Differential Effects of β-Blockers in Patients With Heart Failure

A Prospective, Randomized, Double-Blind Comparison of the Long-Term Effects of Metoprolol Versus Carvedilol

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Background—Both metoprolol and carvedilol produce hemodynamic and clinical benefits in patients with chronic heart failure; carvedilol exerts greater antiadrenergic effects than metoprolol, but it is unknown whether this pharmacological difference results in hemodynamic and clinical differences between the 2 drugs.

Methods and Results—We randomized 150 patients with heart failure (left ventricular ejection fraction ≤0.35) to double-blind treatment with either metoprolol or carvedilol. When compared with metoprolol (124±55 mg/d), patients treated with carvedilol (49±18 mg/d) showed larger increases in left ventricular ejection fraction at rest (+10.9±11.0 versus +7.2±7.7 U, $P=0.038$) and in left ventricular stroke volume and stroke work during exercise (both $P<0.05$) after 13 to 15 months of treatment. In addition, carvedilol produced greater decreases in mean pulmonary artery pressure and pulmonary wedge pressure, both at rest and during exercise, than metoprolol (all $P<0.05$). In contrast, the metoprolol group showed greater increases in maximal exercise capacity than the carvedilol group ($P=0.035$), but the 2 drugs improved symptoms, submaximal exercise tolerance, and quality of life to a similar degree. After a mean of 23±11 months of follow-up, 21 patients in the metoprolol group and 17 patients in the carvedilol group died or underwent urgent transplantation.

Conclusions—The present study demonstrates that during long-term therapy, carvedilol improves cardiac performance to a greater extent than metoprolol when administered to patients with heart failure in the doses shown to be effective in clinical trials. These differences were likely related to a greater antiadrenergic activity of carvedilol. **(*Circulation*. 2000;102:546-551.)**

Key Words: heart failure ■ receptors, adrenergic, beta ■ hemodynamics

Controlled clinical trials have shown that β-blockers produce consistent benefits in patients with chronic heart failure.[1–3] As a result, these agents are now recommended for use in all patients with mild to moderate heart failure caused by left ventricular (LV) systolic dysfunction who do not have contraindications.[4] However, β-blockers differ significantly in their pharmacological properties in ways that may affect their relative efficacy and tolerability. Metoprolol and bisoprolol selectively inhibit β_1-receptors but increase the density of β-receptors and tend to raise cardiac norepinephrine during long-term administration,[5–8] whereas carvedilol blocks α_1-, β_1- and β_2-receptors, decreases cardiac norepinephrine, tends to suppress β-receptor density, and has additional antioxidant and antiproliferative effects.[5–7,9]

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Metoprolol and carvedilol have been directly compared in 3 earlier studies,[10–12] but these trials enrolled only a small number of patients with heart failure, were brief in duration,[11,12] or were not carried out in a double-blind manner.[10,11] To address these deficiencies, we carried out a double-blind comparison of the 2 β-blockers in a relatively large group of patients who were treated for up to 44 months.

Methods

Study Patients

We studied 150 patients with chronic heart failure caused by an ischemic or nonischemic cardiomyopathy. All patients had New York Heart Association class II, III, or IV symptoms for ≥6 months, an LV ejection fraction ≤0.35 by radionuclide ventriculography, and a peak $\dot{V}O_2$ ≤25 mL · kg^{-1} · min^{-1} by cardiopulmonary exercise testing. All patients were receiving treatment with furosemide and an ACE inhibitor (or angiotensin-receptor blocker if the ACE inhibitor was not tolerated) and had constant doses of background medication as an outpatient for 1 week before the study.

Patients were excluded if they had unstable angina, an acute myocardial infarction, or a coronary revascularization procedure

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within 3 months; a history of alcohol abuse, primary valve disease, or congenital heart disease; systolic blood pressure <90 mm Hg; concomitant diseases that might adversely influence prognosis or impair exercise capacity (eg, malignancy, musculoskeletal diseases); contraindications to β-blocker therapy, (eg, asthma, advanced heart block, or bradyarrhythmias); and concomitant treatment with other β-blockers, α-antagonists, calcium antagonists, or antiarrhythmic agents (except amiodarone). The protocol was approved by the local ethics committee and the Italian Ministry of Health. Written informed consent was obtained from all study patients.

