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Scientific Update™

Further Insights into the Therapeutic Role of Beta-Blockers in Patients with Heart Failure: The Impact of COPERNICUS and BEST

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The ß-blockers have been rapidly adopted as the standard therapy of patients with symptomatic left ventricular (LV) dysfunction, including those with advanced symptoms of heart failure (CHF). However, physicians have been hesitant to prescribe these agents to patients with extremely depressed LV ejection fraction (LVEF) and low systolic blood pressure, likely out of concern for tolerability and the potential for worsening CHF as a result of a negative inotropic effect. The recently published Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study has demonstrated that the ß-blocker, carvedilol, improves survival and reduces hospitalizations in patients with severe CHF. On the other hand, the Beta-blocker Evaluation of Survival Trial (BEST) study demonstrated that another ß-blocker, bucindolol, had no impact on mortality in a similar patient population with advanced CHF. This suggests that not every ß-blocker exerts similar favourable effects on patients with CHF. Meta-analyses of the use of ß-blockers in patients with CHF to date have not included the BEST and COPERNICUS studies. In this *Cardiology Scientific Update*, 3 peer-reviewed abstracts presented at the recent American College of Cardiology meeting – 2 on the use of ß-blockers in patients with low LVEF and low blood pressure, and 1 on the impact of BEST and COPERNICUS on overall estimates of ß-blocker survival benefit – will be reviewed. The clinical implications of their findings will be discussed.

Further analyses of the COPERNICUS study

The ß-blockers have been shown to reduce mortality and hospitalizations in patients with symptomatic left ventricular (LV) dysfunction, including those with advanced symptoms of heart failure (CHF).[1-4] As a result, these agents are rapidly adopted as standard therapy in patients with CHF.[5] However, physicians remain hesitant to prescribe them to patients with extremely depressed LV ejection fraction (LVEF) or low systolic arterial blood pressure, presumably out of appropriate concerns for tolerability and the potential for worsening CHF from the negative inotropic effect, especially during the period of drug initiation.

The COPERNICUS trial was a randomized placebo-controlled trial designed to examine the effect of carvedilol, a mixed ß (combined $ß_1$ and $ß_2$) adrenergic receptor blocker with an α-blockade property, versus placebo, on all-cause mortality in patients with severe CHF. The primary results of the COPERNICUS study were reviewed in a previous issue of *Cardiology Scientific Update*.[4] In brief, the trial included patients with CHF of ischemic or non-

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Table 1: Baseline data according to baseline LVEF in COPERNICUS

	LVEF >15% (n=1918)	LVEF ≤15% (n=371)
Age (years)	63	64
Male (%)	80	80
Blood pressure (mm Hg)	125/77	117/73
Heart rate (beats/min)	83	83
Digitalis use (%)	65	73
Diuretics use (%)	99	99

ischemic etiology, LVEF <25%, and symptoms at rest or with minimal exertion despite optimal conventional therapy. The pre-specified primary endpoint was all-cause mortality. The secondary endpoints included composite endpoints of all-cause mortality plus all-cause hospitalization, cardiovascular hospitalization, and hospitalization for CHF, as well as patient global assessment of well-being. The study was event-rate driven with an initial goal of 900 primary events.

The study was terminated early by the data and safety monitoring board in view of the favourable outcome effect demonstrated with carvedilol. A total of 2289 patients were randomized. The severity of CHF in the patients was evidenced by the high annual mortality rate (19%) in the placebo group. Treatment with carvedilol was associated with a 35% reduction in all-cause mortality. The mortality reduction was observed across all pre-specified subgroups, including age, gender, ejection fraction, geographical location, and recent hospitalization. Death and all-cause hospitalization, cardiovascular hospitalization, and hospitalization for heart failure were all significantly reduced. Patient global assessment of well-being was improved by carvedilol and the drug was well tolerated.

