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Scientific Update™

The Expanding Therapeutic Role of the Beta-Adrenergic Receptor Blockers in Patients with Left Ventricular Systolic Dysfunction:
Results of the COPERNICUS and CAPRICORN Trials

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Beta-adrenergic receptor blockade has rapidly emerged to become a standard therapy in patients with symptomatic left ventricular dysfunction. Until last year, the evidence for the beneficial effect of ß-blockers on clinical outcomes was limited only to patients with mild to moderate heart failure. However, the results of the primary outcome of the COPERNICUS study presented late last year indicated that carvedilol, a ß-blocker with α-blockade property, reduced all-cause mortality in patients with advanced heart failure. The recently presented results of the secondary outcomes of the COPERNICUS study demonstrate that carvedilol also reduces morbidity in these sick patients. Although ß-blockers are widely used in patients following myocardial infarction (MI), studies of their use in MI were conducted in the era before the use of thrombolytics and angiotensin-converting enzyme (ACE) inhibitors. Most likely, these earlier trials included few patients with left ventricular dysfunction and heart failure. The recently presented results of the CAPRICORN study demonstrate that carvedilol reduces all-cause mortality in patients post-MI with left ventricular dysfunction. Thus, these new data provide convincing evidence to support the use of ß-blockers in a wide spectrum of patients, from those with left ventricular dysfunction post-MI to stable patients with advanced heart failure.

Beta adrenergic receptor blockade in chronic heart failure

Although the first evidence of the benefits of ß-blockade in patients with dilated cardiomyopathy was reported in the mid- to late-1970s,[1,2] the therapeutic concept of using ß-blockers in patients with heart failure was heavily disputed for the next 15 years. During this period, only small, randomized, controlled, single-centre studies examining surrogate endpoints were available. Accordingly, it was not until the results of the US Carvedilol Program,[3] CIBIS II,[4] and the MERIT-HF[5] were published that the benefits of ß-blockade in patients with mild to moderate heart failure were documented. Following the publication of these results, these agents were recommended for all patients with mild to moderate chronic heart failure.[6,7] However, as very few patients with severe heart failure were enrolled in these studies, the existing database on the effects of ß-blockade in these patients has, at least until last year, been felt to be insufficient to recommend ß-blockade therapy for patients with *severe* heart failure. Subgroup analyses of patients with New York

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Heart Association (NYHA) IV symptoms from these studies failed to reveal any statistically significant benefit of ß-blockade on mortality.

Concerns about the potential benefits of these agents in patients with severe heart failure was further heightened by the preliminary results of the Bucindolol Evaluation Survival Trial (BEST) that was presented early last year.[8] As will be discussed, in BEST, 2708 patients with severe heart failure (as evidenced by a placebo mortality rate of 16.6%) were randomized to receive bucindolol, a non-selective ß-blocker with intrinsic sympathomimetic activity and mild vasodilator property,[9,10] or placebo. No significant mortality benefit was observed in the overall BEST study population. Although there was a decrease in mortality amongst patients with NYHA III symptoms, there was a clear increase in mortality amongst those with NYHA IV symptoms. Given these considerations, a large-scale, prospective study on patients with severe heart failure was therefore required in order to address the issue of the efficacy, as well as the safety, of ß-blockers in patients with severe heart failure.

The COPERNICUS study

The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial was a randomized placebo-controlled trial designed to examine the effect of carvedilol, a non-selective ß-blocker with α-blocker properties, versus placebo on all-cause mortality in patients with severe heart failure. Details of the study design have been published[11] and reviewed in a previous issue of *Cardiology Scientific Update*. In brief, the trial included patients with heart failure of ischemic or non-ischemic etiology, left ventricular ejection fraction less than 25%, and symptoms of heart failure at rest or with minimal exertion despite optimal conventional therapy. Hospitalized patients were also eligible for recruitment provided they were not in the intensive care unit. Patients could be on intravenous diuretics, but not on intravenous vasodilators or inotropic agents within 4 days. 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 heart failure, 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, however, was terminated early on March 14, 2000 at the request of the Data Safety Monitoring Board in view of a favorable outcome effect demonstrated by carvedilol.