Study Protocol

During a 1-week screening period, the following tests were performed to ensure eligibility for the study: (1) radionuclide ventriculography for the assessment of ejection fraction and cardiac volumes[13]; (2) maximal cardiopulmonary bicycle exercise testing with a protocol we used in earlier studies[14,15]; (3) right heart catheterization for measurement of thermodilution cardiac output and intracardiac pressures at rest and during maximal bicycle exercise[14,15]; (4) 6-minute walk test[16]; (5) the Minnesota Living-with-Heart-Failure quality-of-life questionnaire[17]; and (6) NYHA functional classification. The cardiopulmonary exercise tests and the 6-minute walk tests were repeated to ensure stability; this was defined as a ≤1 mL · kg^{-1} · min^{-1} change in peak $\dot{V}O_2$ and a ≤10% change in the 6-minute walk distance between 2 consecutive tests.

Each patient was then randomized (double-blind) in a 1:1 manner to metoprolol tartrate or carvedilol, which were added to the usual treatment for heart failure. Metoprolol and carvedilol were started at 5 mg BID and 3.125 mg BID, respectively, and the doses of these drugs were then increased every 1 to 2 weeks (if tolerated) over an 8-week period to 10 mg BID, 25 mg BID, and 50 mg BID for metoprolol and 6.25 mg BID, 12.5 mg BID, and 25 mg BID for carvedilol. In patients weighing ≥75 kg, the doses could be increased to 100 mg BID of metoprolol and 50 mg BID of carvedilol. These doses were selected on the basis of their prior use in large multicenter trials with the 2 drugs.[1–3,18,19] If side effects developed that were attributed to the study medications, increments in dose were delayed or the dose could be decreased or temporarily discontinued.

Double-blind therapy with the maximal tolerated doses of the study medication was maintained for up to 44 months after randomization, during which time background therapy with digoxin, diuretics, and/or an ACE inhibitor was continued. If the patient's condition deteriorated, the investigator could use any clinically indicated interventions, but physicians were encouraged not to prescribe open-label therapy with metoprolol or carvedilol. The patients were evaluated as an outpatient every 3 months, and all hemodynamic and clinical cardiovascular assessments that were carried out during the baseline period were repeated 13 to 15 months after randomization. Double-blind treatment was continued until the end of the trial (in June 1999) except in patients who were withdrawn for lack of compliance or adverse events.

Statistical Analysis

The primary objective of this study was to compare the effects of metoprolol and carvedilol on LV ejection fraction. The secondary objectives were to compare the effects of metoprolol and carvedilol on hemodynamic variables at rest and peak exercise, maximal and submaximal exercise tolerance, quality of life, NYHA functional class, and the frequency of death and urgent transplantation. Heart transplantation was defined as urgent if it was performed in a patient dependent on the use of intravenous inotropes or mechanical devices.

On the basis of the changes in ejection fraction observed in earlier studies, the present trial was originally designed to enroll 150 patients, which would provide 95% power to detect an absolute difference of 3 U between the metoprolol and carvedilol treatment groups (α=0.05), assuming a dropout rate of 20%. This sample size would also allow the detection of meaningful differences in all secondary end points, except for the frequency of major clinical events.

TABLE 1. Baseline Characteristics

	Metoprolol (n=75)	Carvedilol (n=75)
Age, y	58±11	55±12
Sex, M/F	68/7	68/7
Cause of heart failure, IDC/CAD, n	46/29	47/28
History of hypertension, n	19	20
Diabetes mellitus, n	16	14
NYHA class, II/III/IV, n	23/44/8	23/46/6
LV ejection fraction, %	21±7	20±8
Peak $\dot{V}O_2$, mL · kg^{-1} · min^{-1}	13.4±4.6	14.3±4.4
Cardiac index at rest, L · min^{-1} · m^{-2}	2.50±0.63	2.45±0.67
Pulmonary wedge pressure at rest, mm Hg	24±11	27±12
Concomitant therapy, n		
Furosemide	74	74
Captopril	32	28
Enalapril	43	44
Digoxin	55	52

IDC indicates idiopathic dilated cardiomyopathy; CAD, coronary artery disease.

Results are expressed as mean±SD unless otherwise specified. Baseline data in the 2 treatment groups were compared in all randomized patients by *t* test for continuous variables and by χ^2 test for categorical variables. In patients who underwent a repeat hemodynamic and clinical assessment, changes from baseline were evaluated within each treatment group by a paired *t* test and between the metoprolol and carvedilol groups by 2-way ANOVA. A 2-tailed value of $P<0.05$ was considered significant.

