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ORIGINAL PAPER

# Carvedilol Produces Sustained Long-Term Benefits: Follow-Up at 12 Years

*The authors measured long-term outcomes of patients who initiated carvedilol between 1990 and 1992 to test the hypothesis that carvedilol produces sustained benefits in heart failure patients. The study population consisted of 57 patients who completed a carvedilol placebo-controlled phase II trial. Patients were given open-label carvedilol and were titrated to the maximum dose. Patients were assessed by serial multigated acquisition, echocardiography, and symptom scores. Survival was assessed for all patients and censored as of January 1, 2004. Survival for ischemic vs nonischemic patients was compared using the log-rank test and further compared using Cox regression, controlling for covariates. Etiology of heart failure was ischemic in 15 patients and nonischemic in 42 patients. Median follow-up was 12.9 years. Resting left ventricular ejection fraction (LVEF) and heart failure symptom scores improved at 4 months of treatment and were sustained at 24 months. Left ventricular internal diameter in systole (LVIDS) and left ventricular internal diameter in diastole decreased significantly at 4 and 8 months, respectively, and LVIDS continued to improve at 24 months. Overall mortality was 43% in nonischemic patients and 73% in ischemic patients. In a multivariate analysis, ischemic etiology and baseline LVEF were significant predictors of mortality. Carvedilol produces sustained improvements in left ventricular remodeling and symptoms. Long-term survival is good, particularly in nonischemic patients.* Congest Heart Fail. *2009;15:5–8.* 

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Phase II trials of β-blockers, typically lasting 3 to 6 months, demonstrated that β-blocker treatment in patients with heart failure (HF) results in improvements in right heart hemodynamics, reversal of ventricular remodeling (as evidenced by reductions in left ventricular [LV] volumes, increases in right and LV ejection fraction (LVEF), decrease in LV mass, and favorable effects on LV geometry), and improvements in HF symptoms.[1] Prospective, randomized, placebo-controlled outcomes trials of carvedilol, bisoprolol, and metoprolol succinate in HF patients have shown significant reductions in mortality and hospitalizations, as well as an improvement in patient well-being.[2–5] Premature termination of these trials because of the superior efficacy of these agents compared with placebo limited the duration of post-trial follow-up to <18 months (US Carvedilol Heart Failure Study,[2] 6 months [12 months in the mild HF group]; the Cardiac Insufficiency Bisoprolol Study II [CIBIS II],[3] 1.3 years; the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure [MERIT-HF],[4] 12 months; and the Carvedilol Prospective Randomized Cumulative Survival [COPERNICUS] study,[5] 10.4 months). After completing a prospective, randomized, placebo-controlled phase II trial of the hemodynamic effects of carvedilol,[6] we had the unique opportunity to follow these patients long-term. This manuscript presents the long-term outcomes of the individuals who completed this study and were given open-label carvedilol.

## Methods

**Study Objectives.** The objective of this study was to assess the long-term safety, tolerability, and outcomes associated with long-term use of carvedilol in patients with HF due to LV systolic dysfunction.

**Patient Eligibility.** Patients participating and completing the 4-month placebo-controlled phase II carvedilol study[6] were eligible for study entry. Patient characteristics included mean age 53±2 years (range, 18–80 years), New York Heart Association (NYHA) functional class II through IV, and LVEF ≤0.35. In the phase II trial, patients were excluded if they had valvular heart disease, active myocarditis, unstable angina, sustained (>15 seconds) ventricular tachycardia, symptomatic nonsustained ventricular tachycardia not adequately controlled by antiarrhythmic drugs, or second- or third-degree atrioventricular block unless equipped with a permanent pacemaker. Patients were also excluded if they had comorbidities such as symptomatic peripheral vascular disease; chronic obstructive lung disease; bronchial asthma; insulin-dependent diabetes

**Table I.** Baseline Patient Characteristics

| | |
|---|---|
| Age, y | 53±2 |
| Sex | |
| Male | 53 |
| Female | 4 |
| Diagnosis | |
| Nonischemic | 43 |
| Ischemic | 14 |
| NYHA functional status | |
| Class II | 33 |
| Class III | 23 |
| Class IV | 1 |
| Symptom score | 4.5±0.5 |
| Concomitant medication, No. (%) | |
| Diuretics | 45 (79) |
| Digoxin | 47 (82) |
| ACE inhibitors | 53 (93) |
| Vasodilators | 6 (10) |
| Antiarrhythmic agents | 11 (19) |
| Warfarin | 43 (75) |
| Right heart hemodynamics | |
| Heart rate, beats per min | 86±2 |
| Mean systemic artery pressure, mm Hg | 84±1 |
| Right atrial pressure, mm Hg | 5±1 |
| Mean pulmonary artery pressure, mm Hg | 27±2 |
| Pulmonary wedge pressure, mm Hg | 16±1 |
| Cardiac index, L/min/$m^2$ | 2.2±0.1 |