Table 1: Secondary endpoints of the COPERNICUS study

	Placebo (n=1133)	Carvedilol (n=1156)	Hazard ratio (95% CI)	P-value
Death and all-cause hospitalization	507	425	0.76 (0.67, 0.87)	0.00004
Death and cardiovascular hospitalization	395	314	0.73 (0.63, 0.84)	0.00002
Death and heart failure hospitalization	357	271	0.69 (0.59, 0.81)	0.000004

The preliminary results of the primary endpoint of the COPERNICUS study were first presented at the European Society of Cardiology meeting in August 2000 and were reviewed in a previous issue of *Cardiology Scientific Update*. In brief, a total of 2289 patients were randomized. Treatment with carvedilol was associated with a 35% reduction of all-cause mortality. The mortality benefit of carvedilol was present in all subgroups, including patients believed to have the most advanced disease as defined by low ejection fraction and/or recent hospital admission for heart failure.

Results

The results of the secondary endpoints of COPERNICUS were presented at the ACC meeting in March 2001. Like the data on the primary endpoint reviewed previously, the data on the secondary endpoints have not been published yet and the results presented below are preliminary and may be subject to review and modification. The results of the composite endpoints of mortality and hospitalization are shown in Table 1. Death and all-cause hospitalization, cardiovascular hospitalization, and hospitalization for heart failure were all significantly reduced. Among the pre-specified components of the combined endpoints, all-cause hospitalization, cardiovascular hospitalization, and hospitalization due to heart failure were reduced by 20%, 26% and 33%, p = 0.0012, 0.0056, and 0.0014, respectively. In addition, total days of hospitalization, the number of hospitalizations, and days per hospitalization were reduced by 24%, 27% and 31%, p = 0.0005, 0.0017, and 0.015, respectively. Use of intravenous diuretics and use of intravenous vasodilator and inotropic agents was reduced significantly by 25% and 33%,

respectively, as was the use of tests such as echocardiography. In the patient global assessment, the percentage of patients reporting clinical improvement at 2, 4, and 6 months post-randomization was greater in carvedilol-treated patients, whereas the percentage of patients reporting clinical worsening during the same time frame was greater in the placebo group. These differences between the study groups were significant at all time points and also increased progressively in magnitude as the study proceeded.

Overall, the reported incidence of any adverse events was similar in the 2 groups (75.4% versus 75.7%, placebo versus carvedilol, p = 0.86). However, carvedilol-treated patients were less likely to report serious adverse events (39% versus 45.5%, p = 0.002). These serious adverse events are shown in the upper panel of Table 2 and nearly all reflected worsening of underlying disease. On the other hand, as shown in the lower panel of Table 2, bradycardia, hypotension, and dizziness were reported more frequently in carvedilol-treated patients. These adverse events usually occurred at the time of dose titration and were likely a result of the ß- and α-blockade effects of carvedilol. Despite concerns about the negative inotropic effect of ß-blockade, the carvedilol group did not experience any more worsening of heart failure than the placebo group, whether in the initial uptitration period (p = 0.257), or during the maintenance phase. In fact, the carvedilol group experienced worsening of heart failure less frequently than the placebo group (p < 0.0001). Over the entire maintenance phase, there were fewer permanent discontinuations of the study drug in the carvedilol group than in the placebo group. Over the first 12 weeks (approximately the uptitration period), a majority of patients (73% in carvedilol group and 85% in placebo group) was able to achieve the target dose of 25 mg twice daily. In the maintenance phase, this full dose was maintained in 65% of carvedilol-treated and 75% of placebo-treated patients.

Table 2: Serious adverse events that were less frequent (nominal p < 0.05) in carvedilol-treated patients in COPERNICUS

	Placebo	Carvedilol
Heart failure	33.6%	28.1%
Cardiogenic shock	1.7%	0.4%
Atrial fibrillation	4.3%	2.2%
Supraventricular tachycardia	1.0%	0.2%
Ventricular fibrillation	2.1%	1.0%
Sudden death	6.1%	3.9%
Ventricular tachycardia	3.9%	1.6%
Serious adverse events that were more frequent (nominal p < 0.05) in carvedilol-treated patients		
	Placebo	**Carvedilol**
Bradycardia	3.2%	11.8%
Dizziness	16.2%	24.1%
Hypotension	8.7%	15.1%