Results

The 150 patients had moderately severe heart failure (mean peak $\dot{V}O_2$ of 13.6±4.2 mL · kg^{-1} · min^{-1}) associated with advanced LV dysfunction (mean LV ejection fraction of 20.6±4.2%) despite treatment with digitalis, diuretics, and an ACE inhibitor in most patients. The 75 patients randomized to metoprolol and the 75 patients randomized to carvedilol were similar with respect to all pretreatment characteristics (Table 1). After completion of the uptitration period, patients received an average dose of 115±56 mg/d of metoprolol and 44±17 mg/d of carvedilol. Target doses were achieved in 73% of patients in the metoprolol group and 71% of patients in the carvedilol group. Patients were continued on double-blind treatment for 23±12 months (25±10 months in surviving patients).

Of the 150 randomized patients, 28 patients (14 in the metoprolol group and 14 in the carvedilol group) did not undergo repeat hemodynamic or clinical assessment at 13 to 15 months of follow-up for the following reasons: 11 because of death or transplantation, 12 because of lack of compliance with the study protocol (3 were given open-label treatment with a β-blocker), and 5 because of an adverse reaction that led to withdrawal of the study medication. The remaining 122 patients underwent repeat hemodynamic and clinical assessments, which were carried out while patients were receiving 124±55 mg/d of metoprolol and 49±18 mg/d of carvedilol.

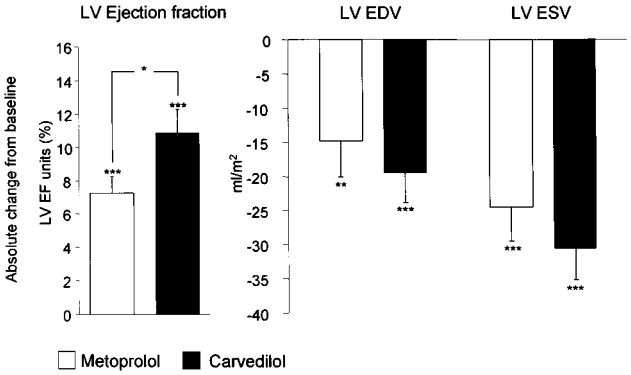

Figure 1. Absolute changes (mean±SEM) from baseline in LV ejection fraction, end-diastolic volume (EDV), and end-systolic volume (ESV) after treatment with metoprolol or carvedilol for 13 to 15 months. Symbols immediately above or below columns designate significance of differences from baseline; symbols between columns designate significance of differences between groups: **P*<0.05; ***P*<0.01; ****P*<0.001.

Primary End Points

After a mean of 13 to 15 months of treatment, the LV ejection fraction increased significantly in both the metoprolol and carvedilol groups, but the change in the carvedilol group was significantly greater than in the metoprolol group (+10.9±11.0% versus +7.2±7.7% units, $P=0.038$, Figure 1 and Table 2). Both groups also showed significant decreases in LV systolic and diastolic volumes, but the differences between the groups were not significant.

Secondary End Points

Both metoprolol and carvedilol increased stroke volume and stroke work indexes and decreased mean pulmonary artery pressure, pulmonary wedge pressure, and heart rate (all $P<0.05$ from baseline). However, the increase in stroke volume and stroke work indexes during exercise and the decreases in mean pulmonary artery pressure and pulmonary wedge pressure at both rest and exercise were greater with carvedilol than with metoprolol (all $P<0.05$ for the differences between the groups, Tables 3 and 4 and Figure 2). In addition, carvedilol (but not metoprolol) increased rest and exercise cardiac index (both $P<0.05$). Heart rate declined with both drugs at rest and exercise, but the decrease in exercise heart rate with carvedilol was greater than with metoprolol ($P<0.05$ for the difference between the groups).

Both metoprolol and carvedilol improved NYHA class, 6-minute walk distance, and quality-of-life scores (all $P<0.05$ from baseline), and there were no differences between the 2 treatments (Table 2 and Figure 3). However, metoprolol (but not carvedilol) increased peak $\dot{V}O_2$ ($P<0.05$ for the comparison between the 2 groups). Both the frequency and complexity of ventricular arrhythmias on Holter monitoring declined nonsignificantly in the 2 treatment groups, with no differences between the groups.

Adverse Reactions

The most common adverse reaction occurring during uptitration of metoprolol therapy was worsening heart failure, which was observed in 13 patients (17.3%). Other side effects of metoprolol included dizziness in 1 patient (1.3%), hypotension in 2 (2.7%), and symptomatic bradycardia in 2 (2.7%). In contrast, the most common adverse reaction during uptitration of carvedilol therapy was dizziness, which was observed in 11 patients (14.7%). Other side effects of carvedilol were worsening heart failure in 6 patients (8.0%), symptomatic bradycardia in 3 (4.0%), hypotension in 2 (2.7%), and Raynaud's phenomenon in 1 (1.3%).

