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Scientific Update™

Carvedilol improves survival in patients with advanced heart failure: Results of the COPERNICUS study

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Along with the angiotensin-converting enzyme (ACE) inhibitors, ß-blockers have gradually emerged as standard therapy in patients with heart failure. However, unlike the ACE inhibitors where a beneficial effect on outcome has been demonstrated in a wide spectrum of patients with heart failure, until recently, studies demonstrating the survival benefit of ß-blockers have involved predominantly patients with mild to moderate heart failure. Accordingly, the COPERNICUS study was designed to assess the effect of the ß-blocker carvedilol on all-cause mortality in patients with advanced heart failure. The study was terminated prematurely because of the beneficial effects demonstrated with carvedilol. The primary results of this trial have recently been presented and are discussed in this *Cardiology Scientific Update*.

The ß-adrenergic receptor blockers have recently been shown to improve survival and reduce hospitalization admissions in patients with heart failure.[1-3] However, it is believed that only 5 to 15% of the estimated 75% of heart failure patients who would benefit from ß-blockade therapy actually receive the treatment. One reason for the underutilization of this class of agents may be the general perception that patients with heart failure do not tolerate agents with negative inotropic properties. Another reason may be that, unlike ACE inhibitors whose beneficial effects on clinical outcomes have been demonstrated in a wide spectrum of patients,[4-6] studies demonstrating a favorable effect with ß-blockers have involved predominantly patients with mild to moderate heart failure.[1-3] Accordingly, the role of ß-blockers in the therapy of patients with *severe* and *advanced* heart failure has not been defined.

COPERNICUS

The CarvedilOl ProspEctive RaNdomIzed CUmulative Survival (COPERNICUS) trial was an international, randomized, placebo-controlled trial, designed to examine the effect of a ß-blocker – carvedilol – versus placebo on all-cause mortality in patients with severe heart failure. The trial included patients with heart failure of ischemic or non-ischemic etiol-

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Table 1: Baseline characteristics		
	Placebo n=1133	Carvedilol n=1156
Age	63.4	63.2
Male	905	919
LVEF	0.20	0.20
Blood pressure	123/76	123/75
Heart failure hospitalization within 1 year	736	751

ogy who had a left ventricular ejection fraction <25% and symptoms of heart failure at rest or with minimal exertion, despite optimal conventional therapy including ACE inhibitors and optimal dose diuretics. Hospitalized patients were also eligible for recruitment if they were not in the intensive care unit. Patients could be on intravenous diuretics, but could not be on intravenous vasodilators or inotropic agents within 4 days. In addition, eligible patients must have been clinically euvolemic at the time of entry into the study, although mild peripheral edema was allowed. Carvedilol or placebo was slowly uptitrated, from 3.125 mg twice daily to 25 mg twice daily, over a 12-week period. The study was event-rate driven with an initial goal of 900 primary events. The study was terminated prematurely in March, 2000 by the Data and Safety Monitoring Board in view of a favorable outcome effect demonstrated in patients on carvedilol.

Results

A total of 2289 patients were randomized. The baseline characteristics are shown in Table 1. The patients had very advanced heart failure at the time of randomization as evidenced by the low left ventricular ejection fraction (LVEF) and the large number of patients who had been hospitalized for heart failure within the past year. The two groups were comparable.

Eighty-two percent of placebo-treated patients and 74% of carvedilol-treated patients were able to take the target dose of 25 mg twice daily. The data on primary outcome – all-cause mortality – are shown on Table 2. The severity of heart failure of the patients is evident by the high annual mortality rate (19%) in the placebo group. Treatment with carvedilol was associated with a 35% reduction of all-cause mortality. The Kaplan-Meier curves separated very early, after 2 months of treatment, and continued to separate over the duration of the study. Mortality reduction was observed across all pre-specified subgroups, including by age, gender, ejection fraction (above or below the median value of 20%), geographical location (recruitment from North America or outside North America), and hospitalization for heart failure within one year.

To address the safety concerns associated with the use of ß-blockers in patients with advanced disease, the outcome data were analyzed in the high risk subgroups by combining baseline characteristics that had been associated with a high placebo mortality rate. Three groups of perceived high risk patients were identified and the data are shown in Table 3. In all three groups, the risk reduction of all-cause mortality ranged from 42 to 50% and the 95% confidence intervals did not overlap unity, suggesting that in this trial there were no patients whose disease was too advanced to respond favorably to carvedilol therapy. Furthermore, carvedilol was

Table 2: Primary endpoint				
	Placebo	Carvedilol	Hazard ratio (95% CI)	P-value
All-cause mortality, number of events	190/1133	130/1156	0.65 (0.52, 0.81)	0.00014 (nominal) 0.0014 (adjusted)
Annual mortality rate	18.5%	11.4%		

