Prospective, Randomized Comparison of Effect of Long-Term Treatment With Metoprolol or Carvedilol on Symptoms, Exercise, Ejection Fraction, and Oxidative Stress in Heart Failure

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Background—With β-blocker use becoming more prevalent in treating chronic heart failure (CHF), the choice of drugs raises important theoretical and practical questions. Although the second-generation compound metoprolol is β1-selective, the third-generation compound carvedilol is β-nonselective, with ancillary pharmacological properties including α-blockade and antioxidant effects. A prospective comparison of these 2 agents can address the issue of optimal adrenergic blockade in selecting agents for therapy in CHF.

Methods and Results—Sixty-seven patients with symptomatic stable heart failure were randomly assigned to receive either carvedilol or metoprolol in addition to standard therapy for CHF. Measured variables included symptoms, exercise, ejection fraction, and thiobarbituric acid–reactive substances (TBARS) as an indirect marker of free radical activity. Metoprolol and carvedilol were well tolerated, and both patient groups showed beneficial effects of β-blocker therapy in each of the measured parameters, with no between-group differences. Ejection fraction increased over 6 months from 18±6.3% to 23±8.7% (P<0.005) with metoprolol and from 19±8.5% to 25±9.9% (P<0.0005) with carvedilol (P=NS between groups). With metoprolol, TBARS values decreased from 4.7±0.9 nmol/mL at baseline to 4.2±1.5 nmol/mL at month 4 to 3.9±1.0 nmol/mL at month 6 (P<0.0001). With carvedilol, there was a parallel decline from 4.7±1.4 to 4.2±1.3 to 4.1±1.2 nmol/mL over the same time frame (P<0.025), with no between-group difference in these changes.

Conclusions—Carvedilol and metoprolol showed parallel beneficial effects in the measured parameters over 6 months, with no relevant between-group differences in this heart failure population. (Circulation. 1999;99:2645-2651.)

Key Words: heart failure ▪ receptors, adrenergic, beta ▪ antioxidants

Numerous placebo-controlled clinical trials have demonstrated multiple benefits of β-blocker therapy in patients with chronic congestive heart failure who remain symptomatic despite the use of optimal triple therapy (digoxin, diuretics, and ACE inhibitors [ACEI]).1–9 One of the earliest and most frequently studied β-blockers in a heart failure population is metoprolol, a second-generation β1-selective agent without specific vasodilating properties. Carvedilol is a third-generation β-blocker that combines nonselective β-blockade, α-blockade, and antioxidant effects.10,11 It is the only β-blocker approved by the US Food and Drug Administration (FDA) with a heart failure indication, and it has been studied extensively in placebo-controlled trials for this disorder. The unique pharmacological profile of carvedilol may offer a particular advantage in its initial and continued use compared with other β-blockers in heart failure. However, it has not been shown that α-blockade is beneficial during up titration or continued use or that the in vitro antioxidant effects distinguish carvedilol from other β-blockers during long-term therapy.

To date, there has been no direct prospective comparison of metoprolol and carvedilol in clinical heart failure trials. Thus, the objective of the present study was to compare metoprolol and carvedilol prospectively in a randomized, positive-controlled study of patients having moderate to severe heart failure symptoms despite triple therapy. Given the laboratory evidence of a selective antioxidant effect of carvedilol, the primary end point was an assessment for differences in measures of oxidative stress between carvedilol- and metoprolol-treated patients over 6 months of therapy. Clinical, hemodynamic (ejection fraction), and exercise indexes were also compared.

Methods

Patients were included with chronic heart failure secondary to ischemic heart disease, valvular myopathy, or idiopathic cardiomyopathy. Patients were symptomatic (NYHA class II, III, or IV) and
had documented systolic dysfunction, with a radionuclide gated blood pool scan ejection fraction ≤35%. Patients entered the trial taking stable outpatient doses of digoxin and ACEIs or angiotensin II receptor antagonists for ≥6 weeks and a stable dose of diuretics for ≥2 weeks. Exclusion criteria included obstructive valvular disease, acute myocardial infarction within 6 weeks, or active angina. The protocol was approved by the Medical Center Institutional Review Board, and all patients signed informed consent before entering the trial.