Values are expressed as mean ± SEM unless otherwise indicated. Abbreviations: ACE, angiotensin-converting enzyme; NYHA, New York Heart Association.

mellitus; alcohol or drug dependency; or chronic renal, hepatic, hematological, neurological, or collagen vascular disease.

**Study Measurements.** Patients were recruited to participate in this study immediately upon completion of the phase II trials. Patients underwent radionuclide ventriculography at rest and during maximal supine bicycle exercise to determine LVEF. Echocardiography was performed to determine LV diastolic and systolic dimensions using standard M-mode measurements. HF symptoms were assessed using a questionnaire modified from that of Lee and colleagues[7] with composite symptom scores that ranged from 0 with no symptoms to 13 with the most severe HF symptoms. Baseline NYHA functional status was assessed by a single investigator (EMG).

**Long-Term Drug Administration.** At the onset of this study, the patients' drug assignments were unblinded. Patients receiving carvedilol were continued in an open-label fashion at their highest tolerated carvedilol dose as demonstrated during the phase II trial. Patients randomized to placebo were initiated on carvedilol (6.25 mg orally twice daily) and up-titrated in weekly intervals until a maximal tolerated dose or maximum dose (25 mg twice a day for patients weighing <75 kg and 50 mg twice a day for those weighing >75 kg) was achieved. At each weekly visit, patients were evaluated for symptoms and signs of worsening HF, hypoperfusion, or other adverse effects possibly related to β-blocker therapy.

**Outcomes Assessment.** Measures of LV internal diameter in diastole, LV internal diameter in systole, and LV fractional shortening by echocardiography, rest and peak exercise radionuclide ventriculogram, and Lee symptom scores were evaluated at 4, 8, 12, and 24 months after initiation of carvedilol in all patients. In the event of missing data, the last available value was carried forward. Survival was assessed by reviewing paper clinic charts and electronic medical records and by telephone interview with patients whenever possible. When patients could not successfully be contacted, further verification of vital status was achieved via the Social Security Death Index. Survival was censored as of January 1, 2004.

**Statistical Analysis.** Continuous variables at baseline and at 4, 8, 12, and 24 months were compared by repeat measures analysis of variance. Survival for ischemic vs nonischemic patients was compared using the log-rank test. Univariable and multivariable Cox regression models were fitted to our list of risk factors. Baseline variables assessed in these Cox models included HF etiology, sex, age, LVEF, NYHA class, norepinephrine level, mean arterial pressure, pulmonary capillary wedge pressure, and oxygen consumption; 4-month LVEF and change in LVEF were also assessed in the model. Results are expressed as mean ± SEM. Differences were considered significant at $P<.05$.

## Results

**Patient Baseline Characteristics.** A total of 57 patients were enrolled in the study, with characteristics shown in Table I. Patients were middle-aged, predominantly male, and most had idiopathic dilated cardiomyopathy. Most patients were classified as having either NYHA functional class II (58%) or class III (40%). The increase in symptom score and reduction of peak maximal oxygen consumption were consistent with this degree of functional impairment. The majority of patients were receiving diuretics and digoxin. All patients were taking angiotensin-converting enzyme (ACE) inhibitors unless they had proven to be intolerant prior to this study. Diuretics, digoxin, and ACE inhibitors were continued throughout the study and were not initiated during the study or follow-up. Baseline right heart hemodynamics were characterized by mild elevation of filling pressures and mild reduction in cardiac output. LVEF was severely reduced and LV diameter was markedly increased.

**Patient Outcomes.** Patients were enrolled from March 9, 1990, to November 12, 1992, and the final data

were censored as of January 1, 2004. The median follow-up was 12.8 years (range, 11.1–13.8 years). The mean carvedilol dose achieved in the course of the study was 85±3 mg/d. At 2 years, 50 patients were alive without transplant, 2 patients had undergone transplant, and 5 patients had died. At the time of last follow-up, 22 patients were alive without transplant, 6 patients had undergone transplant, and 29 patients had died.

