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Influence of Pretreatment Systolic Blood Pressure on the Effect of Carvedilol in Patients With Severe Chronic Heart Failure

The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study

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OBJECTIVES We sought to evaluate the influence of pretreatment systolic blood pressure (SBP) on the efficacy and safety of carvedilol in patients with chronic heart failure (CHF).

BACKGROUND Although beta-blockers reduce the risk of death in CHF, there is little reported experience with these drugs in patients with a low pretreatment SBP, who may respond poorly to beta-blockade.

METHODS We studied 2,289 patients with severe CHF who participated in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial.

RESULTS Compared with placebo, carvedilol improved the clinical status and reduced the risk of death and the combined risk of death or hospitalization for any reason, for a cardiovascular reason, or for worsening heart failure ($p < 0.001$ for all). The relative magnitude of these benefits did not vary as a function of the pretreatment SBP (all interaction: $p > 0.10$). However, because patients with the lowest SBP were at highest risk of an event, they experienced the greatest absolute benefit from treatment with carvedilol. The lower the pretreatment SBP, the more likely that patients would report an adverse event, be intolerant of high doses of the study drug, or require permanent withdrawal of treatment ($p < 0.001$ for all). However, these risks were primarily related to the severity of the underlying illness and not to treatment with carvedilol.

CONCLUSIONS The current study provides little support for concerns about using beta-blockers (particularly those with vasodilatory actions) in patients with severe CHF who have a low SBP. Pretreatment blood pressure can identify patients who have the greatest need for risk reduction with carvedilol. (J Am Coll Cardiol 2004;43:1423–9) © 2004 by the American College of Cardiology Foundation

Although beta-blockers have been shown to reduce the risk of death in patients with chronic heart failure (CHF) (1–4), some physicians hesitate to prescribe these drugs to high-risk patients because of fears that treatment with these agents might interfere with homeostatic actions of the sympathetic nervous system (5). Because adrenergic stimulation serves to support both blood pressure (BP) and cardiac contractility in patients with impaired left ventricular function, the administration of adrenergic blocking drugs can produce both hypotension and worsening heart failure (HF) (5,6). The risk of these adverse circulatory reactions appears to be most marked in patients with the lowest BP or most advanced disease before treatment (6,7). Such patients have generally responded poorly to treatment and have frequently been excluded from participation in clinical studies using beta-blocking drugs. For example, large-scale trials with metoprolol and bisoprolol in HF focused on patients with mild or moderate symptoms and did not enroll those with pretreatment systolic blood pressure (SBP) of <100 mm Hg (2,3).

The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study evaluated the effects of carvedilol in patients with severe CHF, including those with

See page 1430

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JACC Vol. 43, No. 8, 2004
April 21, 2004:1423–9

Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
BP	= blood pressure
CHF	= chronic heart failure
COPERNICUS	= Carvedilol Prospective Randomized Cumulative Survival trial
HF	= heart failure
SBP	= systolic blood pressure

a very low SBP (85 to 100 mm Hg). The trial demonstrated a reduction in the risk of death and of hospitalization in these patients (4,8), but earlier publications did not explore whether pretreatment BP influenced the presence or magnitude of these benefits. Such analyses would be particularly relevant for the use of carvedilol, as the vasodilatory effects of the drug might be expected to lower blood pressure and thus could theoretically place patients with CHF with the lowest BP at risk of hypotension. Such concerns, together with the absence of clinical trial data, may lead physicians to avoid the use of carvedilol and other beta-blockers in patients with a low SBP.

This report describes a retrospective analysis of the influence of the pretreatment SBP on the efficacy and safety of carvedilol in patients with severe CHF.

