 [0.3] mm Hg) at the end of 8 weeks. At 8 weeks, heart rate slowed progressively in the carvedilol group as the dose of the

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study medication and duration of treatment increased (placebo group, -2.2 [0.4] bpm and carvedilol group, -12.5 [0.4] bpm), but body weight did not change in either group (placebo group, 0 [0.07] kg and carvedilol group, 0.1 [0.07] kg).

**Adverse Events During the First 8 Weeks**

Overall, 59 patients (5.2%) in the placebo group and 51 patients (4.4%) in the carvedilol group permanently withdrew from double-blind medication for any reason other than death. There was no difference between placebo and carvedilol in the number of patients withdrawn for worsening heart failure (0.7% vs 0.6%, respectively, for all patients and 1.9% vs 1.6%, respectively, for highest risk patients). In addition, fewer patients in the carvedilol group than in the placebo group experienced a serious adverse event (13.8% vs 15.0% among all randomly assigned patients and 16.2% vs 22.2% among high-risk patients). Only 1 serious adverse event occurred with a frequency greater than 2%, namely worsening heart failure, and it was reported with a similar frequency with placebo and carvedilol (6.4% vs 5.1%, respectively, among all randomly assigned patients; 11.4% and 8.8%, respectively, in patients at highest risk). Patients in the carvedilol group were more likely than in the placebo group to report dizziness, hypotension, edema, and bradycardia (TABLE). In general, these reactions were not considered serious, but in a small number of cases required withdrawal of double-blind medication. Clinically significant differences (ie, greater than 2% difference) between the treatment groups were not observed during the up-titration period for any other adverse event.

### Table. Adverse Events During the First 8 Weeks*

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Placebo (n = 1133)</th>
<th>Carvedilol (n = 1156)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Randomized Patients</strong></td>
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<td></td>
</tr>
<tr>
<td>Bradycardia</td>
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<tr>
<td>Serious adverse event</td>
<td>1 (0.1)</td>
<td>10 (0.9)</td>
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<tr>
<td>Trial drug decreased due to adverse event</td>
<td>3 (0.3)</td>
<td>27 (2.3)</td>
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<td>Withdrawn due to adverse event</td>
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<td>4 (0.3)</td>
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<tr>
<td>Dizziness</td>
<td></td>
<td></td>
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<tr>
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<td>4 (0.4)</td>
<td>5 (0.4)</td>
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<tr>
<td>Trial drug decreased due to adverse event</td>
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<td>10 (0.9)</td>
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<tr>
<td>Edema</td>
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<tr>
<td>Serious adverse event</td>
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<td>3 (0.3)</td>
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<tr>
<td>Trial drug decreased due to adverse event</td>
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<td>11 (1.0)</td>
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<td>2 (0.2)</td>
<td>1 (0.1)</td>
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<tr>
<td>Hypotension</td>
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<td>Serious adverse event</td>
<td>2 (0.2)</td>
<td>6 (0.5)</td>
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<td>Serious adverse event</td>
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<td>Trial drug decreased due to adverse event</td>
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</tr>
<tr>
<td>Withdrawn due to adverse event</td>
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<td>2 (0.6)</td>
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<tr>
<td>Dizziness</td>
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<tr>
<td>Serious adverse event</td>
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<td>0</td>
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<tr>
<td>Trial drug decreased due to adverse event</td>
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<td>17 (5.5)</td>
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<tr>
<td>Edema</td>
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<tr>
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<td>1 (0.3)</td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
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<tr>
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<td>3 (0.9)</td>
<td>14 (4.5)</td>
</tr>
<tr>
<td>Withdrawn due to adverse event</td>
<td>0</td>
<td>2 (0.6)</td>
</tr>
</tbody>
</table>

*Includes adverse events with a frequency of at least 2% in all randomly assigned patients in either treatment group and differences between treatment groups in the frequency of the event of at least 2%. An adverse event was defined in the study protocol as serious if it was fatal or life-threatening, required or prolonged hospitalization or resulted in persistent or significant disability or incapacity.