Discussion

Although COPERNICUS, the largest trial of the use of ß-blockers in patients with severe heart failure, clearly demonstrated overwhelming benefits of carvedilol, it is still worthwhile to compare the results of COPERNICUS with the different results obtained from BEST. As mentioned earlier, the BEST study also recruited a sufficient number of patients with severe heart failure (annualized placebo mortality rate of 16.6%). The primary endpoint of BEST was total mortality; the secondary endpoints were cardiovascular mortality, hospitalization, death or transplant, ejection fraction, incidences of MI, quality of life, and the need for concomitant therapy. The preliminary results of BEST indicated that, compared to placebo, bucindolol reduced plasma norepinephrine levels and improved ejection fraction at 3 and 12 months. Bucindolol also reduced cardiovascular death by 14%, hospitalization by 12%, and MI by 50%. However, all-cause mortality, sudden death and pump death, as well as non-cardiovascular death were not significantly reduced by bucindolol.

Although both the BEST and COPERNICUS studies recruited patients with severe heart failure, unlike COPERNICUS, the BEST study recruited a considerable number of African Americans. This group of patients had a much higher rate of hypertension and had a more pronounced decline in plasma norepinephrine level as a result of bucindolol treatment. The bucindolol-treated African American patients actually experienced a 17% increase in mortality despite improved ejection fraction equivalent to the degree experienced by the whites. Indeed, if this subgroup was excluded from the analysis, the remaining 2100 patients did experience a statistically significant reduction in all-cause mortality. The reasons for the heterogeneous response to bucindolol in BEST and the consistently favorable response to carvedilol in COPERNICUS are unclear. These differences, however, raise several possibilities that may be important to clinicians:

• First, the differential response suggests that not every racial subgroup with advanced heart failure may respond to ß-blockade therapy.

• Second, excessive lowering of the plasma norepinephrine level (as also evidenced by the observations in the MOXCON study) and intrinsic sympathomimetic activity may be detrimental.

• Third and most important, the beneficial effect demonstrated with the three ß-blockers is not a "class effect," patients with advanced heart failure may not respond to simply any ß-blocker. In this regard, carvedilol is the only agent with ß-blockade activity demonstrated to improve mortality and morbidity in stable patients with truly severe heart failure.

COPERNICUS conclusions

The COPERNICUS study is the largest trial ever conducted in patients with severe heart failure with ß-blocker, and indeed with any therapy. Incorporating the primary outcome data reviewed in a previous issue of *Cardiology Scientific Update*, one can make the following conclusions from the results of the COPERNICUS study:

• In stable patients with severe heart failure, long-term therapy with carvedilol reduces the risk of death and composite risk of death and hospitalization; the frequency, duration of stay and severity of hospitalizations; as well as the risk of repeat hospitalizations.

• Carvedilol reduces the risk of progression of heart failure.

• Carvedilol is well tolerated, with fewer patients requiring permanent withdrawal of study medication for any reasons.

• Carvedilol does *not* worsen heart failure, either in the initial uptitration phase, or in the long-term maintenance phase, despite the advanced disease of the patient population.

The CAPRICORN study

Although early studies demonstrated beneficial effects of ß-blockers on mortality in patients with acute myocardial infarction (AMI),[12,13] the applicability of these early studies to the contemporary management of patients with AMI has been questioned.[14] There are several reasons for this uncertainty. First, the early trials were all conducted in the era before the wide use of aspirin, thrombolysis and ACE inhibitors. Second, elderly patients were largely excluded from these early trials. Third, there are reasons to believe that the populations of patients enrolled in these trials were relatively low risk in terms of cardiovascular events and early mortality, and the number of patients with left ventricular dysfunction and/or heart failure was relatively small. Accordingly, the therapeutic role of ß-blockers in AMI patients with impaired left ventricular function has never been addressed in an appropriately designed, randomized, controlled trial against a background of contemporary management of AMI.