Carvedilol in patients with extremely depressed ejection fractions

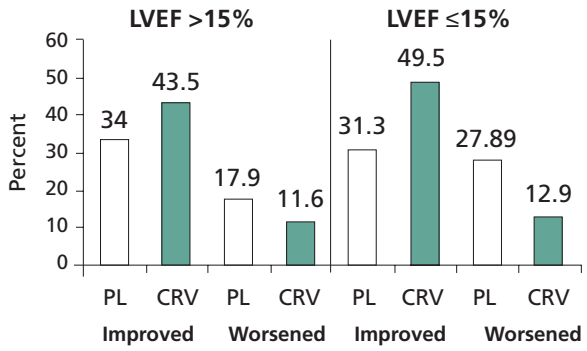
To assess whether patients with extremely depressed LVEF may benefit equally from ß-blockade therapy, a retrospective analysis was conducted to compare the frequency of major clinical endpoints, patient global assessment of well-being, and adverse effects in patients with LVEF ≤15% and those with >15% in the COPERNICUS study.[6] The results of this analysis were reported in an oral presentation session at the American College of Cardiology meeting. Since the data have not been published, the results should be considered preliminary. Of the 2289 patients enrolled in COPERNICUS, 371 patients (16.2%) had LVEF ≤15%. The baseline demographics are shown in Table 1. Patients with low LVEF had lower systolic blood pressure (SBP) and were more likely to be treated with digitalis. Both subgroups of patients were randomized to placebo (n=191 for low LVEF, n=942 for higher LVEF) or carvedilol (n=180 for low LVEF, n=976 for higher LVEF) for up to 29 months.

As a subgroup, all-cause mortality and the hospitalization rate were both significantly higher in the low LVEF group. The one-year Kaplan-Meier rate of major clinical outcomes and risk reductions with carvedilol from the Cox model are shown in Table 2. The beneficial effects of carvedilol on all-cause mortality and on the risks of death or hospitalizations, all-cause or cause-specific hospitalizations, were similar in patients with low or higher baseline LVEF. Data on patient global assessment are shown in Figure 1. In both subgroups, with low and higher baseline LVEF, more patients improved and fewer worsened after treatment with carvedilol compared to treatment with placebo. The frequency of adverse events and the rate of permanent withdrawal of study medication are shown in Table 3. In

Table 2: Major clinical outcomes according to baseline LVEF in COPERNICUS

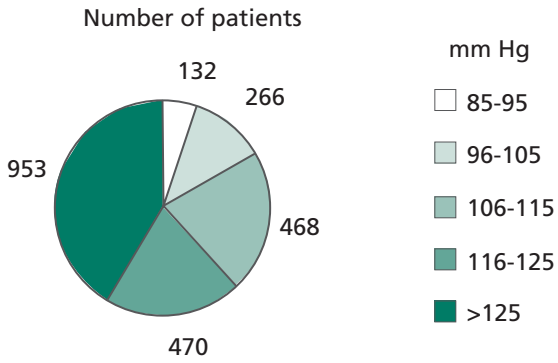
	LVEF ≤15%			LVEF >15%		
	Placebo (n=191)	Carvedilol (n=180)	Risk reduction	Placebo (n=942)	Carvedilol (n=976)	Risk reduction
All-cause mortality	23.8%	18.9%	30%	17.4%	9.7%	36%
Death or CHF hospitalization	46.3%	30.3%	39%	36.0%	24.6%	28%
Death or CV hospitalization	52.1%	34.6%	41%	39.4%	29.4%	23%
Death or any hospitalization	59.9%	47.2%	33%	50.7%	40.4%	21%

Figure 1: Patient global assessment in COPERNICUS



PL, placebo; CRV, carvedilol

Figure 2: Baseline systolic blood pressure in COPERNICUS



both subgroups of patients, more carvedilol-treated patients reported dizziness, hypotension, and bradycardia as adverse events, whereas fewer carvedilol-treated patients required permanent withdrawal of study medication compared to placebo-treated patients. These data suggest that carvedilol is effective and well tolerated, even in patients with extremely depressed LVEF.