Baseline vital signs were obtained with patients in the sitting and standing positions. All patients completed 2 quality-of-life (QOL) questionnaires administered 2 weeks apart during baseline examination, with the values from the second test used. Heart failure symptom score (scale, 0 to 21) and the Minnesota Living With Heart Failure questionnaire (scale, 0 to 105) were used.12

Each patient performed a minimum of three 6-minute corridor walk tests13 once a week over a 3-week period, with the last value used as the baseline value if it was within 10% of the previous study. Similarly, patients performed 2 maximal exercise bicycle tests with gas exchange,14 with the last value considered to be baseline if it was within 10% of the previous test.

Ejection fraction by gated blood pool scan was performed at baseline and was calculated and interpreted by a single blinded observer. Plasma norepinephrine specimens were collected from an indwelling venous line after patients had been in the supine position in a quiet room for 30 minutes.

Thiobarbituric acid–reactive substances (TBARS)15,16 in patient plasma were considered the measure of oxidative stress.17–19 Plasma for TBARS was collected twice at baseline before any exercise tests on that day in sodium heparin tubes and placed on ice (week 0). Both baseline values were averaged. The plasma was then cold centrifuged at 1000g for 20 minutes. Aliquots (1.5 mL) were placed in Eppendorf tubes and frozen at −70°C. Assays were run in batches within 2 months of collection by a technician who was blinded to both treatment assignment and collection date.

TBARS were measured by a modification of a colorimetric assay described by Satoh.20 Briefly, an aliquot of plasma was mixed with 20% trichloroacetic acid and 0.67% thiobarbituric acid (in a 2 mol/L sodium sulfate solution). After they were agitated in a vortex mixer, the samples were placed in a boiling water bath for 30 minutes and allowed to cool, and butanol was added. The samples were mixed vigorously over a 45 minute period to facilitate extraction of the colored pigments by butanol. Before absorbance of the butanol phase was measured, the sample was centrifuged at 1000g for 10 minutes to ensure purity. Absorbance was measured at 530 nm in comparison to a water blank by use of a Perkin-Elmer Lambda 2S spectrophotometer. A malondialdehyde (Sigma Chemical Co; model T-1642) standard curve was shown to be linear up to 20 nmol/mL for this assay. Malondialdehyde standards of 5 and 10 nmol were included with every assay batch, and plasma values of TBARS were expressed in reference to these standards.

Patients were randomly assigned to receive open-label metoprolol tartrate (Lopressor) or carvedilol (Coreg), initially taking a total daily dose of 6.25 mg of β-blocker for 1 week: either metoprolol mg 6.25 daily or carvedilol 3.125 mg twice daily. The dose was doubled the following week to metoprolol 6.25 mg BID or carvedilol mg 6.25 BID and then uptitrated weekly with a doubling of the twice-daily dose to a target of 25 mg BID. Concomitant adjustment of diuretics and ACEI as clinically indicated was allowed, with resumption of the previous dose when the patient was stabilized. Metoprolol was recompounded by the hospital research pharmacist for doses up to 25 mg BID. When patients reached a dose of 25 mg BID, they were given prescriptions for metoprolol. Carvedilol was supplied by the manufacturer (SmithKline Beecham). For those patients who weighed >85 kg, the β-blocker target was 50 mg BID.

After 4 and 6 months of continuous oral therapy at maintenance dose, all clinical, exercise, QOL, and biochemical assessments, including TBARS, were repeated. Patients were seen before the scheduled morning dose of β-blocker on evaluation day. The gated blood pool scan and neurohormonal measurements were repeated only at month 6.

### Results

The study population consisted of 67 patients with chronic left heart failure. They ranged in age from 29 to 87 years, with a mean of 57 years. There were 46 men and 21 women. Thirteen patients were NYHA functional class II, 48 were class III, and 6 were class IV. All patients were taking digoxin and diuretics, with 96% taking ACEI or angiotensin II antagonist. Left ventricular ejection fraction ranged from 5% to 35%, with a mean of 19%. The origin of heart failure was idiopathic in 34 patients, ischemic in 28, and valvular cardiomyopathy in 5.

