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Scientific Update™

Managing Chronic Heart Failure Improving LV Function and Mortality with Comprehensive Beta-Blockade

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ß-blockers are increasingly becoming standard therapy in patients with heart failure. However, the mechanisms mediating the favourable effects of these agents on clinical outcomes remain unclear. In this issue of *Cardiology Scientific Update*, the impact of ß-blockers on two important processes that may contribute to heart failure progression – namely myocardial hibernation in patients with ischemic heart disease and left ventricular (LV) remodeling – will be examined. Finally, new data regarding the relative safety of using these agents in patients with heart failure will be reviewed.

The hibernating myocardium in chronic HF: The CHRISTMAS study

Patients with chronic heart failure (HF) due to coronary artery disease (CAD) may present with a number of manifestations. One such manifestation is hibernation, in which prolonged downregulation of contractile function occurs due to reduced resting myocardial blood flow.[1] Since one of the leading causes of LV dysfunction is CAD, pharmacological approaches that might ameliorate myocardial ischemia and hibernating myocardium in patients with HF due to CAD will likely confer advantages over therapies that do not involve anti-ischemic mechanisms. There are reasonable theoretical arguments to support the use of carvedilol in patients with CAD and hibernating myocardium. Besides protecting the ischemic myocardium by its combined $ß_1$ and $ß_2$ receptor blockade, the α_1 blockade effect of carvedilol exerts coronary and peripheral vasodilation that, combined with its antioxidative properties,[2] could further improve myocardial perfusion and potentially improve systolic function.

The CHRISTMAS study

The Carvedilol Hibernation Reversible Ischemia Trial; Markers of Success (CHRISTMAS) study was a mechanistic study designed to determine whether the presence or absence of hibernating myocardium predicts the degree of improvement in LV ejection fraction in patients with chronic LV systolic dysfunction due to CAD and treated with carvedilol. The inclusion criteria included stable HF (New York Heart Association [NYHA] class I-III) due to LV systolic dysfunction, background therapy with angiotensin-converting enzyme (ACE) inhibitors, CAD as evidenced by a history of prior myocardial infarction (MI), revascularization procedures, or diagnostic coronary angiography. Patients required an echocardiographic wall motion index ≤1.3 (equivalent to a LV ejection fraction ≤39%).

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Study design

The study rationale and design of the CHRISTMAS study has been reported previously.[3] In brief, at the time of screening, patients were classified as hibernators or non-hibernators and were then randomized to receive carvedilol or placebo. Randomized therapy consisted of an up-titration period of about 2 months, followed by a maintenance period of 4 months. The target dose of carvedilol or placebo was 25 mg BID for patients <85 kg and 50 mg bid for patients ≥85 kg. Myocardial hibernation and reversible ischemia were assessed using a 9-segment model of the left ventricle. Contractile function was assessed in each segment by echocardiography, while perfusion was assessed by perfusion imaging in the same segments, at rest for defining hibernating segments, or during stress to assess for myocardial ischemia. A hibernating segment was present if there was a mismatch between contractile dysfunction and preserved perfusion:

- contractile dysfunction: severely hypokinetic, akinetic, or dyskinetic segment (echocardiography)
- preserved perfusion: >60% of isotope uptake on rest imaging

Only patients with at least 2 of 9 segments based on the above definition, or 1 such segment anatomically adjacent to 2 dysfunctional segments with 51%-60% uptake, were defined as having hibernating myocardium.

Primary endpoint

The primary endpoint was the mean change from baseline to final visit in the radionuclide-determined LV ejection fraction, carvedilol versus placebo, between patients with or without hibernating myocardium. Secondary endpoints included a comparison of the mean number of segments with rest isotope uptake ≤50%, 51%-60%, and >60% from baseline to final visit, and the relationship between volume of hibernating myocardium and mean change in LV ejection fraction between carvedilol and placebo. The study was designed to reach at least 80% power to detect a difference in the effect of carvedilol on LV ejection fraction for the primary endpoint.