METHODS

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 CHF due to an ischemic or non-ischemic cardiomyopathy were enrolled at 334 centers in 21 countries. All patients had dyspnea or fatigue at rest or on minimal exertion for two or more months and a left ventricular ejection fraction <25%, despite appropriate conventional therapy. Such therapy was defined as treatment with diuretics (in doses adjusted to achieve clinical euvolemia) and an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor antagonist (unless such therapy was not tolerated). Treatment with digitalis, spironolactone, vasodilators, and amiodarone was allowed but not required. 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 non-cardiac causes. Hospitalized patients could be enrolled, but only if they had no acute cardiac or non-cardiac illness that required continued inpatient care. Unlike earlier survival trials, the COPERNICUS trial imposed no stability criteria with respect to the use of background medications and allowed patients in the study as long as their SBP was >85 mm Hg.

Patients were not enrolled in the study if they had a reversible or surgically correctable cause of HF; had received or were likely to receive a heart transplant; had severe primary pulmonary, renal, or hepatic disease; or had a contraindication to beta-blocker therapy. In addition, within the preceding two months, patients were not allowed to have had cardiac surgery or angioplasty, a myocardial or cerebral ischemic event, or sustained a hemodynamically destabilizing ventricular tachyarrhythmia. Patients who had received an alpha-adrenergic blocker, calcium channel blocker, or class I antiarrhythmic drug within four weeks; a beta-adrenergic blocker within two months; or an intravenous positive inotropic agent or intravenous vasodilator within four days were not permitted into the study. Finally, patients were excluded if they had a heart rate <68 beats/min, serum creatinine >2.8 mg/dl, serum potassium <3.5 or >5.2 mmol/l, or an increase in serum creatinine by >0.5 mg/dl, or a change in body weight ≥1.5 kg within 3 to 14 days of randomization.

Study design. Patients who fulfilled all the entry criteria were randomly assigned in a 1:1 ratio and in a double-blinded fashion to receive either oral carvedilol (n = 1,156) or matching placebo (n = 1,133), in addition to their usual medications for HF. Patients received an initial dose of 3.125 mg 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. The rapidity of up-titration could be slowed according to clinical need, as judged by the investigator. Patients then entered a maintenance phase during which they were seen as outpatients every two months until the end of the study. Blood pressure measurements were obtained every two weeks during up-titration and every two months during the maintenance phase. 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 beta-blocker.

The primary end point of COPERNICUS was all-cause mortality. Prespecified secondary end points included the combined risk of death or hospitalization for HF, the combined risk of death or cardiovascular hospitalization, the combined risk of death or hospitalization for any reason, and the patient's global assessment. Hospitalization for HF was defined as an admission due to worsening HF (as the primary cause), due to another cause but associated with worsening HF at the time of admission, or due to another cause but complicated by worsening HF during its course. Cardiovascular hospitalization was defined as an admission due to or associated with atrial or ventricular tachyarrhythmias, symptomatic bradycardia, heart block, myocardial infarction, or unstable angina pectoris, or an admission for HF. The cause of hospitalization was adjudicated by an end point committee, which had no knowledge of the patient's treatment assignment. Hospitalizations <24 h in duration, ongoing at the time of randomization, or carried out only to provide housing for reasons of social service were not included as end points. The patient's global assessment is a record of how a patient feels compared with the start of the

Table 1. Baseline Characteristics of Study Population (n = 2,289)