Table 3: Analysis of high risk patients

- **LVEF <20%, and heart failure hospitalization within 1 year**

	Placebo	Carvedilol	Hazard ratio (95% CI)
Annual mortality rate	22.5%	17.9%	0.58 (0.34, 0.98)

- **LVEF <15%, or 3 heart failure hospitalizations within 1 year**

	Placebo	Carvedilol	Hazard ratio (95% CI)
Annual mortality rate	25%	19%	0.64 (0.48, 0.98)

- **Signs of fluid retention, use of intravenous inotropes or vasodilators within 2 weeks, or 3 heart failure hospitalizations within 1 year**

	Placebo	Carvedilol	Hazard ratio (95% CI)
Annual mortality rate	25.3%	16.7%	0.50 (0.27, 0.90)

LVEF = left ventricular ejection fraction

well tolerated since at 12 months, 13% of the carvedilol-treated patients and 16% of the placebo-treated patients required withdrawal from the randomized therapy.

Discussion

The primary outcome data of the COPERNICUS study demonstrate that chronic therapy with carvedilol, a non-selective ß-blocker that also has α-blockade and antioxidant properties,[7] reduces all-cause mortality in patients with severe heart failure who are in stable condition. The survival benefit applies to a wide spectrum of patients, including those with the most advanced disease. Most can attain the target dose, and withdrawal is no more frequent in carvedilol-treated than in placebo-treated patients.

The saga of ß-blocker use in heart failure has taken a tortuous route. From 1980 to 1997, more than 20 randomized controlled clinical trials using various ß-blockers were reported.[8] However, a few trials accounted for most of the patients. These trials reported variable effects on heart failure symptoms and exercise tolerance, but a consistent finding has been improvement of left ventricular function.[7] More than half the patients took part in trials of non-selective agents, of which carvedilol was the most commonly used (The US and the Australian-New Zealand carvedilol trials).[1,8,9]

In 1999, two adequately powered studies, CIBIS-II and MERIT-HF, were published.[2,3] Both demonstrated a 34% reduction in all-cause mortality and thus firmly established the role of ß-blockers in the treatment of heart failure.

It should be noted, however, that almost all of the above trials recruited primarily patients with moderate heart failure. This is evident by the percentage of patients with New York Heart Association (NYHA) class II to III symptoms, as well as the relatively low placebo mortality in these trials (Table 4). This raises the question about whether patients with more advanced disease can benefit equally from ß-blockade therapy. This concern was height-

Table 4: Recent outcome trials of ß-blockers in heart failure

Trial	Agent	NYHA II/III/IV (%)	Annual placebo mortality rate	Hazard ratio
US Carvedilol	Carvedilol	52/44/4	12% (annualized from 6 months)	0.35
CIBIS-II	Bisoprolol	0/83/17	13%	0.66
MERIT-HF	Metoprolol	41/56/3	11%	0.66
BEST	Bucindolol	0/92/8	17%	0.90 (*NS*)
COPERNICUS	Carvedilol	—	19%	0.65

Table 5: Number of patients needed to treat for one year to save one life

Trial	Number of patients
HOPE	333
SOLVD-Prevention	285
SOLVD-Treatment	77
CIBIS-II	23
MERIT-HF	25
COPERNICUS	14

ened when the recently presented Beta-Blocker Evaluation of Survival Trial (BEST) showed no benefit with the use of bucindolol, a third-generation non-selective ß-blocker with vasodilator properties. The BEST study recruited patients with advanced disease and also a considerable number of African Americans. The results of the COPERNICUS study are therefore reassuring and demonstrate that even in patients with very advanced heart failure, carvedilol exerts a beneficial effect on all-cause mortality.

What are the clinical implications of the COPERNICUS study?

• First, stable patients with advanced heart failure should be treated with a ß-blocker, such as carvedilol, unless there are clinical contraindications. Based on the findings, treating 1000 patients with advanced heart failure for 3 years would save 200 lives. As shown in Table 5, this compares very favorably with other secondary prevention trials.[1-5,10]

• Second, the totality of data from other outcome trials strongly suggests that the benefit of ß-blockade therapy is not a class effect. Indeed, unlike the ACE inhibitors which are relatively homogeneous as a class, the ß-blockers are very heterogeneous as a class. Accordingly, only ß-blockers that have demonstrated an improvement in survival in large outcomes trials (ie, carvedilol, bisoprolol [not available in Canada], and metoprolol) should be used. Whether there is an advantage in using carvedilol over metoprolol, or vice-versa, awaits the completion of the COMET study.

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