Effects of Carvedilol on Left Ventricular Remodeling After Acute Myocardial Infarction
The CAPRICORN Echo Substudy

Robert N. Doughty, MD, MRCP, FRACP; Gillian A. Whalley, MHSc, DMU; Helen A. Walsh, BSc; Greg D. Gamble, MSc; José López-Sendón, MD, PhD, FESC; Norman Sharpe, MD, FRACP; on behalf of the CAPRICORN Echo Substudy Investigators

Background—The CAPRICORN trial has shown that carvedilol improved outcome in patients with left ventricular dysfunction after acute myocardial infarction treated with ACE inhibitors. The aim of this substudy was to determine the effects of carvedilol on left ventricular remodeling in this patient group.

Methods and Results—Patients entering the CAPRICORN trial from 13 centers in New Zealand, Australia, and Spain were recruited for this echocardiographic substudy. In 127 patients, quantitative 2D echocardiography was performed according to a standard protocol before randomization and repeated after 1, 3, and 6 months of treatment with carvedilol or placebo. Left ventricular volumes, ejection fraction (Simpson’s method), and wall motion score index were determined in a blinded analysis at the Core Echo Laboratory. At 6 months, left ventricular end systolic volume was 9.2 mL less in the carvedilol group than in the placebo group (P=0.023), and left ventricular ejection fraction was 3.9% higher (P=0.015). Left ventricular end diastolic volume and wall motion score index were not statistically different between the 2 groups at 6 months.

Conclusions—In patients with left ventricular dysfunction after acute myocardial infarction treated with ACE inhibitors, carvedilol had a beneficial effect on ventricular remodeling, which may, in part, mediate the substantial clinical beneficial effects of carvedilol in this patient population. (Circulation. 2004;109:201-206.)

Key Words: remodeling ■ infarction ■ ventricles ■ echocardiography
Echocardiographic Methods

Two-dimensional echocardiography was performed within 24 hours before randomization. This was at a time when ACE inhibitor therapy had already been titrated and the dose was stable. After randomization, echocardiograms were performed at the end of the up-titration phase with carvedilol or placebo (≈1 month) and then at 3 and 6 months. Echocardiograms were performed by experienced ultrasonographers and repeated by the same operator within each center wherever possible. Images were recorded onto videotape, and measurements were made at the end of expiratory phase of normal respiration. A standard imaging protocol was used based on apical 4- and 2-chamber views according to the recommendations of the American Society of Echocardiography.

All echocardiograms were analyzed at the Core Echo Laboratory (University of Auckland), with each echocardiographic variable analyzed by 1 observer who had no knowledge of treatment allocation. Cine loops of apical 4- and 2-chamber views were digitized using a dedicated offline computer (ImageVue, Kodak Eastman) and stored on optical disc. End diastole was defined as the frame with the largest cavity immediately before the onset of the QRS and end systole as the frame with the smallest cavity area. Manual planimetry of the endocardial border was performed, and papillary muscles and intracavitary thrombi (if present) were included in the blood volume. Biplane enddiastolic and end systolic volumes were calculated from the planimetered areas by computer software according to a modified Simpson’s rule. Three cycles (or 7 in the presence of atrial fibrillation) were measured for each assessment, avoiding postectopic beats, and the average volumes were obtained. Measurement reproducibility and normal ranges have previously been described from our laboratory.

The primary end point was change in LV end systolic volume (LVESV) at 6 months. Secondary end points were change in LV end diastolic volume (LVEDV) at 6 months and change in regional wall motion score index (WMSI) at 6 months. Other end points included changes in LVEF at 1, 3, and 6 months and changes in LVESV, LVEDV, and LV WMSI at 1 and 3 months.