	Pretreatment SBP (mm Hg)				
	85–95	**96–105**	**106–115**	**116–125**	**>125**
No. of patients	132 (5.8%)	264 (11.5%)	468 (20.4%)	472 (20.6%)	953 (41.6%)
Age (yrs)*	61.2 ± 12.4	60.9 ± 11.8	63.5 ± 12.2	62.6 ± 11.6	64.5 ± 10.6
Males (%)	82.6	78.8	82.5	80.3	77.9
Duration of heart failure (yrs)	2.6 ± 3.0	2.5 ± 2.8	2.6 ± 2.8	2.8 ± 3.4	2.7 ± 3.1
Ischemic etiology (%)	65.2	65.2	64.1	66.1	70.1
Left ventricular ejection fraction (%)*	18.3 ± 4.6	18.5 ± 4.1	19.6 ± 4.4	20.0 ± 3.8	20.5 ± 3.6
Heart rate (beats/min)	83.7 ± 13.4	83.2 ± 12.8	82.6 ± 12.4	83.3 ± 12.2	82.5 ± 12.3
Diastolic blood pressure (mm Hg)*	62.3 ± 6.7	67.8 ± 8.0	71.6 ± 7.6	76.4 ± 7.8	83.1 ± 9.9
Serum sodium (mmol/l)*	135.9 ± 2.8	136.4 ± 3.5	136.8 ± 2.7	137.0 ± 2.6	137.2 ± 2.5
Serum creatinine (μmol/l)*	142.3 ± 40.0	137.1 ± 40.8	134.5 ± 38.5	130.6 ± 33.9	133.0 ± 34.8
Body mass index (kg/m^2)*	24.2 ± 4.7	26.2 ± 5.1	26.4 ± 4.9	27.1 ± 4.7	27.6 ± 4.5
Hemoglobin (g/dl)*	13.3 ± 1.8	13.8 ± 2.0	13.9 ± 1.7	14.0 ± 1.7	13.9 ± 1.7
Concomitant medications (%)	78.8	74.2	66.9	67.0	61.3
Digitalis*	98.5	100.0	99.4	98.7	99.0
Diuretics	95.5	97.0	97.9	96.2	97.7
ACE inhibitor/ATII	31.1	25.4	21.6	19.7	15.0
Spironolactone*	21.2	16.3	16.0	18.4	17.6
Amiodarone					

*Significant differences among SBP subgroups ($p < 0.05$). Continuous data are expressed as the mean value ± SD.
ACE = angiotensin-converting enzyme; ATII = angiotensin II antagonist; SBP = systolic blood pressure.

study, according to a seven-category ordinal scale ranging from markedly improved to markedly worse.

The trial was monitored by an independent Data and Safety Monitoring Board, which recommended early termination of the study when it observed a marked effect of carvedilol on survival (4). At the time of this early termination, the mean follow-up of patients in the study was 10.4 months, and the maximum follow-up was 28.7 months.

Statistical analysis. Patients in the trial were retrospectively grouped according to their pretreatment SBP into 10-mm Hg categories, starting from the lowest entry value (85 mm Hg) and collapsing patients with SBP >125 mm Hg into a single group. Baseline characteristics among the five BP subgroups were compared using the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables.

Cumulative survival curves for the risk of a major clinical event were constructed by the Kaplan-Meier method (using a time-to-first-event approach). Analyses of major outcome variables included all randomized patients, and all events were assigned to the patient's randomized treatment group (according to the intention-to-treat principle). Patients who underwent heart transplantation or withdrew consent were censored from the date of these events. The relationships between pretreatment SBP, the effect of treatment, and the risk of major clinical end points and other clinical events were examined using Cox proportional hazards regression models with pretreatment SBP included as a continuous variable. A treatment group by SBP interaction term was included in the model to assess the influence of SBP on the relative magnitude of the treatment effect. These models were also used to estimate hazard ratios and 95% confidence intervals.

The effect of carvedilol on the patient's global assessment after six months of maintenance therapy was evaluated using the Wilcoxon rank-sum test. The relationship between pretreatment SBP and the effect of carvedilol on this end point was assessed using a proportional odds model, which considered SBP as a continuous variable and included a treatment by SBP interaction term. Analyses were carried out for all patients with available data, both with and without worst rank assignment for the occurrence of a missing value due to death.

The relationship between pretreatment SBP and the proportion of patients on the target dose of study drug (including the possibility of an interaction between pretreatment BP and treatment) was tested using a logistic model in which pretreatment SBP was included as a continuous variable.

Changes in BP from baseline were analyzed across time using repeated measures analysis of covariance and an unstructured covariance matrix for the repeated measures in order to test for a differential pattern of change in BP over time, according to pretreatment SBP. Differences between treatment groups at individual visits were compared using the Wilcoxon rank-sum test.

All reported p values are two-sided and nominal.

RESULTS

Of the 2,289 patients who were enrolled into the trial, the pretreatment SBPs were 85 to 95 mm Hg in 132 patients (5.8%), 96 to 105 mm Hg in 264 patients (11.5%), 106 to 115 mm Hg in 468 patients (20.4%), 116 to 125 mm Hg in 472 patients (20.6%), and >125 mm Hg in 953 patients (41.6%).