**Two-Year Follow-Up of Noninvasive Parameters.** Values for baseline and 4-, 8-, 12-, and 24-month radionuclide ventriculography, echocardiography, and symptom questionnaire are given in Table II. Resting and exercise LVEF increased significantly throughout the first 2 years of carvedilol treatment. Resting ejection fraction did not differ significantly throughout the months of actual treatment. Compared with the 4-month value, exercise ejection fraction at 8, 12, and 24 months was modestly higher. There was a progressive decrease in LV end-diastolic diameter throughout the first 24 months of treatment at 8, 12, and 24 months compared with baseline. By 24 months, end-diastolic diameter was significantly smaller than it had been at 4 months. Symptom scores were significantly reduced at all time points during the first 24 months of treatment. There was a trend for a slight increase in symptom score as time progressed, but these differences were not statistically significant.

**Survival of Patients on Long-Term Carvedilol Therapy.** Stratifying patients based on etiology, Kaplan–Meier curves for death are given in the Figure for both ischemic cardiomyopathy and idiopathic dilated cardiomyopathy patients. After a median follow-up of 12.9 years, overall mortality between the time of carvedilol initiation and January 1, 2004, was 43% in nonischemic and 73% in ischemic patients. Risk factors for death that were significant in univariable models were ischemic etiology, age older than 60 years at enrollment, LVEF at baseline, LVEF 4 months after initiation of carvedilol, LVEF change vs baseline (4 months after initiation of carvedilol), LVEF change in the highest tertile of study patients, and NYHA functional class III at baseline. Results of multivariable Cox regression models for the death outcome in our study population are given in Table III. Note that LVEF and NYHA class are correlated and placing them in the model simultaneously creates a collinear relationship, but they both appear nonsignificant (model 1). Model 2 shows the hazard ratio for death predicted by LVEF in the absence of NYHA functional class. Model 3 shows the hazard ratio for death predicted by NYHA functional class in the absence of LVEF. In all models, the presence of ischemic cardiomyopathy was the strongest predictor of death.

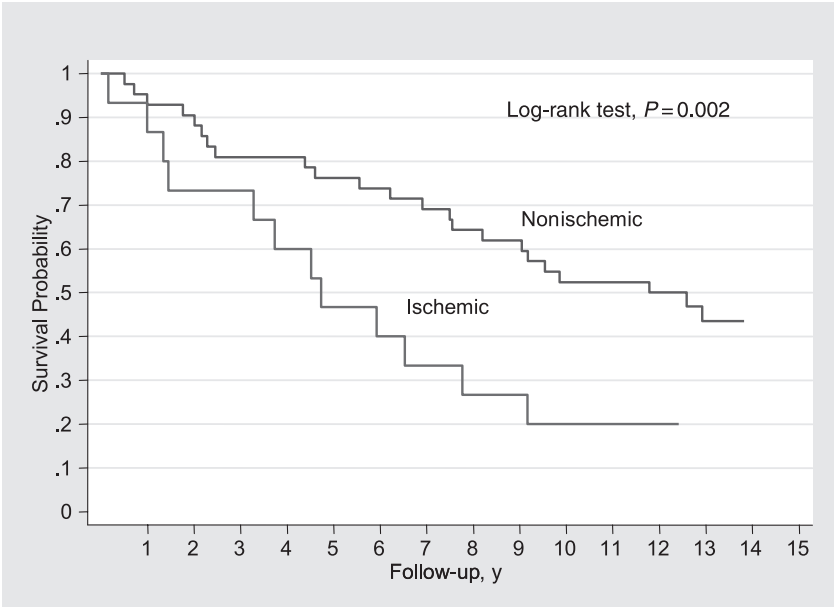


**Figure. Kaplan–Meier curves for the death end point in ischemic and nonischemic patients.**

**Table II.** Noninvasive Measures and Symptom Scores During 24 Months of Therapy

| | Baseline | 4 Months | 8 Months | 12 Months | 24 Months | *P* Value |
|---|---|---|---|---|---|---|
| Rest LVEF, % | 20±1 | 30±2[a] | 31±2[a] | 31±2[a] | 31±2[a] | <.001 |
| Exercise LVEF, % | 21±1 | 28±2[a] | 30±2[a,b] | 31±2[a,b] | 32±2[a,b] | <.001 |
| LVIDD, mm | 74±2 | 71±1 | 68±2[a] | 68±2[a] | 68±2[a,b] | <.001 |
| LVIDS, mm | 62±2 | 58±2[a] | 54±2[a,b] | 54±2[a,b] | 54±2[a,b] | <.001 |
| LVFS, % | 17±1 | 20±1[a] | 22±1[a] | 21±1[a] | 21±1[a] | <.001 |
| Symptom score | 4.4±0.5 | 2.7±0.3[a] | 3.0±0.6[a] | 3.2±0.4[a] | 3.3±0.3[a] | <.001 |

Values are expressed as mean ± SEM. Abbreviations: LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; LVIDD, left ventricular internal diameter in diastole; LVIDS, left ventricular internal diameter in systole. [a]*P*<.05 vs baseline. [b]*P*<.05 vs 4 months.