Worsening heart failure was treated only by an increased dose of furosemide in 9 patients (5 taking metoprolol and 4

TABLE 2. Effect on Exercise, Clinical Status, Cardiac Function, and Holter Recordings

	Metoprolol (n=61)		Carvedilol (n=61)		
	Baseline	12 mo	Baseline	12 mo	*P* (ANOVA)
Radionuclide ventriculography					
LV ejection fraction, %	21.6±7.2	28.8±11.3‡	20.4±7.6	31.2±11.9‡	0.038
LV end-diastolic volume, m/m^2	175±52	160±57†	167±67	147±63‡	NS
NYHA class, I/II/III/IV	0/22/36/3	14/32/15/0‡	0/18/40/3	17/32/11/1‡	NS
Minnesota Living with Heart Failure score	39±20	32±22‡	32±19	24±16‡	NS
6-Minute walk test, m	416±121	479±138†	447±136	497±126‡	NS
Cardiopulmonary exercise testing					
Exercise duration, s	593±176	649±199‡	531±174	576±191*	NS
Peak $\dot{V}o_2$, mL · kg^{-1} · min^{-1}	13.7±4.5	15.0±5.1†	14.2±3.9	14.0±4.6	0.035
$\dot{V}o_2$ at anaerobic threshold, mL · kg^{-1} · min^{-1}	9.8±3.8	10.4±3.5	9.7±2.9	9.7±2.9	NS
Holter recordings, h^{-1}					
Ventricular ectopic beats	134±284	57±132	269±543	105±158	NS
Ventricular couplets	0.33±0.94	0.25±0.75	0.41±1.05	0.14±0.35	NS
Nonsustained ventricular tachycardia	0.02±0.04	0.01±0.03	0.09±0.38	0.01±0.05	NS

**P*<0.05, †*P*<0.01, ‡*P*<0.001 for differences between pretreatment and posttreatment values (within each group). *P* (ANOVA) denotes significance of differences in the magnitude of change in the metoprolol group vs magnitude of change in the carvedilol group. Values reflect data in patients with paired measurements.

TABLE 3. Hemodynamic Responses at Rest

	Metoprolol (n=61)		Carvedilol (n=61)		
	Baseline	12 mo	Baseline	12 mo	*P* (ANOVA)
Heart rate, bpm	80±14	64±11*	84±15	65±10*	NS
Mean arterial pressure, mm Hg	91±10	91±10	92±12	91±11	NS
Cardiac index, L · min^{-1} · m^{-2}	2.58±0.63	2.65±0.69	2.36±0.57	2.56±0.65*	NS
Stroke volume index, mL/m^2	33±10	43±14*	29±9	40±12*	NS
Stroke work index, g · mL^{-1} · m^{-2}	31±13	42±17*	26±12	41±16*	NS
Systemic vascular resistance, dyne · s · cm^{-5}	1426±415	1414±446	1553±380	1487±394	NS
Mean right atrial pressure, mm Hg	11±5	9±4	11±6	8±5	NS
Mean pulmonary artery pressure, mm Hg	32±13	26±10*	33±14	24±11*	0.049
Pulmonary wedge pressure, mm Hg	25±11	20±9*	27±12	17±9*	0.002
Pulmonary vascular resistance, dyne · s^{-1} · cm^{-5}	125±99	113±87	120±86	124±82	NS

*$P<0.001$ for differences between pretreatment and posttreatment values (within each group). *P* (ANOVA) denotes significance of differences in magnitude of change in the metoprolol group vs magnitude of change in the carvedilol group. Values reflect data in patients with paired measurements.

taking carvedilol) but required hospitalization and intravenous medications in 10 patients (6 taking metoprolol and 2 taking carvedilol). Dizziness was treated by a reduction in the dose of furosemide in 4 patients taking carvedilol and by a transient reduction in the dose of an ACE inhibitor in 8 patients (1 taking metoprolol and 7 taking carvedilol). Bradycardia was managed by permanent pacemaker implantation in all 5 patients who developed symptoms and was followed by further drug uptitration. Side effects led to permanent discontinuation of the study medication in 5 patients: 3 for worsening heart failure in the metoprolol group and 2 for symptomatic hypotension in the carvedilol group.