Characterization of BP subgroups. The baseline characteristics of patients grouped according to their pretreatment

JACC Vol. 43, No. 8, 2004
April 21, 2004:1423–9

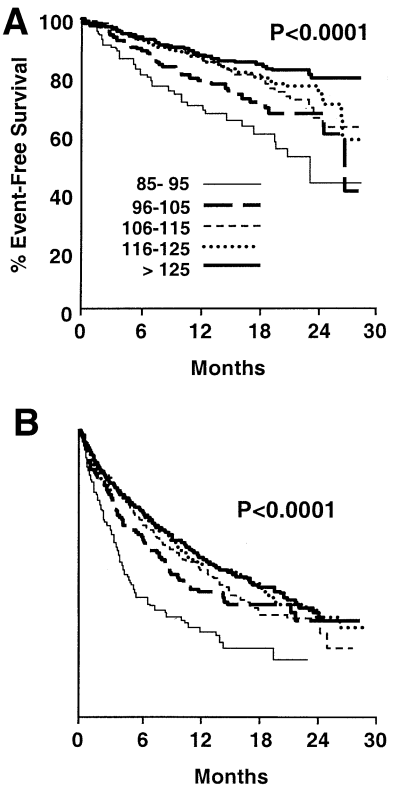

Figure 1. Kaplan-Meier survival curves of the time to all-cause mortality **(A)** and time to death or hospitalization for any reason **(B)** in subgroups defined by pretreatment systolic blood pressure (both treatment groups combined). The lower the blood pressure, the higher the risk of a major clinical event (both $p < 0.0001$).

SBP are shown in Table 1. The lower the pretreatment SBP, the more advanced HF, as reflected by lower values for left ventricular ejection fraction, serum sodium concentration, hemoglobin, and body mass index, higher values of serum creatinine, and a greater prevalence of the use of digitalis and spironolactone.

The lower the pretreatment SBP, the higher the risk of a major clinical event, irrespective of treatment (Figs. 1A and 1B). For each 10-mm Hg decrease in the pretreatment SBP, the risk of death increased by 18%, the combined risk of death or hospitalization for HF increased by 11%, and the combined risk of death or hospitalization for any reason or for a cardiovascular reason increased by 9% (all $p < 0.001$).

Influence of SBP on effects of carvedilol. In the trial as a whole and within each BP subgroup, patients randomized to placebo or carvedilol were similar in their baseline characteristics (data not shown). Overall, carvedilol reduced the risk of death by 35%, the combined risk of death or cardiovascular hospitalization by 27%, death or hospitalization for worsening HF by 31%, and death or hospitalization for any reason by 24% (all $p < 0.001$). The relative benefit, as assessed by the Cox model hazard ratio, did not vary as a function of the pretreatment SBP (all interaction: $p > 0.10$) (Fig. 2). However, because patients with the lowest SBP were at the highest risk of an event, they experienced the greatest absolute benefit from treatment with carvedilol.

More patients considered themselves moderately or markedly improved (49.6% vs. 40.0%) and fewer patients considered themselves moderately or markedly worse in the carvedilol group (1.6% vs. 4.2%) compared with the placebo group after six months of maintenance therapy ($p < 0.001$). A difference in favor of carvedilol was observed irrespective of the pretreatment SBP (interaction: $p = 0.21$) (Figs. 3A and 3B) and continued to be observed even when missing values due to death were assigned the worst rank.

Influence of carvedilol on SBP. Overall, SBP declined more in patients treated with carvedilol than in those who received placebo. At the final up-titration visit, SBP was decreased from baseline by a mean of 4.6 mm Hg in the carvedilol group and by 2.4 mm Hg in the placebo group ($p = 0.001$). This 2-mm Hg mean difference between the two groups persisted for approximately four months, but then dissipated and was no longer apparent after eight months (Fig. 4). The results were similar whether the analyses focused on all patients with data available at any time point or on all patients with complete data for all time points.