Thirty patients were randomized to metoprolol and 37 to carvedilol. The groups were evenly matched at baseline, as shown in the Table, with no statistical difference between

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Metoprolol (n=30)</th>
<th>Carvedilol (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>2</td>
<td>3</td>
</tr>
<tr>
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<td>16</td>
</tr>
<tr>
<td>Ischemic</td>
<td>10</td>
<td>18</td>
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<td>NYHA II/III/IV</td>
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<td>Systolic BP, mm Hg</td>
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<td>108±16</td>
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<td>Norepinephrine, pg/mL</td>
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<td>Ejection fraction, %</td>
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<tr>
<td>Symptom score</td>
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<tr>
<td>Mln LwHFQ</td>
<td>52±19.4</td>
<td>52±24.2</td>
</tr>
<tr>
<td>6-Min walk, feet</td>
<td>1228±283</td>
<td>1133±371</td>
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<tr>
<td>Peak VO2, mL · kg⁻¹ · min⁻¹</td>
<td>106±3.6</td>
<td>11.0±4.1</td>
</tr>
<tr>
<td>TBARS, nmol/mL</td>
<td>4.7±0.9</td>
<td>4.7±1.3</td>
</tr>
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</table>

Mln LwHFQ indicates Minnesota Living with Heart Failure Questionnaire. Values are mean±SD. There is no statistical difference in any parameter between groups.

### Statistical Analysis

This study was designed so that a sample size of 50 patients completing the study (25 in each group) would have 80% power to detect a difference in TBARS of 0.93 nmol/mL or a difference of 5.8% in ejection fraction by a 2-tailed t test at a level of significance of P<=0.05.

Group values are presented as mean±SD. Within-group analyses were performed with paired 2-tailed t tests comparing baseline and 6-month values for patients who completed the study. A repeated-measures ANOVA was used to compare the changes in the 2 treatment groups with respect to baseline, month 4, and month 6 data. NYHA functional class at months 4 and 6 was also analyzed by repeated measurements for dichotomous data (specifically, generalized estimating equations as described by Liang and Zeger21). The analysis was performed with PROC GENMOD (SAS).

Data were also analyzed with an intention-to-treat model with a carry-forward analysis of the last obtained value for those patients who did not complete the study. Because there were comparable numbers of dropouts in both groups, this analysis demonstrated identical results.
groups. TBARS were measured twice at baseline, 2 weeks apart, to assess for test variability. The correlation was good ($r=0.57$, $P<0.0001$).

A total of 81% of patients in the carvedilol arm achieved target dose, whereas 83% of patients in the metoprolol arm achieved target dose. During uptitration, there was no difference between drug groups requiring an increase in diuretic dose (21 [57%] of 37 in the carvedilol group versus 19 [63%] of 30 in the metoprolol group; $P=NS$). Only 1 patient (taking metoprolol) required a temporary decrease in his diuretic dose.

Fourteen patients failed to complete the 6-month study, with 7 withdrawals in each group. In the metoprolol withdrawal group, there was 1 death, 1 patient underwent cardiac transplant, and 5 patients developed worsening heart failure symptoms. In the carvedilol withdrawal group, there were 2 deaths, 1 patient developed heart block, 3 patients developed worsening heart failure symptoms, and 1 patient developed refractory ventricular tachycardia causing incessant firing of his automated implantable cardioverter-defibrillator. The patient was withdrawn from carvedilol and hospitalized for inotropic therapy and eventually underwent successful cardiac transplant.

Overall, the 53 patients who completed the protocol demonstrated significant improvements in all clinical and exercise parameters. Systolic blood pressure did not change with β-blocker therapy. As expected, heart rate declined significantly with both β-blockers ($P<0.0001$). The decline with carvedilol of 19 bpm (86±14.5 to 67±8.9 bpm) was significantly greater than the 12-bpm decline (84±10.3 to 72±10.0 bpm) seen with metoprolol ($P<0.025$ by ANOVA).