Statistical Analysis

Based on previous studies of patients with LV dysfunction after MI, a sample size of approximately 65 patients per group was estimated to provide ≥80% power at the 0.05 level of statistical significance to detect an absolute change in LVESV of 12 mL between the groups (assuming a SD for LVESV of 26 mL). Data were analyzed on an intention-to-treat basis using a fixed-effects mixed model (PROC MIXED SAS v8, SAS Institute Inc). Significant main and interaction effects were explored using the method of Tukey. Maximum likelihood estimation was used to enable all of the available data to contribute to the estimation of the effect size. The maximum likelihood estimate of a parameter is the value of the parameter that is most likely to have resulted from the observed data and uses all data observed for each case rather than imputing data. Categorical modeling (PROC CATMOD SAS v8, SAS Institute Inc) was used to examine effects of treatment in categorical data observed repeatedly throughout the trial. A 5% significance level was maintained throughout. All tests were 2-tailed.

Results

Study Patients

One hundred twenty-seven patients from 13 sites were included in the substudy, of whom 60 were randomized to carvedilol and 67 to placebo. The study group characteristics are presented in the Table. Infarct characteristics, site of MI, and echocardiographic indices were well matched between treatment groups. Mean age was 61 years (SD 12), 103 (81%) were male, 53 (42%) had a prior history of HF, 31 (24%) had a prior MI, and 72 (57%) had an anterior MI as the index infarct. Ninety-three percent of the patients were receiving ACE inhibitors at baseline. The patients had increased LV volumes at baseline, with mean LVEDV of 132.4 mL (SD 43.9 mL) and LVESV of 81.9 mL (SD 34.9 mL) and impaired LV systolic function (mean LVEF, 39.3% [SD 8.0%]).

The mean time from the index infarction to the substudy echocardiogram was 9 days (SD 5.7, Figure 1). Over the course of the study, 10 patients in the placebo group and 2 patients in the carvedilol group died (χ² = 6.9, P = 0.0088). Eight of the 10 deaths in the placebo group occurred before the 6-month echo. In addition, 6 patients in the placebo group and 7 in the carvedilol group did not have an echo that was suitable for measurement of LV volumes at 6 months; thus, 104 patients had an interpretable echo at 6 months (53 in the placebo group and 51 in the carvedilol group). The mean dose of study medication at 6 months was 38 mg/d in the carvedilol group and 42 mg/d in the placebo group, and 93% of surviving patients were receiving ACE inhibitors.

Heart Rate and Blood Pressure

Heart rate was reduced by 9.9 bpm (95% CI, −15 to −4.8) in the carvedilol group compared with the placebo group at 1
month, 12.8 bpm (95% CI, −18.3 to −7.3) at 3 months, and 8.1 bpm (95% CI, −14.9 to −1.3) at 6 months (all \( P < 0.05 \)). Systolic blood pressure was reduced by 6.6 mm Hg (95% CI, −11.7 to −1.5; \( P = 0.016 \)) and 6.1 mm Hg (95% CI, −12.3 to 0.06; \( P = 0.06 \)) in the carvedilol group compared with the placebo group at 1 and 3 months, respectively (Figure 2). However, the difference between the groups at 6 months was only 2.9 mm Hg (95% CI, −10.9 to 5.1; \( P = 0.28 \)). Diastolic blood pressure was reduced by 7.2 mm Hg (95% CI, −11.3 to −3.1; \( P < 0.0001 \)) in the carvedilol group compared with the placebo group at 1 month, but the between-group differences at 3 and 6 months were not statistically significant, 2.4 mm Hg (95% CI, −6.6 to 1.7; \( P = 0.17 \)) and 1.8 mm Hg (95% CI, −6.7 to 4.8; \( P = 0.5 \)), respectively.