**COMMENT**

Many physicians believe that for patients with severe chronic heart failure to experience the long-term benefits of β-adrenergic blockade, they must undergo a period of initiation and up-titration that may be troublesome. There is concern that the withdrawal of sympathetically mediated inotropic support following the start of treatment with a β-blocker carries a high risk of worsening heart failure, pulmonary edema, or cardiogenic shock. Patients with severe heart failure are considered most likely to experience early worsening and delayed benefit of treatment, since such individuals show the most marked activation of the sympathetic nervous system and are assumed to be the most dependent on adrenergically mediated circulatory support.

The findings of the COPERNICUS study with carvedilol challenge beliefs about the efficacy and safety of β-blockade during the first several weeks of treatment. During both initiation and up-titration, patients treated with carvedilol had no increase in the risk of worsening heart failure, pulmonary edema, cardiogenic shock, or other serious adverse cardiovascular events, including death. The principal adverse events attributable to carvedilol during the first...
8 weeks of therapy were those expected as a result of the inhibitory effects of the drug on α-receptors (dizziness and hypotension) and β-receptors (bradycardia and peripheral edema). However, these adverse reactions were mild and infrequent, occurring in 3 to 7 more patients in the carvedilol group per 100 patients treated. Importantly, because these adverse reactions were self-limited and not considered serious, they rarely led to the discontinuation of effective treatment.

The results of the COPERNICUS study also challenge the belief that the benefits of β-adrenergic blockade in patients with heart failure are delayed. During the first 8 weeks of treatment, fewer patients died or were hospitalized in the carvedilol group, and the magnitude of risk reduction by carvedilol during this early phase of therapy was similar to that seen during the entire study. The ability of carvedilol to produce beneficial effects early during the course of treatment was particularly striking in the patients at highest risk, that is, those with recent or recurrent decompensation or a very depressed left ventricular ejection fraction. These observations indicate that the clinical benefits of sympathetic antagonism are not necessarily delayed and suggest that the mechanisms by which such benefits are mediated are not of necessity dependent on changes in left ventricular function or geometry, which are known to require months to become apparent. It also is noteworthy that the Kaplan–Meier curves for the placebo and carvedilol groups (Figure 3) began to separate after about 21 days of treatment; this was at a time when patients were generally receiving a dosage of only 6.25 mg of carvedilol twice daily. This finding in patients with severe heart failure is consistent with the results of an earlier study, which showed that even 6.25 mg of carvedilol twice daily was effective in patients with mild-to-moderate symptoms.

The findings of the present study should be interpreted in light of the fact that the investigators and coordinators were highly experienced in the treatment of heart failure, and they selected patients carefully and followed them closely during the course of the trial. Furthermore, the protocol specified that patients were to be clinically euveleomic before they were randomly assigned, and every effort was made to maintain euveloma during initiation and up-titration of the study medication. Patients were encouraged to report any adverse effects or weight gain, and the dose of other medications could be modified or the rapidity of upward titration of the dose of the study drug could be decreased, if such adjustments were clinically warranted. These approaches will need to be followed in clinical practice; similar precautions have been recommended for general use in recent guidelines.

In conclusion, the relation of benefit to risk during initiation of treatment with carvedilol is similar to that seen during long-term treatment with the drug. In clinically euveleomic patients with advanced heart failure, initiation of treatment with carvedilol was well-tolerated and was associated with fewer major adverse events than initiation of treatment with placebo. If concerns about efficacy and safety during the initiation of β-blocker therapy have caused physicians to deny or delay the use of these drugs, our findings should provide the reassurance needed to encourage the high levels of use that are warranted by the results of clinical trials.

Author Contributions: Dr Roeger has had full access to the data for the COPERNICUS study and takes responsibility for the accuracy of the data analysis presented in this article.

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Statistical Expertise: Roeger.

Obtained Funding: Packer.

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Study Supervision: Krum, Mohacsi, Rouleau, Tendera, Coats, Katus, Fowler, Packer.

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Data and Safety Monitoring Board: Christoph Staiger, MD, Lidikó Amann-Zalán, MD, and Diethelm Messinger, MS, of Roche Pharmaceuticals; Ellen L. Curtis, MD, Terry L. Holcslaw, PhD, and Neil Shusterman, MD, of GlaxoSmithKline Ltd, and Melissa K. Schultz, MS, and Barbara Kowalczyk, MS, of the University of Wisconsin for their invaluable contributions to the study.

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REFERENCES


Every quotation contributes something to the stabil- ity or enlargement of the language.
—Samuel Johnson (1709-1784)