There was an overall mild improvement in NYHA class for those patients who completed the study ($P<0.001$). With metoprolol, the number of patients in NYHA class I/II/III/IV was 0/5/17/71 at baseline, 0/8/15/0 at month 4, and 1/11/11/0 at month 6. With carvedilol, the number of patients in NYHA class I/II/III/IV was 0/5/22/3 at baseline, 0/9/21/0 at month 4, and 0/9/21/0 at month 6. The difference between interventions based on the repeat-measurements analysis for dichotomous data was not significant.

With both metoprolol and carvedilol, heart failure symptom score improved (for metoprolol, from 10±4.7 at baseline to 7.8±4.8 at month 4 to 7.0±4.4 at month 6 [$P<0.001$]; for carvedilol, from 9.9±4.5 to 8.3±4.9 to 7.3±3.8 for the same time points [$P<0.001$]). There was no between-group difference in changes. Using the Minnesota Living With Heart Failure questionnaire, the metoprolol group demonstrated a significant decline (from 51±20.0 to 41±25.3 to 36±24.4 points; $P<0.025$), with a similar decline of 15 points in the carvedilol group (from 52±23.7 to 41±19.9 to 37±21.9 points; $P<0.01$) over the 6 months, with no between-group differences (Figure 1).

With regard to exercise parameters, both groups showed a trend toward improvement in the 6-minute walk, with neither group achieving statistical significance (metoprolol: 1220±284, 1341±346, and 1301±320 feet; carvedilol: 1147±387, 1172±372, and 1210±387 feet at baseline, month 4, and month 6, respectively). Maximal exercise capacity as measured by oxygen consumption showed a slight but significant improvement of 1 mL · kg$^{-1}$ · min$^{-1}$ in both groups, with no between-group difference (metoprolol: 10.8±4.0, 11.9±4.2, and 12.4±4.2 mL · kg$^{-1}$ · min$^{-1}$ [$P<0.0025$]; carvedilol: 11.1±4.5, 12.1±4.2, and 12.3±4.4 mL · kg$^{-1}$ · min$^{-1}$ [$P<0.025$] at baseline, month 4, and month 6, respectively) (Figure 1).

Over the 6 months of the study, there was no significant change either within or between the treatment groups in measurements of norepinephrine. With metoprolol, plasma norepinephrine was 500±304 pg/mL at baseline and 486±324 pg/mL at month 6; in the carvedilol group, norepinephrine was 651±338 pg/mL at baseline and 532±312 pg/mL at month 6.

Ejection fraction as measured by nuclear gated blood pool scans improved significantly by ~5% in both groups over the 6 months of therapy, with no between-group difference. Metoprolol-treated patients improved from 18±6.3% to 23±8.7% ($P<0.005$), and carvedilol-treated patients improved from 19±8.5% to 25±9.9% ($P<0.0005$) (Figure 2).

Measurement of antioxidant activity showed a response similar to the clinical parameters. With metoprolol, TBARS decreased from 4.7±0.9 nmol/mL at baseline to 4.2±1.5 nmol/mL at month 4 and 3.9±1.0 nmol/mL at month 6 ($P<0.0001$). With carvedilol, there was a parallel decline from 4.7±1.4 nmol/mL to 4.2±1.3 nmol/mL to 4.1±1.2 nmol/mL over the same time frame ($P<0.025$). Importantly, there was no between-group difference in these changes (Figure 3).

**Discussion**

Both metoprolol and carvedilol have been shown previously to have significant beneficial effects in clinical trials that used a variety of end points. Although both are β-blockers, metoprolol and carvedilol do differ pharmacologically. Metoprolol is a β1-selective agent, whereas carvedilol combines nonselective β-blockade with α-blockade and antioxidant effects. The 2 drugs have not as yet been tested prospectively and directly against each other in a heart failure population. The purpose of the present study was to determine whether the unique pharmacological profile of carvedilol may offer a particular advantage in its initial and continued use compared with metoprolol.

The results showed that patients in both groups tolerated initiation and uptitration of β-blockade well, although the total number of patients in the present study may be too small to definitively assess tolerability. There were similar numbers of adverse events with metoprolol and carvedilol that required withdrawal from the study. There was no demonstrated advantage with carvedilol in terms of ease of initiation, despite the vasodilating (α-blockade) effects of the drug.