Pretreatment SBP values were a significant determinant of the effects of carvedilol on BP across time (interaction: $p < 0.001$). Most importantly, among patients with a pretreatment SBP of 85 to 95 mm Hg, there was no evidence of any initial decline, and there may even be an increase in SBP relative to placebo (Fig. 4).

Influence of SBP on safety and tolerability of carvedilol. After initiation of treatment, 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), 78% and 65% of the placebo and carvedilol groups, respectively, were receiving the target dose of the study drug at four months. The proportion of patients at the target dose increased as the pretreatment SBP increased ($p < 0.001$), with no influence of treatment on this relationship (interaction: $p = 0.66$) (Fig. 5A). Fewer patients in the carvedilol group than in the placebo group required permanent discontinuation of the study drug because of adverse effects or for reasons other than death (12.6% vs. 15.9%, $p < 0.05$). The frequency of permanent drug withdrawal increased as the pretreatment SBP decreased ($p < 0.001$), with no influence of treatment on this relationship (interaction: $p = 0.25$) (Fig. 5B).

The frequency of adverse events commonly associated with adrenergic blockade in the five BP subgroups is shown in Table 2. The lower the pretreatment SBP, the higher the frequency of dizziness, hypotension, and HF events in both treatment groups. More carvedilol-treated than placebo patients reported dizziness, hypotension, syncope, and bradycardia, whereas fewer carvedilol-treated patients reported HF, to a similar extent in each BP subgroup.

The pretreatment SBP was also an important determinant of the risk of a serious adverse event, with the risk of