Results

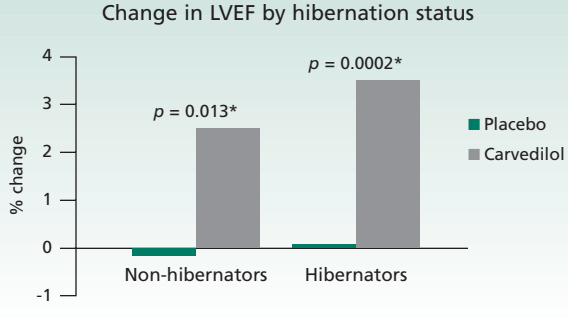
In total, 489 patients were screened for the study. Of these, 387 patients were randomized to receive study treatment (carvedilol 193, placebo 194). The final intention-to-treat population included 142 patients in the carvedilol group and 163 patients in the placebo group; patient losses were due to inadequate core laboratory assessments and adverse events. The baseline characteristics are shown in Table 1. Treatment groups were well-matched. In addition, mean LV ejection fraction was 30%, while 87% of patients were on ACE inhibitors and 83% were on diuretics.

Table 1: CHRISTMAS – Baseline characteristics of the study population

	Placebo (n=163)	Carvedilol (n=142)
• Hibernating myocardium	60%	59%
• Angina-free at rest	61%	59%
• Angina during exercise	13%	14%
• Diabetes	23%	21%
• Previous MI	91%	89%
• Previous revascularization	55%	51%

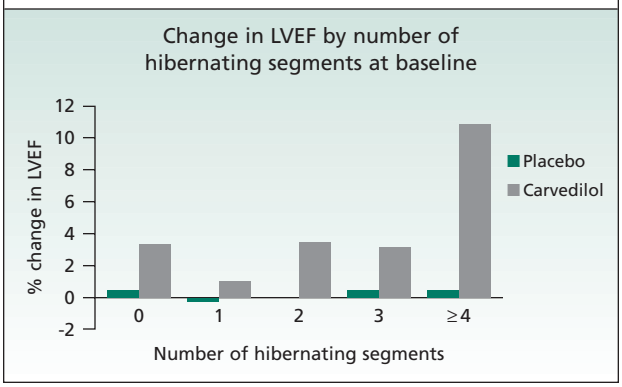
The primary efficacy results are shown in Figure 1. Treatment with carvedilol significantly increased LV ejection fraction by 3.2%. Increases were observed in both the hibernators and non-hibernators. The interaction between randomized treatment and hibernation status at baseline was not statistically significant ($P=0.64$). When analyzing the distribution of patients according to LV ejection fraction at final visit, there was no change with placebo compared to baseline values, whereas in carvedilol-treated patients, there was a significant shift in distribution towards an increase in LV ejection fraction. For secondary outcomes, among patients with hibernating myocardium, the increase in LV ejection fraction by carvedilol was greatest (+6%) in patients with baseline LV ejection fraction ≤24%, and was negligible in patients with baseline LV ejection fraction >34%. Furthermore, as shown in Figure 2, the greater increase in LV ejection fraction with carvedilol was observed in patients with a large number of baseline hibernating segments and was greatest in those with ≥4 segments. An analysis of the mean change in the number of segments with rest uptake ≤50% and >60% compared to baseline at the end of the study revealed that carvedilol both prevented ischemia deterioration and preserved myocardial perfusion. These effects were statistically significant compared to placebo ($P=0.003$).

Figure 1: CHRISTMAS – Primary endpoint



* Adjusted for baseline covariates

Figure 2: CHRISTMAS – Secondary endpoint



Carvedilol appeared to be well-tolerated in these patients. The incidence of adverse events in the carvedilol group (80.2%) was comparable to that in the placebo group (70.2%), as was the incidence of serious adverse events (20.3% and 19.1%, respectively). Mortality was 4.3% in the carvedilol group and 3.2% in the placebo group.

Discussion

The CHRISTMAS study was the first randomized, placebo-controlled study to examine the role of hibernating myocardium in LV systolic function response to pharmacotherapy in patients with HF due to CAD. Hibernating myocardium, at least based on the definition of CHRISTMAS, appears to be relatively frequent in patients with LV systolic dysfunction and CAD (about 60%). In patients with CAD and HF, treatment with carvedilol significantly improves LV systolic function, regardless of the presence or absence of hibernating myocardium. The most favourable effects, however, were seen in patients with a large amount of hibernating myocardium and a low baseline ejection fraction. Furthermore, carvedilol maintains myocardial perfusion in these patients. Carvedilol appears to be well-tolerated. Therefore, these data suggest that clinicians should consider carvedilol when initiating ß-blockade therapy in patients with LV systolic dysfunction and CAD.