During initiation of carvedilol, there are theoretical benefits of the vasodilating effect due to α-blockade that could improve tolerability of this drug. However, in the present study, there was no difference between the carvedilol and metoprolol groups in terms of achieving target dose, withdrawals, or the need for concomitant change in diuretics during uptitration. In terms of long-term benefits of α-blockade, previous studies in chronic congestive heart failure with the α-blocker prazosin alone showed hemody-
namic tolerance by day 3 of therapy. The Veterans Administration Heart Failure Trial I (VHeFT-I) showed no mortality difference between placebo and prazosin.

We previously studied whether α-blocking effects might persist in the presence of β-blockade during long-term use. In that study, we compared chronic metoprolol therapy with combination therapy with metoprolol and the α-blocker doxazosin. After 3 months of therapy, there was no hemodynamic difference between β-blockade and combined αβ-blockade, which implied tolerance to α-blockade despite the presence of β-blockade. Furthermore, hemodynamic studies with carvedilol show diminution of its vasodilating effects during long-term use. Thus, the long-term benefit of α-blockade in heart failure has yet to be demonstrated.

Carvedilol and metoprolol therapy resulted in significant parallel clinical and exercise benefits over 6 months in this heart failure population. The only difference between the 2 drug groups was the greater decrease in heart rate with carvedilol. Although previous trials with metoprolol have used higher daily doses than were used in the present study, we chose to compare equal doses of carvedilol and metoprolol. The greater decline in heart rate seen with carvedilol compared with metoprolol probably reflects the greater degree of adrenergic blockade achieved with the relatively

Figure 1. Comparison of response for patients who completed the protocol (metoprolol, n=23; carvedilol, n=30) at baseline, month 4, and month 6 of respective β-blocker therapy. A, Symptom score; B, Minnesota Living With Heart Failure Questionnaire (Minn LwHFQ) score; C, 6-minute walk results; and D, maximal oxygen consumption. Values are mean±SEM; P values inside boxes are within group by paired t tests between baseline and month 6; P values above boxes are between groups by ANOVA for all time points.
higher equivalency dose of carvedilol compared with metoprolol. Despite this difference in heart rate, there were no differences in any clinical parameters. This heart rate effect may also reflect a specific effect of carvedilol on reducing coronary sinus norepinephrine.25

This study is the first prospective comparison of metoprolol and carvedilol measuring the end points of symptoms, exercise duration, and ejection fraction. The study by Gilbert et al25 was not a direct comparison of metoprolol and carvedilol. Rather, it was a combination of 2 different studies, each of which was similar in design (but not identical). The comparative analysis included 1 protocol that compared metoprolol and placebo and another protocol that compared carvedilol and placebo. Common end points were then compared. Furthermore, the study by Gilbert et al25 only included patients with idiopathic dilated cardiomyopathy, whereas the present study also included patients with ischemic and valvular cardiomyopathy. There is a remarkable concordance of findings between the Gilbert study and the present study. Both carvedilol and metoprolol increased ejection fractions in a parallel manner, with no between-group differences. There was an average increase of 11% in the Gilbert study25 of idiopathic cardiomyopathy patients and an average increase of 5% in the present study of patients with mixed origins of heart failure. A study by Metra et al26 prospectively compared carvedilol and metoprolol by use of hemodynamic end points. They also showed similar parallel changes with metoprolol and carvedilol. There was only a slightly greater decline in pulmonary capillary wedge pressure with carvedilol than with metoprolol. All other measured parameters were not different between groups.

Despite the distinct pharmacological properties of carvedilol and metoprolol, the question remains whether these differences translate into relevant outcome parameters. One issue is whether β-blocker selectivity or nonselectivity offers an advantage in heart failure patients. Metoprolol has been shown to effect an upregulation of β-receptors during long-term use,27,28 which might explain the physiology of its benefit. However, the β-nonselective drug carvedilol does not cause β-receptor upregulation.25,26 Thus, the primary benefit of β-blockade may be to counteract the toxic effects of circulating catecholamines.