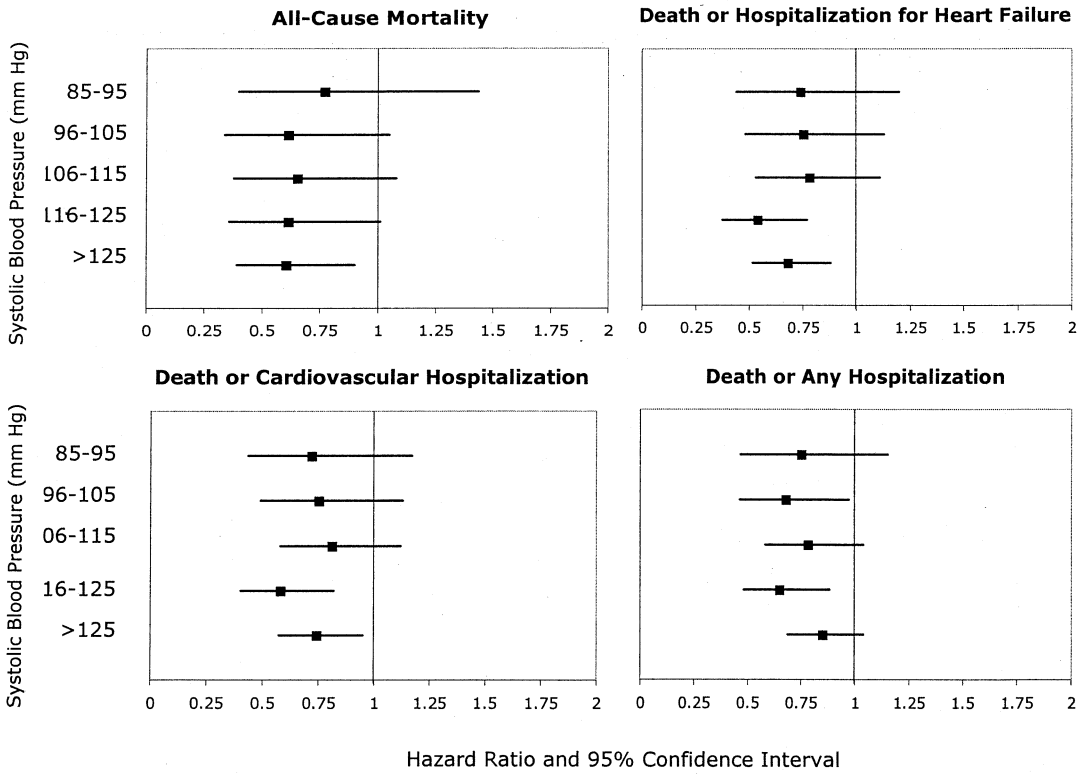

Figure 2. Hazard ratios and 95% confidence intervals for all-cause mortality, death or hospitalization for heart failure, death or cardiovascular hospitalization, and death or any hospitalization in subgroups defined by pretreatment systolic blood pressure. Hazard ratios <1.0 indicate lower risk in the carvedilol group. The benefit of carvedilol was consistent across all levels of pretreatment systolic blood pressure for each end point (all interaction: $p > 0.1$).

such an event increasing as the pretreatment BP decreased ($p < 0.001$). Nevertheless, patients treated with carvedilol were less likely to experience a serious adverse event during the trial than patients who received placebo (39.0% vs. 45.5%, $p = 0.002$). The benefit associated with carvedilol treatment increased as the pretreatment SBP decreased (interaction: $p = 0.03$) (Fig. 6).

DISCUSSION

Systolic BP is the most common physiologic measurement performed in patients with CHF and is frequently used by clinicians to determine the eligibility of patients for, the therapeutic response to, and the tolerability of specific treatments. Patients with an elevated BP are often regarded as ideal candidates for treatment with ACE inhibitors and beta-blockers, whereas both classes of drugs are commonly avoided in patients with a low SBP because of concerns about their hypotensive effects. The validity of using SBP as a guide to treatment has not been critically evaluated, however. Systolic BP does not appear to be a determinant of the response to ACE inhibitors in large-scale trials (9), and preliminary evidence suggests that it may also not influence the response to beta-blockers in HF (3). However, data on the importance of SBP in modulating the effects of both ACE inhibitors and beta-blockers are limited, as patients with a low SBP were not enrolled in most large-scale trials with these drugs (2,3).

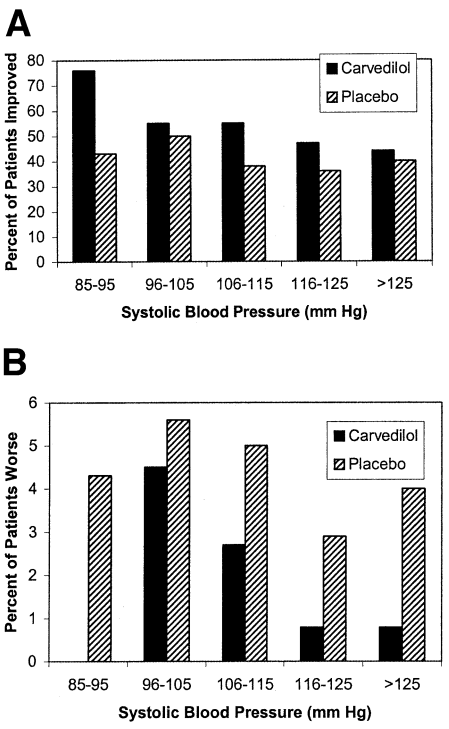

Figure 3. Proportion of patients reporting themselves to be moderately or markedly improved **(A)** or moderately or markedly worse **(B)** after six months of maintenance therapy, according to pretreatment systolic blood pressure and treatment. The benefit of carvedilol on patient well-being was similar, irrespective of pretreatment systolic blood pressure (interaction: $p = 0.21$).