The Carvedilol Post-infarct Survival Controlled Evaluation (CAPRICORN) was a multinational, randomized, controlled study on the effects of carvedilol on mortality and morbidity in patients with left ventricular dysfunction following AMI. The trial involved 163 investigators in 17 countries from Europe, Israel, North America, Australia, and New Zealand. Details of the study design of CAPRICORN have been published recently.[15] Patients with confirmed AMI within 3 to 21 days (mean 10 days) were recruited. To enter the study, patients had to have an ejection fraction <40% as determined by echocardiography, radionuclide scan, or contrast ventriculography. Patients also received contemporary therapy for AMI including aspirin, thrombolysis, and percutaneous coronary intervention. Use of ACE inhibitor was mandatory and must have been administered for 48 hours prior to randomization. Patients with systemic hypotension and those who required the use of intravenous inotropic agents and the ongoing use of ß-blockers were excluded. A small number of patients who were taking ß-blockers at the time of recruitment had their drug withdrawn in order to enter the study. A total of 1959 patients were randomly assigned to carvedilol (n = 984) or placebo (n = 984).

The original primary endpoint was all-cause mortality. The secondary endpoints were sudden death and hospitalization for heart failure. Exploratory analyses included cardiovascular mortality, all-cause hospitalizations, cardiovascular hospitalizations, unstable ischemic events and non-fatal cardiovascular events. During the study, the steering committee was informed by the data and safety monitoring board that the observed event rate was much lower than predicted, and the study was unlikely to achieve completion. The primary endpoint

Table 3: Baseline characteristics of patients in the CAPRICORN study		
	Placebo (n=984)	Carvedilol (n=975)
Mean age (years)	63	63
Female	26%	27%
Ejection fraction	31.7%	31.9%
Thrombolytic therapy	47%	45%
Intravenous nitrates use	73%	73%
Intravenous diuretics use	33%	35%
Aspirin use	86%	86%
ACE inhibitors use	97%	98%

Table 4: Primary endpoints of CAPRICORN			
All-cause mortality			
Placebo	Carvedilol	Hazard ratio (95% CI)	P-value (nominal)
15%	12%	0.77 (0.60, 0.980)	0.031
151/984	116/975		
All-cause mortality and cardiovascular hospitalization			
Placebo	Carvedilol	Hazard ratio (95% CI)	P-value (nominal)
37%	35%	0.92 (0.80, 1.07)	0.296
364/984	340/975		

was therefore modified to two co-primary endpoints: all-cause mortality and cardiovascular hospitalization, and all-cause mortality as originally planned. To correct for the change in primary endpoint, the original α level was distributed from 0.05 to 0.005 for all-cause mortality and 0.045 for the combined endpoint. The sample size calculation was based on the combined endpoint, with a 90% power to detect a 23% reduction in the combined endpoint. Based on this calculation, a recruitment of 1850 patients with 633 primary events was thought to be required. The study medication was uptitrated from 6.25 mg twice daily over 2-4 weeks to the full dose of 25 mg twice daily.

Results

The results of CAPRICORN were presented at the ACC meeting in March. Again, these results are not yet published and may be subject to revision. Baseline characteristics in the two arms are shown in Table 3. Both arms were comparable. Mean ejection fraction was 32%, more than 45% of the patients received thrombolytic therapy, more than 85% received aspirin, and 97% received ACE inhibitors. The active medication was well-tolerated, 83% of the placebo group and 74% of the carvedilol group was able to maintain the full dose of the study medications. Permanent withdrawal occurred in 18% of the placebo group and 20% of the carvedilol group. Forty-four percent of the placebo group and 41% of the carvedilol group experienced more than one serious adverse event.

Data on the two primary endpoints are shown in upper and lower panels of Table 4. As shown in the upper panel, all-cause mortality was reduced by 23% in the active treatment arm. The nominal p value was significant, but failed to reach significance if based on the value adjusted for endpoint modification. As shown in the lower panel, the second primary endpoint of combined all-cause mortality and cardiovascular hospitalization was not significantly different between the two arms even though the point estimate favoured carvedilol. In the secondary endpoints, there was a trend for reduction of sudden death (26% reduction, p = 0.098) and hospitalization for heart failure (14% reduction, p = 0.215). Post hoc analysis showed a major reduction in nonfatal MI (41% reduction, p = 0.014), as well as a combined endpoint of all-cause mortality and nonfatal MI (29% reduction, p = 0.002), endpoints that were commonly examined in contemporary clinical trials of acute ischemic syndrome.