Free radicals have been implicated in the pathogenesis of a variety of diseases. In heart failure, circulating free radicals may contribute to disease progression and possibly mediate the process of apoptosis. By measuring byproducts of lipid peroxidation, several studies27–19 have shown that patients with heart failure have increased oxygen-derived free radical production and/or decreased reducing ability compared with age-matched controls. Despite the laboratory evidence of an antioxidant effect with carvedilol in rat brain homogenates,11 there has been no clinical demonstration of this selective effect in heart failure patients. The present study is the first to measure for a specific (in vivo) antioxidant effect of carvedilol in a heart failure population. Two previous studies30,31 in patients with hypertension or hypertension with diabetes have shown a selective antioxidant effect of carvedilol. However, patients in those studies did not have heart failure or evidence of increased oxidative stress at baseline compared with normal laboratory values.

We have previously shown that there is a progressive increase in TBARS with worsening NYHA functional class.32 Despite the laboratory evidence of a unique antioxidant effect of carvedilol compared with other β-blockers,10,11 our results showed that TBARS (as a measure of lipid peroxidation) declined with treatment in both groups as functional status improved. Thus, as patients improved clinically over time, this measure of oxidative stress declined in parallel for both metoprolol- and carvedilol-treated patients.

The present study was unable to demonstrate any significant difference between carvedilol and metoprolol in clinical or exercise parameters, symptoms, ejection fraction, or antioxidant activity measurements. Although this does not prove that the 2 drugs are clinically equal despite their different pharmacological profiles, there is scant evidence to the contrary. However, from a practical standpoint, it is important to note that at present, carvedilol is the only FDA-approved

**Figure 2.** Ejection fraction at baseline and month 6 for patients who completed the study protocol with metoprolol and carvedilol, respectively. Values are mean±SEM; P value inside box is within group by paired t tests; P value above box is between groups by ANOVA.

**Figure 3.** TBARS values for those who completed the protocol at baseline, month 4, and month 6 for metoprolol and carvedilol, respectively. Values are mean±SEM; P value inside box are within group by paired t tests between baseline and month 6; P value above box is between groups by ANOVA for all time points.
β-blocker with a heart failure indication. It is the only β-blocker available in the low (3.125, 6.25, and 12.5 mg) dosing range necessary for gradual initiation and uptitration of β-blocker therapy in heart failure. The lowest available dose of metoprolol is a scored 50-mg tablet.

Study Limitations
This study was randomized but not blinded to treatment. This could bias the subjective end points, such as NYHA class, and perhaps unknowingly influence the exercise results. However, we demonstrated no differences in these end points. Furthermore, radionuclide analysis and antioxidant analysis were performed in a blinded manner with regard to both treatment group and time. Optimal doses of β-blockers in chronic heart failure have not been established. Equal but not equivalent doses of carvedilol and metoprolol in the present study may have affected the results. This was a positive-controlled study, and hence there was no placebo group. Because the benefits of β-blockade have already been demonstrated in numerous placebo-controlled trials,2–9 the present study was specifically designed to test for relevant differences between these 2 pharmacologically distinct β-blockers.

Conclusions
Recent studies7–9 of various β-blockers compared with placebo have shown a mortality benefit in heart failure. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) showed a 32% mortality reduction with the β1-selective drug bisoprolol.8 The Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF) was prematurely terminated owing to a significant 35% reduction in mortality with metoprolol succinate (β1-selective).9 Whether carvedilol may have unmeasured actions to effect a greater mortality benefit than β1-selective agents awaits further study.7,33 The ongoing COMET trial is directly and prospectively comparing the 2 β-blockers used in the present study in a double-blind study and could provide answers about the relative mortality benefits of carvedilol and metoprolol. That study could also determine whether maximal adrenergic blockade (α1, β1, and β2) with a possible antioxidant effect versus β1-blockade alone confers any advantage in treating heart failure. The present study reconfirms the benefit of β-blockade in heart failure, as well as demonstrating no significant difference between metoprolol and carvedilol therapy in heart failure.

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References
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