**Left Ventricular Volumes**

In the carvedilol group, LVESV decreased by 2.0 mL (SEM 2.1 mL) at 1 month, by 4.8 mL (SEM 2.5 mL) at 3 months, and by 4.8 mL (SEM 4.9 mL) at 6 months of treatment. In contrast, in the placebo group, LVESV increased by 4.9 mL (SEM 3.0 mL) at 1 month, by 3.1 mL (SEM 2.7 mL) at 3 months, and by 4.5 mL (SEM 2.8 mL) at 6 months of treatment. At 6 months, there was a difference of 9.2 mL (95% CI, −17.1 to −1.3 mL; 2-tailed \( P = 0.023 \)) in LVESV between the carvedilol and placebo groups (Figure 3B).

In the carvedilol group, there were no significant changes in LVEDV over the duration of the study, as follows: +2.7 mL (SEM 2.5 mL) at 1 month, +0.5 mL (SEM 3.0 mL) at 3 months, and +1.6 mL (SEM 3.6 mL) at 6 months of treatment. In contrast, in the placebo group, LVEDV increased by 4.9 mL (SEM 3.0 mL) at 1 month, by 3.1 mL (SEM 2.7 mL) at 3 months, and by 4.5 mL (SEM 2.8 mL) at 6 months of treatment. At 6 months, there was no statistically significant difference in LVEDV between the carvedilol and placebo groups (−6.7 mL; 95% CI, −16.4 to +2.9 mL; 2-tailed \( P = 0.17 \); Figure 3A).

In the carvedilol group, LV stroke volume increased by 4.7 mL (SEM 1.4 mL) at 1 month, 5.3 mL (SEM 1.7 mL) at 3 months, and 6.4 mL (SEM 1.8 mL) at 6 months of treatment. In contrast, in the placebo group, LV stroke volume decreased by 0.7 mL (SEM 1.5 mL) at 1 month, increased by 0.5 mL (SEM 1.6 mL) at 3 months, and increased by 3.7 mL (SEM 1.6 mL) at 6 months of treatment. Overall, there was a statistically significant difference of 5.4 mL (95% CI, +1.3 to +9.5 mL; 2-tailed \( P = 0.01 \)) and 4.8 mL (95% CI, +0.21 to
Carvedilol and placebo are MANOVA over 6 months of treatment. There has a favorable effect on LV remodeling, reducing LVEDV and LVESV, and improves survival. Carvedilol alone (without concomitant ACE inhibitor therapy) has been shown to reduce both LVEDV and LVESV in patients with LV dysfunction after acute MI. The present study demonstrates that carvedilol, when used in addition to ACE inhibitor therapy in patients after acute MI, inhibits progression of LV remodeling.

**Clinical Relevance of Beneficial Effects of Carvedilol on LV Remodeling**

In chronic HF, ACE inhibitors reduce total mortality, primarily attributable to fewer deaths from progressive HF, with only a modest effect on sudden death. In comparison, when added to ACE inhibitors in patients with chronic HF, β-blockers decrease deaths attributable to both worsening HF and sudden death, and these effects are probably mediated via anti-ischemic, antiarrhythmic, and reverse remodeling effects. Indeed, the reductions in all-cause mortality, non-fatal recurrent infarction, and arrhythmias may in part reflect the design of this study, where carvedilol was added to background ACE inhibitor therapy. Although longer-term follow-up may have been required to reveal greater clinical benefits on HF end points in the CAPRICORN trial, the overall effects of carvedilol probably relate to anti-ischemic and antiarrhythmic effects and inhibition of progressive LV remodeling.

**Time Course and Potential Mechanisms of Effects on Remodeling**

This study provides insight into the time course of the effect of carvedilol on remodeling in the postinfarction period. At 1 month of treatment with carvedilol, there was a marked reduction in heart rate and blood pressure, with an associated increase in LV stroke volume and LVEF and trends to improvement in LVESV. These effects were maintained at 3 months of treatment and are consistent with the β-blocking and α1-blocking (vasodilating) properties of carvedilol. However, at 6 months, although the reduction in heart rate was maintained, the effects of carvedilol on blood pressure and stroke volume were attenuated such that there were no significant differences between treatment groups. At this time interval, there was a significant improvement in LVESV with carvedilol compared with placebo. The magnitude of the effect on LVESV at 1 and 3 months seems similar to that seen at 6 months, suggesting that the vasodilating effects of carvedilol may represent an important part of the mechanism of improvement in stroke volume and LVEF at 1 month with carvedilol. The effects at 6 months would be consistent with
attenuation of the vasodilating effects of carvedilol, as has previously been demonstrated.21