Discussion

The preliminary results of CAPRICORN indicate that carvedilol reduces all-cause mortality in patients post-AMI against contemporary background therapy for AMI complicated by left ventricular dysfunction. Interestingly, the number of patients needed to treat for 1 year to prevent 1 death in CAPRICORN is 43. This number is almost identical to that calculated from studies of ACE inhibitor therapy post-AMI, except that in the case of the CAPRICORN study, this number is achieved in addition to the use of ACE inhibitors. Carvedilol also appears to

Table 5: Number of deaths prevented per 1000 patients treated with β-blockade therapy

Trial	Patient population	Drug	Deaths prevented
CAPRICORN	Post-AMI with LV dysfunction	Carvedilol	23
MERIT-HF	Mild to moderate CHF	Metoprolol CR/XL	40
CIBIS-II	Mild to moderate CHF	Bisoprolol	43
COPERNICUS	Advanced CHF	Carvedilol	71

AMI, acute myocardial infarction; CHF, congestive heart failure

All patients had LV systolic dysfunction and were on background therapy of ACE inhibitors

reduce ischemic events, most notably nonfatal MI, in this patient population.

Summary

In summary, the favorable results of the CAPRICORN and COPERNICUS studies extend the use of ß-blockers from the currently recommended patient population with mild to moderate heart failure to stable patients with advanced heart failure, as well as patients post-AMI with left ventricular dysfunction. The number of deaths prevented per 1000 patients treated with ß-blockers for 1 year for different patient populations with left ventricular dysfunction are shown in Table 5. Taking in consideration the totality of the data, one can conclude that unless there are specific contra-indications, almost every stable patient with left ventricular dysfunction would benefit from and therefore should receive ß-blockade therapy.

References:

1. Waagstein F, Hjalmarson A, Warnauskas E. Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy. *Br Heart J* 1975;37:1022-36.
2. Swedberg K, Hjalmarson A, Waagstein F, Wallentin I. Prolongation of survival in congestive cardiomyopathy by beta-receptor blockade. *Lancet* 1979;1:1374-6.
3. Packer M, Bristow M, Cohen J, et al. The effect of carvedilol on survival and hospitalization for cardiovascular complications in patients with chronic heart failure. *N Engl J Med* 1996;334:1349-55.
4. CIBIS-II Investigators and Committee. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomized trial. *Lancet* 1999;353:9-13.
5. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF). *Lancet* 1999;353:2001-7.
6. The Task Force on Heart Failure of the European Society of Cardiology. The treatment of heart failure. *Eur Heart J* 1997;18:736-53.
7. Packer M. Consensus Recommendations for the Management of Chronic Heart Failure. *Am J Cardiol* 1999;83 (suppl 2A):2A-77A.
8. Domanski MJ for the BEST Investigators. ß-blocker Evaluation of Survival Trial (BEST) (abstract). *Am J Cardiol* 2000;35:202A-203A.
9. Willette RN, Aiyar N, Yue TL, et al. In vitro and in vivo characterization of intrinsic sympathomimetic activity in normal and heart failure rats. *J Pharmacol Exp Ther* 1999;289:48-53.
10. Maack C., Cremers B, Flesch M, et al. Different intrinsic activity of bucindolol, carvedilol and metoprolol in human failing myocardium. *Br J Pharmacol* 2000;130:1131-9.
11. McGowan J, Murphy R, Cleland JGF. Carvedilol for heart failure: clinical trials in progress. *Heart Failure Rev* 1999;4:89-95.
12. Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med* 1981;304:801-7.
13. ß-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *J Am Med Assoc* 1982;247:1707-14.
14. Freemantle N, Cleland J, Young P, Mason J, Harrsion J. ß-Blockade after myocardial infarction: a systematic review and meta-regression analysis. *Br Med J* 1999;318:1730-8.
15. Dargie HJ for the CAPRICORN Steering Committee: Design and methodology of the CAPRICORN trial – a randomized double-blind placebo-controlled study of the impact of carvedilol on morbidity and mortality in patients with left ventricular dysfunction after myocardial infarction. *Eur J Heart Failure* 2000;2:325-32.