Carvedilol in patients with low SBP

Since most survival trials of ß-blockers in CHF have excluded patients with low SBP (ie, <100 mm Hg),[1,2] many physicians are reluctant – as in the case of patients with low LVEF – to use ß-blockers in these patients, especially ß-blockers with a vasodilatory effect. To assess the efficacy and safety of carvedilol in patients with severe CHF and low SBP, a retrospective analysis was carried out to evaluate the effects of carvedilol versus placebo in patients recruited into the COPERNICUS study, using 5 quintiles of baseline SBP.[7]

The distribution of pre-treatment SBP is depicted in Figure 2. Of the 2289 patients recruited into the COPERNICUS study, 132 (5.4%) had a low baseline SBP of 85-95 mm Hg. Baseline LVEF, serum sodium, and creatinine concentrations, all markers of the severity of LV dysfunction in these patients, are shown in Table 4. Left ventricular systolic function and renal function were similar among patients with low and higher blood pressures. The risks of death, as well as combined death and CHF hospitalization, were lowest in patients with baseline SBP >125 mm Hg. These risks, however, increased progressively with decreasing baseline blood pressure, with the greatest risk observed in the subgroup of patients with SBP < 96 mm Hg.

Following initiation of study medications, patients with a baseline SBP of 85-95 mm Hg had an increase in SBP, the magnitude of which was greater in carvedilol- than placebo-treated patients. On the other hand, in patients with higher baseline SBP (>95 mm Hg), blood pressure declined

Table 3: Adverse events according to baseline LVEF in COPERNICUS

	LVEF >15%		LVEF ≤15%	
	Placebo	Carvedilol	Placebo	Carvedilol
Dizziness	15%	23%	25%	31%
Hypotension	5%	14%	12%	22%
Bradycardia	3%	12%	5%	12%
Permanent withdrawal of study drug	14%	12%	23%	17%

Table 4: Cardiac and renal function according to baseline SBP in COPERNICUS

Systolic blood pressure	85-95 (mm Hg)	96-105 (mm Hg)	106-115 (mm Hg)	116-125 (mm Hg)	>125 (mm Hg)
LVEF (%)	18	19	20	20	21
Serum Na (mEq/mL)	136	136	137	136	137
Serum creatinine (mg/dL)	1.6	1.6	1.5	1.5	1.5

Table 5: Major clinical outcomes according to baseline SBP in COPERNICUS				
Systolic BP	One year all-cause mortality		Death or CHF hospitalization	
	Placebo	Hazard ratio	Placebo	Hazard ratio
85-95 mm Hg	34%	0.77	61%	0.74
96-105 mm Hg	25%	0.61	43%	0.75
106-115 mm Hg	18%	0.65	37%	0.78
116-125 mm Hg	17%	0.61	40%	0.54
>125 mm Hg	15%	0.60	32%	0.68

transiently following initiation of therapy and increased gradually thereafter, the increase was greater in the carvedilol-treated patients.

The effects of carvedilol on all-cause mortality and combined death or CHF hospitalizations grouped according to baseline SBP are summarized in Table 5. The placebo one-year mortality rate and risk of death increase with decreasing baseline SBP. Carvedilol significantly reduced all-cause mortality and the risk of the combined endpoint in all blood pressure subgroups; there was no significant difference between blood pressure subgroup interaction for either all-cause mortality ($P = 0.64$) or combined death and CHF hospitalization ($P = 0.80$).

Data for adverse events are shown in Table 6. Dizziness, hypotension, and bradycardia were reported more frequently in the carvedilol-treated groups. These differences, however, were not accentuated in the low SBP subgroup. The risk of worsening CHF was lower with carvedilol in all blood pressure subgroups (interaction $P = 0.25$). As a whole group (ie, carvedilol and placebo patients combined), the rate of permanent drug withdrawal decreased with increasing baseline SBP ($P = 0.001$). In the low pressure group (85-95 mm Hg), the rate was slightly higher (7%) in the carvedilol group. In the rest of the subgroups, the rate was lower in the carvedilol groups. The overall blood pressure subgroup interaction, however, was not significant ($P = 0.25$).

The results of the blood pressure subgroup analysis therefore suggest that carvedilol is effective and well tolerated in patients with severe CHF and low SBP.