Overall, 21 patients in the metoprolol group and 17 patients in the carvedilol group died or underwent urgent transplantation during the 23±11 months of follow-up.

Discussion

The present study demonstrates that carvedilol improves cardiac performance to a greater extent than metoprolol during the long-term treatment of patients with chronic heart failure. When compared with the metoprolol group, the carvedilol group showed larger increases in LV ejection fraction at rest and in LV stroke volume and stroke work during exercise. In addition, carvedilol produced greater decreases in mean pulmonary artery pressure and pulmonary wedge pressure, both at rest and during exercise, than metoprolol. In contrast, therapy with metoprolol was associated with greater increases in maximal exercise capacity than carvedilol, but the 2 drugs improved symptoms, submaximal exercise tolerance, and quality of life to a similar extent.

These observations are consistent with the results of 3 earlier trials that compared the effects of metoprolol and carvedilol in patients with heart failure.[10–12] In all 3 studies, carvedilol produced greater increases in LV ejection fraction and decreases in LV chamber size but less marked increases in maximal exercise capacity than metoprolol, although these differences were significant only in the study that treated patients for >6 months.[10] These earlier trials, however, were not double-blind or were small[10–12] and thus did not have adequate statistical power to detect meaningful differences

TABLE 4. Hemodynamic Responses at Peak Exercise

	Metoprolol (n=61)		Carvedilol (n=61)		
	Baseline	12 mo	Baseline	12 mo	*P* (ANOVA)
Heart rate, bpm	140±18	121±18‡	143±22	116±17‡	0.006
Mean arterial pressure, mm Hg	107±12	103±13	106±16	104±12	NS
Cardiac index, L · min^{-1} · m^{-2}	4.93±1.65	5.15±1.83	4.54±1.65	4.92±2.03*	NS
Stroke volume index, mL/m^2	35±11	42±13‡	32±11	43±18*	0.016
Stroke work index, g · mL^{-1} · m^{-2}	34±15	42±18‡	29±17	46±26‡	0.002
Systemic vascular resistance, dyne · s · cm^{-5}	920±309	860±285*	1005±391	944±370*	NS
Mean right atrial pressure, mm Hg	11±6	10±5	10±7	9±7	NS
Mean pulmonary artery pressure, mm Hg	49±11	43±12‡	49±14	39±14‡	0.009
Pulmonary wedge pressure, mm Hg	39±10	33±10‡	41±13	29±12‡	0.001
Pulmonary vascular resistance, dyne · s · cm^{-5}	94±57	99±76	92±59	105±70	NS

*$P<0.05$, ‡$P<0.001$ for differences between pretreatment and posttreatment values (within each group). *P* (ANOVA) denotes significance of differences in magnitude of change in the metoprolol group vs magnitude of change in the carvedilol group. Values reflect data in patients with paired measurements.

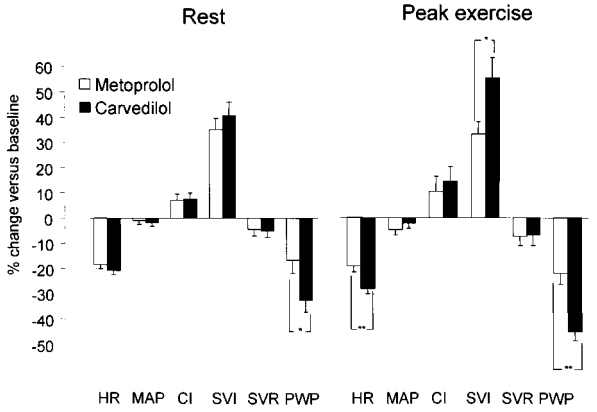

Figure 2. Percent change from baseline (mean±SEM) in hemodynamic variables at rest and during peak exercise after treatment with metoprolol or carvedilol for 13 to 15 months. Symbols designate significance of differences between treatment groups, where *$P<0.05$ and **$P<0.01$. HR denotes heart rate; MAP, mean arterial pressure; CI, cardiac index; SVI, stroke volume index; SVR, systemic vascular resistance; and PWP, pulmonary wedge pressure.

between the 2 treatment groups. In addition, earlier trials generally involved brief exposures to the drugs,[11,12] too short a time to allow time-dependent differences between the 2 treatments to become apparent.[20] In contrast, the present study had sufficient power and duration to detect relevant differences between the treatments.