Left ventricular remodeling and β-blockade: The CARMEN trial

The hallmark of HF is that of progression, and therefore, the principal goal of the treatment of HF is to prevent or attenuate disease progression. LV remodeling is a key process in the development of LV dysfunction and disease progression in patients with HF.[4] Preferably, treatment should be initiated at the stage of asymptomatic LV dysfunction with an aim of attenuating LV remodeling. Recently, ß-blockers have been shown to reduce mortality in patients with mild to severe HF.[5-8] Moreover, ß-blockers such as carvedilol have been shown to improve LV ejection fraction and reduce LV volume in patients with HF, observations supportive of a powerful antiremodeling effect.[9,10] However, most of these studies with ß-blockers were conducted in patients who had background therapy with ACE inhibitors. Indeed, based on currently available data, if clinicians choose to attenuate LV remodeling in patients with early HF, they would have to combine an ACE inhibitor and a ß-blocker, a practice of polypharmacy that may not necessarily be desirable in patients with mild or no symptoms. Furthermore, recent studies of endothelin receptor antagonists (ENABLE, EARTH), vasopeptidase inhibitors (OVERTURE), and cytokine inhibition (RENEWAL), have suggested that additional neurohormonal modulation beyond that of inhibition of the renin-angiotensin-aldosterone and sympathetic nervous system may not produce additional benefits. Accordingly, it may be reasonable to evaluate more individualized, severity-oriented, and patient-centered treatment in subsets of patients such as those with LV systolic dysfunction and minimal or no symptoms of HF.

The CARMEN Study

The Carvedilol and ACE-inhibitor Remodeling Mild heart failure EvaluatioN (CARMEN) trial was designed to compare the effects of carvedilol alone (Group 1), and carvedilol plus an ACE inhibitor (Group 2), versus an ACE inhibitor alone (Group 3) on various parameters of LV remodeling in patients with LV systolic dysfunction and mild symptoms of HF. The rationale and design of this study have been previously published.[11] The key inclusion criteria were mild HF with at least a 2-month history of symptoms of mild CHF, LV ejection fraction ≤0.39, and echocardiographic recordings of sufficient quality.

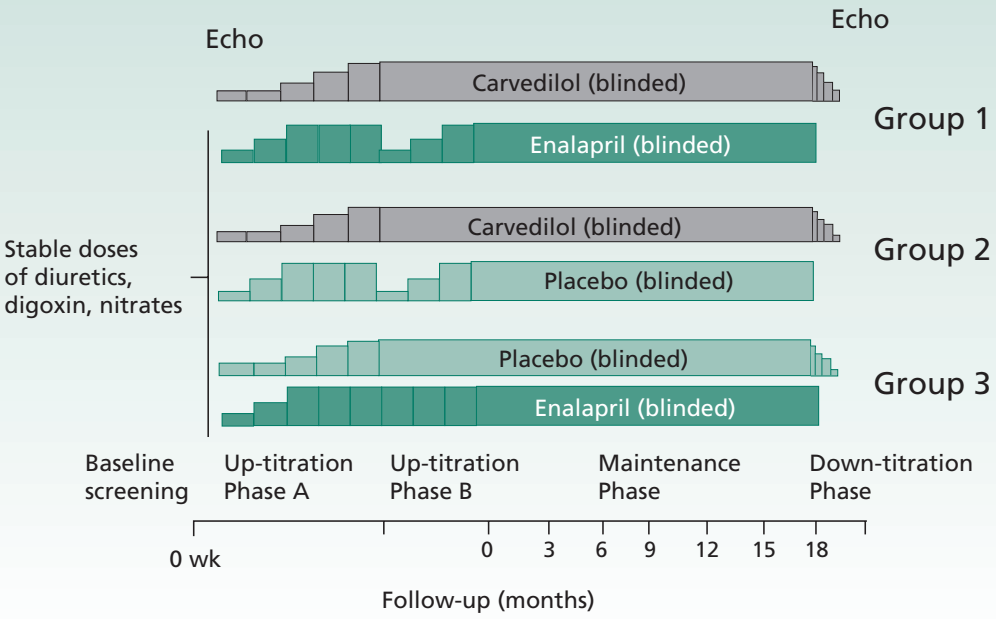
Study design

The study protocol consisted of 4 phases as summarized in Figure 3.