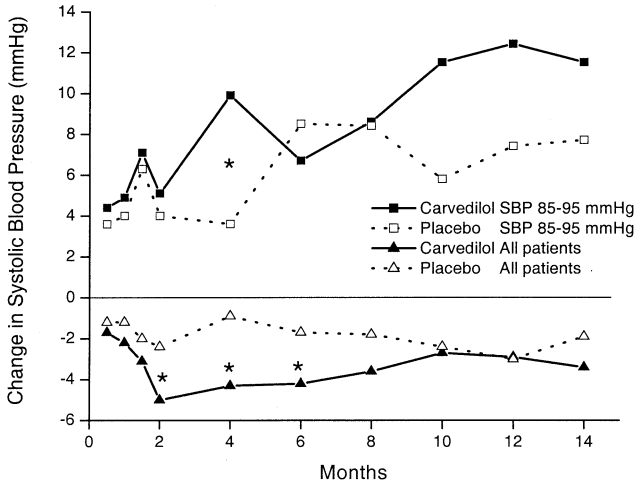

Figure 4. Mean change in systolic blood pressure (SBP) from baseline at specific visits in the placebo and carvedilol groups for all patients and for patients with the lowest pretreatment systolic blood pressure (85 to 95 mm Hg). *Significant treatment group difference ($p < 0.05$).

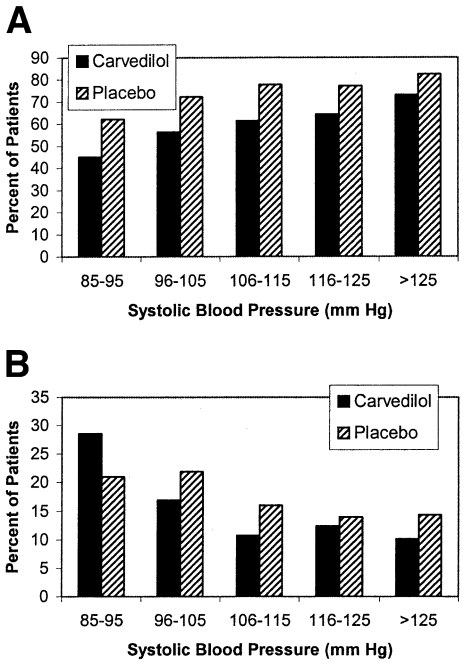

Figure 5. Proportion of patients at target dose of study drug at four months **(A)** or permanently withdrawn from the study drug **(B)**, according to pretreatment systolic blood pressure and treatment. Pretreatment blood pressure influenced the frequency of both occurrences (both $p < 0.001$), irrespective of pretreatment systolic blood pressure (interaction: $p > 0.24$).

The current analysis demonstrates that, in a trial enrolling patients with a wide spectrum of values for SBP, long-term treatment with carvedilol exerts favorable clinical effects in patients with severe CHF, and this benefit is observed regardless of the pretreatment BP. Carvedilol substantially reduced the risk of death and the combined risk of death or all-cause or cause-specific hospitalization, and the magnitude of these effects was similar in patients with low or preserved SBP. The pretreatment SBP also did not influence the magnitude of symptomatic improvement produced by the drug, as evaluated by the patient's global assessment. These observations challenge the conventional belief that patients with a low SBP respond poorly to adrenergic blockade (10). In fact, because SBP is a major determinant of risk, patients with the lowest SBP might be expected to derive the greatest absolute benefit from treatment. In the current trial, assuming a homogeneous relative reduction in the risk of death with carvedilol by 35%, the number of patients needed to treat with carvedilol for one year to save one life would be 20 in patients with SBP of >125 mm Hg, but only 10 in patients with SBP of 85 to 95 mm Hg, based on the observed one-year placebo absolute mortality risks of 15.4% and 33.9%, respectively, in the two subgroups.

To achieve these benefits, physicians must be willing to initiate and maintain treatment with a beta-blocker in patients with a low SBP, but many of them may be hesitant to do so based on the fear that treatment will be poorly tolerated in this cohort. In the current analysis, the lower the pretreatment SBP, the more likely that patients would report hypotension, dizziness, and worsening HF (Table 2). Furthermore, patients with the lowest SBP before the start of treatment were most likely to be unable to achieve high doses of the study drug and to require permanent withdrawal of treatment. However, our analyses indicate that