Impact of BEST and COPERNICUS on heart failure survival: An updated meta-analysis

Previous published meta-analyses of the use of ß-blockers in patients with CHF have included trials conducted mostly in patients with moderate CHF,[8] and have not included the recently published BEST and the COPERNICUS study.[4,9] Both BEST and COPERNICUS recruited patients with severe CHF. Furthermore, unlike COPERNICUS, in BEST, bucindolol did not demonstrate a beneficial effect on all-cause mortality (hazard ratio 0.90; 95% CI, 0.78,1.02, $P = 0.1$).[9] Accordingly, incorporation of data from BEST and COPERNICUS may impact on the totality of data regarding the use of ß-blockers in patients with CHF.

In order to assess the impact of BEST and COPERNICUS on the overall estimated efficacy of ß-blockers in CHF, a new meta-analysis that incorporates BEST and COPERNICUS has been conducted and the preliminary results were presented at the American College of Cardiology meeting.[10] In this renewed meta-analysis, Medline and Cochrane Controlled Trials Register were searched for randomized controlled trials comparing ß-blockers versus placebo among patients with symptomatic LV systolic dysfunction. All trials had to have mor-

Table 6: Adverse events according to baseline SBP in COPERNICUS						
Systolic BP	Dizziness		Hypotension		Bradycardia	
	Placebo	Carvedilol	Placebo	Carvedilol	Placebo	Carvedilol
85-95 mm Hg	32%	39%	26%	27.9%	5%	11%
96-105 mm Hg	27%	32%	20%	29%	3%	10%
106-115 mm Hg	20%	27%	10%	19%	2%	15%
116-125 mm Hg	13%	27%	6%	17%	4%	11%
>125 mm Hg	12%	17%	4%	7%	3%	11%

tality as one of the outcomes. Trials that followed patients for < 3 months and patients post-myocardial infarction were excluded. The trials were evaluated independently by two physicians. The primary outcome was all-cause mortality. A randomized effect model was used to pool hazard ratios with weighing of treatment effect in each trial by the inverse of its variance. Twenty-six randomized controlled trials that enrolled 15,369 patients were identified.

The trials were published between 1985 and 2001. Abstracted data included patient exclusion criteria, patient baseline characteristics, trial interventions, trial outcomes, and trial quality. The median LVEF ranged from 16% to 34% and the median follow-up period ranged from 3 to 52 months. Ten trials studied metoprolol, while 9 studied carvedilol. Two trials (465 patients) involved patients with non-ischemic etiology, 6 trials (542 patients) with ischemic etiology, and the remaining 18 trials (14,362 patients) had mixed etiologies. Data of pooled risk ratios of death, using a random effects model among patients treated in the 24 trials published between 1985 and 2000 (before BEST and COPERNICUS), are shown in Table 7. In these 24 trials, there were 1094 deaths with a 35% reduction in the risk of death attributable to ß-blockade therapy.

The BEST study, a study that did not demonstrate a benefit of ß-blockade therapy on mortality, added 860 deaths to the database (2nd row of Table 7). In spite of the great number of deaths contributed by BEST, the analysis of data from the 24 trials and BEST still yielded a 27% reduction in the risk of death by ß-blockade therapy (3rd row of Table 7). The COPERNICUS study added only 320 deaths since the trial was terminated early due to the efficacy demonstrated by carvedilol. The analysis of data combining the 24 trials, including BEST and COPERNICUS, therefore yielded a final risk reduction of 29% by ß-blockade therapy (5th row of Table 7). The χ^2 test for heterogeneity of the effect across the trials was not significant (*P* values ranged from 0.545 to 0.937).