## Discussion

At 2 years from initiation of carvedilol in an HF population, improvements in remodeling and symptoms were maintained. There is a difference in the time course for improvement in resting LVEF and LV dimensions. Near-maximal improvements in ejection fraction were observed at 4 months. In contrast, reductions in LV diastolic diameter continued to occur throughout 2 years of carvedilol treatment. This suggests that different biologic mechanisms may be impacting these measures of the remodeling process. During the total

**Table III.** Multivariable Cox Regression Models for Death Outcome (N=57)

| Baseline Predictor Variables[a] | Hazard Ratio | 95% CI | *P* Value |
|---|---|---|---|
| Model 1 | | | |
| Ischemic, present/absent | 2.81 | 1.26–6.29 | .011 |
| LVEF baseline, per 1 additional unit | 0.95 | 0.90–1.01 | .080 |
| NYHA, class III/II | 2.05 | 0.93–4.51 | .075 |
| Model 2 | | | |
| Ischemic, present/absent | 2.99 | 1.34–6.66 | .007 |
| LVEF baseline, per 1 additional unit | 0.94 | 0.89–0.99 | .027 |
| Model 3 | | | |
| Ischemic, present/absent | 3.03 | 1.39–6.65 | .006 |
| NYHA, class III/II | 2.54 | 1.18–5.43 | .017 |

Abbreviations: CI, confidence interval; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association. [a]Follow-up was years from initiation of carvedilol therapy to death outcome or censored.

duration of follow-up, there does not appear to be a significant increase in the year-specific risk of death. This suggests maintenance of the beneficial effects of carvedilol. Multivariate analysis indicated that etiology, functional class, and LVEF were predictors of survival.

This is a prospective, nonrandomized follow-up of long-term treatment with carvedilol in an HF population. A growing body of evidence supports the use of β-blockers in chronic HF, regardless of etiology or severity of symptoms. β-Blockers have proven both safe and well tolerated in HF patients in a number of phase III clinical trials. Recently, the Carvedilol or Metoprolol European Trial (COMET),[8] a double-blind, randomized, controlled trial assessing carvedilol and metoprolol tartrate in a head-to-head study of chronic HF patients, reported outcomes after a mean follow-up of 57.9 months, or 4.8 years. This was by far the longest follow-up of any outcomes trial of β-blocker use in chronic HF to date. In COMET, patients treated with metoprolol tartrate experienced an annual mortality of 10.0%. This finding was consistent with previous publications reporting approximately a 10% to 20% annual mortality rate and a 50% 5-year mortality rate for patients with chronic HF.[2–5,9] Carvedilol-treated patients in COMET experienced an improvement in outcomes, with a reduction in annual mortality to 8.3%.

We report outcomes of treatment with carvedilol in a chronic HF population over a median of 12.9 years from the date of carvedilol initiation. Our findings are suggestive that long-term β-adrenergic blockade with carvedilol in dilated cardiomyopathy leads to sustained improvements in LV remodeling and HF symptoms. Our 2-year follow-up of these variables represents one of the longest follow-ups of the effects of β-blockade on LV remodeling. Our prospective follow-up of patient survival is the longest duration of follow-up for a group of dilated cardiomyopathy patients treated with both ACE inhibitors and β-blockers.

## Limitations

There are several limitations of this study worth noting. First, there were a relatively small number of patients. In addition, there is no control group for comparison of long-term outcomes. However, current practice guidelines in chronic HF would preclude withholding β-blocker therapy in similar patients. Finally, our study group underrepresented women, the elderly, and patients with multiple comorbidities that are frequently seen in the general HF population. Such individuals might have a higher risk of death during a similar period of follow-up.

## Conclusions

Carvedilol produces sustained benefits on LV remodeling and HF symptoms. Chronic HF patients treated with carvedilol have a good long-term outcome, specifically patients with a nonischemic etiology of their cardiomyopathy.

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