Table 2. Frequency of Adverse Events Commonly Attributed to Adrenergic Blockade*

		Pretreatment SBP (mm Hg)					
Adverse Event	**Treatment Group**	**85–95 (n = 132)**	**96–105 (n = 264)**	**106–115 (n = 468)**	**116–125 (n = 472)**	**>125 (n = 953)**	**All Patients (n = 2,289)**
Heart failure	Placebo	58%	45%	32%	34%	28%	34%
	Carvedilol	44%	40%	28%	26%	24%	28%
Dizziness	Placebo	32%	27%	20%	13%	12%	17%
	Carvedilol	39%	32%	27%	27%	17%	24%
Hypotension	Placebo	26%	20%	10%	6%	4%	9%
	Carvedilol	27%	29%	19%	17%	7%	15%
Syncope	Placebo	6%	9%	5%	7%	3%	5%
	Carvedilol	10%	7%	8%	8%	7%	8%
Bradycardia	Placebo	5%	3%	2%	4%	3%	3%
	Carvedilol	11%	10%	15%	11%	11%	12%

*Numbers in the table represent the percentage of patients reporting the event.
SBP = systolic blood pressure.

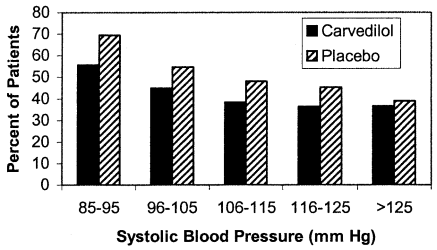

Figure 6. Proportion of patients experiencing a serious adverse event, according to pretreatment systolic blood pressure and treatment. There was a decrease in the risk of an event with increasing systolic blood pressure in both treatment groups ($p < 0.001$). The decrease associated with carvedilol treatment increased significantly with decreasing systolic blood pressure (interaction: $p = 0.03$).

these risks were related to the severity of the underlying illness of these patients and not to the treatment they received. Patients with a lower SBP were as likely to be intolerant of and require the withdrawal of placebo as they were of carvedilol. Moreover, patients treated with carvedilol were less likely to experience a serious adverse event than those treated with placebo, and this difference in favor of carvedilol was most apparent in patients with the lowest SBP (interaction: $p = 0.03$). Consequently, the results of the present analysis support concerns about the fragility of patients with a low SBP, but suggest that this fragility is not enhanced and may be reduced by treatment with carvedilol.

Our findings indicate that carvedilol was remarkably well tolerated in patients with the lowest SBP. Although BP declined with carvedilol in patients with higher pretreatment values, there was little decrease or actually a small increase in BP after therapy with carvedilol in patients with the lowest SBP before treatment. As a result, in patients with SBP of 85 to 95 mm Hg, the frequency of hypotension reported as an adverse event was not increased by treatment with carvedilol. Furthermore, despite the advanced severity of disease in patients with the lowest pretreatment BP, the risk of worsening HF was lower in the carvedilol group in this subgroup than it was in subgroups with higher BPs. Most of the episodes of hypotension and worsening HF that occurred in patients with the lowest SBP were related to the underlying disease (as reflected by the frequency of occurrence in the placebo group), with little incremental risk related to treatment with carvedilol. Hence, if physicians are concerned about prescribing beta-blockers because of fears of hypotension and worsening HF, such concerns should not be magnified simply because the SBP is low before treatment.

The current analysis suggests that the clinical importance of a low SBP is primarily related to its ability to identify patients with advanced disease, rather than to its ability to identify patients at risk of treatment with a beta-blocker. The lower the pretreatment SBP, the more advanced HF, as reflected by lower values of left ventricular ejection fraction and serum sodium concentration, higher values of serum creatinine, and a greater prevalence of the use of digoxin and spironolactone. Not surprisingly, the lower the pretreatment SBP, the higher the risk of death and hospitalization, irrespective of treatment. Previous studies have only infrequently identified SBP as a prognostic factor (11–14), possibly because BP declines when patients with HF are treated with drugs that prolong life. Furthermore, earlier reports also focused on patients with mild to moderate symptoms, and the prognostic importance of BP may increase as HF advances.

The results of the COPERNICUS trial indicate that patients with a low SBP benefit from and tolerate treatment with carvedilol to the same degree as patients with higher BPs. In fact, by identifying patients at highest risk, the pretreatment BP can identify patients with the greatest need for risk reduction with carvedilol.

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