1. Up-titration phase A: Patients were up-titrated on either carvedilol (Groups 1 and 2) or enalapril (Group 3) in a blinded fashion until the maximum tolerated dose of carvedilol, (25 mg bid for patients < 85 kg and 50 mg bid for patients > 85 kg), or enalapril (10 mg bid) was reached.
2. Up-titration phase B: Patients were up-titrated on enalapril (Group 1) or matching placebo (Groups 2 and 3) until maximum dose was reached.
3. Maintenance phase: Patients received stable doses of blinded study medications twice daily for 18 months.
4. Down-titration phase: Study medications were down-titrated and patients were continued on optimal open-label therapy at the discretion of the investigators.

The primary endpoints were the absolute change in LV end-systolic volume index (LVESVI) from baseline to month

Figure 3: CARMEN Study Design



18 for the following 2 between-treatment comparisons: carvedilol + enalapril (Group 1) versus enalapril alone (Group 3), and carvedilol alone (Group 2) versus enalapril alone (Group 3). With 187 patients randomized and 135 patients scheduled to complete each of the 3 treatment regimens and with adjustments for multiple comparisons, the study had 80% power at a significance level of $P = 0.025$ to show a difference in LVESVI for each of the 2 primary comparisons of interest of 6.07 ml/m^2 (standard deviation, 16.1 ml/m^2).

Results

The results of CARMEN were recently presented for the first time at the European Society of Cardiology Meeting. The data have not yet been published and should be considered preliminary. In total, 745 patients were screened from 65 centres in 13 European countries. Of these, 572 patients received at least 1 dose of a study drug and were enrolled in the study. The final intention-to-treat population included 479 patients, since 93 patients had no evaluable post-baseline echocardiographic recording for assessment of primary endpoint. The baseline characteristics of the patients are shown in Table 2. The majority of patients had NYHA class II or lower symptoms. It is important, however, to note that about two-thirds of the patients were already treated with an ACE inhibitor before entry into the study. On the other hand, <6% of patients were on ß-blockers.

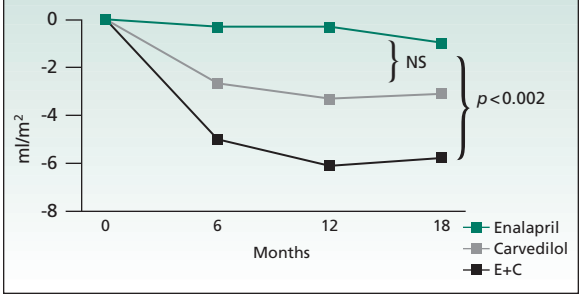
The primary efficacy results are shown in Figure 4. Combination therapy resulted in a significant reduction in LVESVI at 18 months when compared to enalapril or carvedilol alone. This superior effect was evident at 6 months. Although the carvedilol group appeared to have a greater decline in LVESVI than the enalapril group, the differences between the 2 monotherapy groups did not reach statistical significance. The mean changes from

Table 2: Baseline characteristics of the CARMEN study population with data for assessment of primary endpoint

	Carvedilol + enalapril (n=158)	Carvedilol (n=161)	Enalapril (n=160)
NYHA I (%)	7	9	7
NYHA II (%)	68	65	62
NYHA III (%)	25	26	31
LVESVI (ml/m^2)	59	64	63
LVEDI (ml/m^2)	83	88	88
LVEF (%)	30	29	30

LVESVI, LVEDI, and LVEF = LV end-systolic volume index, LV end-diastolic volume index and LV ejection fraction, respectively

Figure 4: CARMEN Primary Endpoint: Absolute change in LVESI



baseline at 6, 12, and 18 months within each treatment group, one of the secondary analyses, were significant only in the combination and carvedilol groups, but not in the enalapril group. The safety and mortality results are summarized in Table 3. During the 530-day treatment period, the frequency of adverse events was similar in the 3 treatment groups, as was mortality and hospitalization data, although CARMEN was not designed to assess clinical outcomes.