Table 7: Hazard ratios of death in pooled analysis of 24 trials published in 1985 to 2000 prior to BEST and COPERNICUS, in BEST, COPERNICUS published in 2001 and in 26 pooled trials

Trials	Sample size	Number of deaths	Hazard ratio (95% CI)
24 trials, 1985-2000	10372	1094	0.65 (0.57,0.74)
BEST, 2001	2708	860	0.88 (0.75,1.03)
24 trials and BEST	13080	1954	0.73 (0.66,0.81)
COPERNICUS, 2001	2289	320	0.63 (0.49,0.89)
24 trials, BEST and COPERNICUS	15369	2274	0.71 (0.65,0.78)

Discussion

Data from the studies presented in this *Cardiology Scientific Update* provide new insights into the role of ß-blockade therapy in patients with CHF. The analyses of patients with impaired LVEF and low baseline SBP suggest that these patients with advanced CHF benefit equally in the improvement of mortality and CHF hospitalization as the patients with higher LVEF and SBP. Furthermore, carvedilol was well tolerated in these patients.

When applying these data to practice, however, clinicians should keep in mind the inclusion criteria and the up-titration schedule in the COPERNICUS study.[4] First, the study included patients who were "clinically euvolemic," defined as the absence of ascites, rales, and the presence of no more than minimal peripheral edema. Patients were excluded if they were treated with intravenous vasodilator and inotropic agents or treated in the intensive care setting within 4 days of screening. Furthermore, patients were excluded if they had SBP < 85 mm Hg and heart rate < 68 beats/min. Up-titration of study medication was cautious, with an increase in dose occurring no earlier than at 2-week intervals. In many instances, up-titration was delayed. With this careful dosing schedule, 78.2% of the surviving patients in the placebo group and 65.1% in the carvedilol group were still on the target dose of the study medication at 4 months. Clinicians should therefore ensure that all patients with severe symptoms, including those with low LVEF and SBP as low as 85 mm Hg, are in stable condition before the initiation of carvedilol, in order for them to accrue the same benefits as patients with higher LVEF and SBP.

The differential blood pressure response to carvedilol in patients with baseline SBP 85-95 mm Hg and those >95 mm Hg is interesting. Following initiation of study medication, blood pressure declined transiently in patients with SBP >95 mm Hg, the magnitude of decline

was greater in the carvedilol than the placebo group. This observation likely reflected the α-receptor blockade-mediated vasodilator effect of carvedilol.[11] On the other hand, in patients with SBP 85-95 mm Hg, blood pressure increased following initiation of therapy, with a greater increase observed in the carvedilol than in the placebo group. This difference in initial blood pressure response to carvedilol raises the possibility that patients with low SBP and potentially worse LV function may be less sensitive to the vasodilator effect of carvedilol. The subsequent increase in blood pressure observed in both the patients with low and higher SBP is likely reflective of a ß-blockade-induced improvement in the biologic property of the heart that, in turn, leads to an improvement of LV systolic function. Indeed, previous sequential assessments of LVEF in patients with dilated cardiomyopathy have demonstrated an initial decline of LVEF on day 1, but subsequently, an increase of LVEF above baseline at 1 and 3 months following initiation of therapy with metoprolol.[12] As a recent meta-analysis has demonstrated, carvedilol increases LVEF more than metoprolol,[13] and the subsequent increase in blood pressure following carvedilol in patients with low and higher baseline SBP is within expectations.

The meta-analysis of the ß-blocker CHF trials, including BEST and COPERNICUS restates the mortality benefit of ß-blockade therapy when data are pooled from 26 trials in patients with LV systolic dysfunction and varying degrees of symptoms. It is intriguing to find that, in spite of the high number of deaths attributed to the neutral BEST study, the overall risk reduction of death from ß-blockade remains substantial in the pooled analysis, with or without the addition of the COPERNICUS study. This favourable result is likely accounted for, at least in part, by the similarly favourable effect demonstrated in pooled analysis of the 24 trials conducted in 1985-2000, prior to BEST and COPERNICUS. Further details regarding the methodology of the current analysis of the 24 trials are hopefully forthcoming.

In summary, preliminary data presented in this report indicate that the ß-blocker, carvedilol, is beneficial and well tolerated in patients with LV systolic dysfunction and severe symptoms, including those with low ejection fraction and SBP. Therefore, physicians should be more willing to prescribe this useful therapy to a broader spectrum of patients with heart failure.

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