The differences we observed in the hemodynamic and clinical effects of metoprolol and carvedilol may be explained by the greater antiadrenergic activity of carvedilol.[7] Whereas metoprolol acts selectively on β_1-receptors, carvedilol blocks all 3 adrenergic receptors (α_1, β_1, and β_2) that have been implicated in mediating the deleterious effects of catecholamines on the heart and peripheral blood vessels.[8] Furthermore, carvedilol decreases levels of cardiac norepinephrine and tends to suppress β-receptors,[6,7] whereas metoprolol tends to increase myocardial catecholamines and enhances the sensitivity of the heart to β-receptor stimulation.[5–7] These actions may explain why the chronotropic response to exercise—an accurate measure of the cardiac response to sympathetic stimulation[21,22] —was attenuated more effectively by

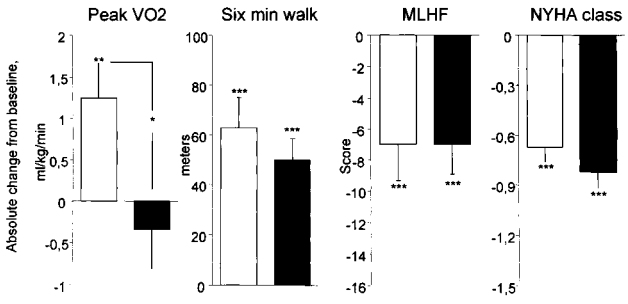

Figure 3. Absolute changes (mean±SEM) from baseline in peak $\dot{V}O_2$, 6-minute walk distance, Minnesota Living with Heart Failure (MLHF) score, and NYHA functional class after treatment with metoprolol or carvedilol for 13 to 15 months. Symbols immediately above or below columns designate significance of differences from baseline; symbols between columns designate significance of differences between groups: *$P<0.05$; **$P<0.01$; ***$P<0.001$.

carvedilol than metoprolol in the present study. Hence, the greater improvement in LV performance in the carvedilol group may have been related to its ability to provide more comprehensive protection against the deleterious actions of the sympathetic nervous system on the heart.[5] Although carvedilol may also exert favorable effects on cardiac function as a result of its peripheral vasodilating actions, the importance of such activity during long-term therapy remains uncertain because metoprolol and carvedilol produced similar changes in systemic vascular resistance in the present study. Tolerance may develop to the vasodilatory actions of α_1-blockers during prolonged treatment in patients with heart failure,[23] even when they are combined with β-blockers.[24]

Differences in antiadrenergic activity may also explain why metoprolol (but not carvedilol) improved maximal exercise capacity. The greater reduction in peak exercise heart rate with carvedilol may have impaired the increase in exercise capacity that would have been expected to accompany an improvement in cardiac performance. However, because the correlation between maximal exercise performance and clinical symptoms is poor,[25] it is not surprising that metoprolol and carvedilol improved symptoms, quality of life, and submaximal exercise tolerance to a similar degree.

Some observers might propose that the hemodynamic advantages of carvedilol were related to the doses of the 2 β-blockers selected for the present study. However, the doses of both drugs were comparable to those that have been shown in multicenter trials to reduce the risk of death and hospitalization in patients with heart failure. The mean dose of carvedilol (44 to 49 mg/d) is similar to that used in the US Carvedilol Multicenter Trial Program and the Australia–New Zealand Carvedilol Heart Failure trials.[1,19] The mean dose of metoprolol (115 to 124 daily of the tartrate) was larger than that used in the Metoprolol in Dilated Cardiomyopathy Trial (108 mg/d)[18] and was pharmacokinetically equivalent to that used in the Metoprolol CR/XL Randomized Intervention Trial in Heart Failure.[3] This latter trial used a mean dose of 159 mg/d of metoprolol succinate, a sustained-release formulation that is 25% less bioavailable than immediate-release metoprolol tartrate[26,27] and thus equivalent to a mean dose of 119 mg/d of metoprolol tartrate (compared with the mean dose of 115 to 124 mg/d used in the present study). Although one might speculate that a sustained-release formulation might allow for more continuous antiadrenergic activity than an immediate-release formulation, the 2 formulations of metoprolol produce similar long-term hemodynamic effects in patients with heart failure.[28] Therefore, it seems unlikely that the differences we observed in favor of carvedilol were related to underdosing of metoprolol or overdosing of carvedilol.

In conclusion, the present study demonstrates that pharmacological differences among β-blockers in the degree of antiadrenergic activity can result in meaningful differences in their effects on LV function and on maximal exercise capacity. Whether these 2 drugs also differ in their effects on survival is now being evaluated in a large-scale trial known as the Carvedilol or Metoprolol European Trial (COMET).

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