Discussion

CARMEN is the first, large-scale, direct comparison of the effects of ß-blockade versus ACE inhibition on LV remodeling in mild HF. Patients who received carvedilol or the combination of enalapril and carvedilol had significant attenuation of LV remodeling. In addition, combined therapy with ACE inhibitor and carvedilol was superior to monotherapy with either agent. Furthermore, carvedilol was safely initiated before starting ACE inhibition. The lack of an effect of enalapril on LV remodeling in CARMEN contrasts with previous observations from the SOLVD study.[12] This apparent lack of an effect, however, can be explained in part by the fact that two-thirds of the patients in CARMEN were already on ACE inhibitors at the time of randomization. Findings from CARMEN, however, are consistent with previous studies of smaller sample sizes. In a study with 49 patients that compared the effects of carvedilol, captopril, and combination therapy,[9] patients were randomized to monotherapy for 3 months followed by combined therapy for 3 months. Both carvedilol and captopril alone reduced LV mass and sphericity by a similar degree, but only carvedilol reduced LV volume. Adjunctive therapy with carvedilol produced significantly greater reductions in the wall-thickening index than captopril. These data support the concept that carvedilol exerts favourable effects on LV remodeling in the absence of ACE inhibitor background therapy in patients with HF. Indeed, the beneficial effects on LV remodeling may explain the reported favourable effect of carvedilol on clinical progression in patients with mild HF, as documented in the MILD study.[13] Therefore, the results from MILD and those from CARMEN further support the practice of starting ß-blockade therapy with carvedilol early, in conjunction with ACE inhibitors, even in patients with mild HF.

Table 3: Adverse events of patients who had received at least one dose of study drug

	Carvedilol + enalapril (n=191)	Carvedilol (n=191)	Enalapril (n=190)
Any AE	497 (79%)	426 (77%)	461 (74%)
Serious AE	81 (28%)	101 (29%)	94 (34%)
AE leading to withdrawal	45 (18%)	43 (18%)	48 (21%)
All-cause mortality	14 (7%)	14 (7%)	14 (7%)
CV mortality	9 (5%)	13 (7%)	14 (7%)

AE, adverse events; CV, cardiovascular

Early tolerability of ß-blockade: Still a cause for concern?

A general reluctance by clinicians to prescribe ß-blockers is the principal reason why these agents remain underutilized in clinical practice despite evidence of their clinical efficacy in major clinical trials[5-8] and their recommendation as mandatory therapy in recent treament guidelines.[14,15] The reluctance to prescribe ß-blockers may be related, in part, to the perception that they are difficult to titrate, not well-tolerated, and suitable only for a few patients.

Data from the major ß-blocker HF trials, however, strongly suggest otherwise. Discontinuation of study medication has been less than or equal to placebo in CIBIS-II, MERIT-HF, US Carvedilol Program, and COPERNICUS (Table 4). In COPERNICUS, statistically signifi-

Table 4: Treatment discontinuation rates in major ß-blocker heart failure trials

	Average duration (months)	Discontinuation rate (%)		
		Placebo	ß-blocker	Relative risk
US Carvedilol	6	7.8	5.7	0.73
CIBIS-II	15	15.0	15.0	1.00
MERIT-HF	12	15.3	13.9	0.90
COPERNICUS	10.5	11.3	9.5	0.84

cant fewer patients withdrew from carvedilol therapy than from placebo ($P = 0.02$). Interestingly, in COPERNICUS, discontinuation rates with carvedilol were similar to placebo in the first 3 months. This contrasts with MERIT-HF, where a recent report indicated that the discontinuation rate of metoprolol CR/XL was higher than placebo during the same early period.[16] In a recent *post hoc* analysis of COPERNICUS, there was no increase in adverse events in the first 8 weeks and there were fewer serious adverse events and permanent withdrawals with carvedilol than placebo.[17] There was no increase in worsening HF with carvedilol versus placebo in the first 90 days. By study end, this was significantly lower than placebo ($P = 0.001$).

To date, open-labeled experience with carvedilol has indicated tolerability of 69% to 95%. These findings, coupled with those reviewed in a previous *Cardiology Scientific Update*, of equal survival benefit and tolerability of carvedilol in patients with low ejection fraction compared to less-impaired ejection fraction, as well as in patients with low systolic blood pressure compared to less hypotensive patients,[18,19] indicate that clinicians should not withhold ß-blocker/carvedilol therapy in patients with severe HF if this is based only on concerns about early intolerability. To further evaluate safety, the Carvedilol Open Label Assessment (COLA) program that tracks the use of carvedilol in elderly HF patients with low ejection fraction, is currently underway.

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