The results over the 6 months demonstrate a substantial beneficial effect on inhibiting progression of LV remodeling. The underlying mechanisms of this effect are probably multifactorial. Short-term ß-blockade with conventional ß-blockers in both healthy subjects and those with impaired LV function increases LV volumes.22,23 It remains uncertain to what degree the effect of carvedilol on remodeling at 6 months depends on the early marked effects on blood pressure and stroke volume associated with the vasodilating properties of this drug. Other effects of ß-blockade, including reduced myocardial oxygen consumption, reduced filling pressures,24 and neurohormonal blockade, are likely to play a role. However, additional mechanisms underlying the beneficial effect of carvedilol on remodeling cannot be determined from this study, because LV function was not assessed under standard loading conditions. At the end of the CAPRICORN trial, patients were titrated onto open-label ß-blocker therapy, and thus it was not possible to study the effects of withdrawal of the ongoing loading effects of carvedilol on LV volumes.

Interestingly, the LV volumes in the placebo group of the study tended to increase despite ACE inhibitor therapy. Previous studies have shown that ACE inhibitor therapy prevents LV remodeling in patients with acute MI and LV dysfunction.3–5 However, these studies have usually involved patients presenting with a first MI and usually without a prior history of clinical HF. In the present study, approximately one quarter of the patients had a prior MI and half had a history of HF before the index infarction, suggesting that this patient population is intermediate between the initial postinfarction ACE inhibitor remodeling studies3,5 and the chronic HF remodeling studies.10 This suggests that ACE inhibitor therapy alone is not sufficient to completely prevent additional LV remodeling in the setting of an acute MI in an already damaged ventricle.

Conclusions
In summary, the results from this echocardiographic substudy of the CAPRICORN trial demonstrate that carvedilol inhibits progressive LV remodeling in patients with LV dysfunction after acute MI. This effect may mediate, in part, the substantial clinical benefits of carvedilol in this patient population. The results support the complementary effects of combination therapy with ACE inhibitors and carvedilol initiated early after acute MI in patients with LV dysfunction.

Appendix
CAPRICORN Echo Substudy participating centers are listed below. * indicates Study Principal Investigator; †, Echo SubStudy Co–Principal Investigator.

Australia
Liverpool Hospital, Sydney (D. Gallagher,* D. Leung,* and E. Newland); The Nepean Hospital, Sydney (D. Fitzpatrick,* D. Schoever, and I. Ting); Princess Alexandra Hospital, Brisbane (R. Calvert, P. Garraty,* C. Hall, and C. Wood); Royal Perth/Hollywood Hospital, Perth (P. Currie,* T. Young, and K. Lynch); St Vincent’s Hospital, Sydney (F. Ali,* T. Campbell,* and S. D’Arcy); and Wollongong Hospital, Wollongong (M. Kuster, J. Keshby, S. MacKinley, and D. Owensby*).

New Zealand

Spain
Hospital Civil de Basurto, Bilbao (M. Arrillaga and J. Etxebeste); Hospital Gregorio Maranon, Madrid (J. Lopez-Sendon, M. Moreno, and J. Palomo); and Hospital Puerta de Hierro, Madrid (A. Alonso, M. Caverio, and M. Gonzalez).

Core Echo Laboratory and Coordinating Centre
Cardiovascular Research Laboratory, University of Auckland, Auckland, New Zealand (R.N. Doughty,† G.D. Gamble, N. Sharpe,† H. Walsh, and G.A. Whalley†).

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References


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