Prospective Crossover Comparison of Carvedilol and Metoprolol in Patients With Chronic Heart Failure

Christoph Maack, MD,* Thomas Elter, MD,† Georg Nickenig, MD,* Karl LaRosee, MD,† Marina Crivaro, MD,† Alexander Stäblein, MD,† Henrike Wuttke, MD,‡ Michael Böhm, MD*

Homburg, Köln and Erlangen, Germany

OBJECTIVES This study investigates the effects of a change of beta-adrenergic blocking agent treatment from metoprolol to carvedilol and vice versa in patients with heart failure (HF).

BACKGROUND Beta-blockers improve ventricular function and prolong survival in patients with HF. It has recently been suggested that carvedilol has more pronounced effects on left ventricular ejection fraction (LVEF) compared with metoprolol. It is uncertain whether a change from one beta-blocker to the other is safe and leads to any change of left ventricular function.

METHODS Forty-four patients with HF due to ischemic (n = 17) or idiopathic cardiomyopathy (n = 27) that had responded well to long-term treatment with either metoprolol (n = 20) or carvedilol (n = 24) were switched to an equivalent dose of the respective other beta-blocker. Before and six months after crossover of treatment, echocardiography, radionuclide ventriculography and dobutamine stress echocardiography were performed.

RESULTS Six months after crossover of beta-blocker treatment, LVEF had further improved with both carvedilol and metoprolol (carvedilol: 32 ± 3% to 36 ± 4%; metoprolol: 27 ± 4% to 30 ± 5%; both p < 0.05 vs. baseline), without interindividual differences. There were no changes in either New York Heart Association functional class or any other hemodynamic parameters at rest. Dobutamine stress echocardiography revealed a more pronounced increase of heart rate after dobutamine infusion in metoprolol-treated patients. After dobutamine infusion, LVEF increased in the carvedilol- but not in the metoprolol-treated group.

CONCLUSIONS When switching treatment from one beta-blocker to the other, improvement of LVEF in patients with HF is maintained. Despite similar long-term effects on hemodynamics at rest, beta-adrenergic responsiveness is different in both treatments. (J Am Coll Cardiol 2001;38:939–46) © 2001 by the American College of Cardiology

Clinical trials have revealed beneficial effects of beta-adrenergic blocking agent treatment in patients with heart failure (HF). This benefit was achieved by the beta1-selective compounds metoprolol (1) and bisoprolol (2) as well as by the nonselective antagonist carvedilol (3). These agents are recommended for the treatment of HF. Nevertheless, it is currently being discussed whether any of these compounds is superior to the others in terms of hemodynamics or prognosis (4).

A number of studies have compared clinical effects of metoprolol and carvedilol in patients with HF (5–9). While two of these studies (6,8) revealed no differences between both agents regarding their effects on symptoms and left ventricular ejection fraction (LVEF), Metra et al. (9) observed more favorable effects of carvedilol compared with metoprolol on LVEF, left ventricular (LV) stroke volume and pulmonary artery pressure despite similar effects on cardiovascular outcome. Although an improvement of ventricular function may predict a reduction of mortality in patients with HF (10), definite data on comparative mortality effects of both agents are not expected before the termination of the Carvedilol Or Metoprolol European Trial (COMET).

Nevertheless, assuming that one agent was superior to the other, the question that will arise in daily practice is whether it is justified to substitute a well-tolerated beta-blocker with another beta-blocker despite improvement of LV function by the former one. Di Lenarda et al. (7) observed that, in patients who were poor responders to metoprolol treatment in terms of LV function, crossover of treatment to carvedilol improved LVEF and reduced LV volumes. In contrast, this study determines whether, in patients who have responded well to metoprolol or carvedilol treatment, crossover to the other beta-blocker, respectively, results in any change of ventricular function, ventricular volumes and other hemodynamic parameters. It further investigates the response of either treatment group to dobutamine stress echocardiography (DSE) in order to estimate the in vivo response to beta-adrenergic stimulation.

METHODS

Patients with chronic HF were included due to ischemic or idiopathic dilated cardiomyopathy. Patients were in New York Heart Association (NYHA) class I, II or III and had documented systolic dysfunction with an LVEF ≤35% determined by radionuclide ventriculography (RNV). Con-
comitant medication consisted of angiotensin-converting enzyme inhibitors (82%), AT1 antagonists (3%), diuretics (91%), digitalis (76%) and nitrates (21%) and was not different between both groups. Exclusion criteria were valvular disease, acute myocardial infarction within six weeks or active angina. All patients gave informed consent before entering the trial.

A flow chart of the study design is given in Figure 1. Eighty patients were randomly assigned to receive open-label metoprolol (n = 42) or carvedilol (n = 38). Initiation doses were 12.5 mg of metoprolol and 3.125 mg of carvedilol. Doses were doubled every two weeks (if tolerated) until target doses of 100 mg of metoprolol twice a day or 25 mg of carvedilol twice a day, or the maximum tolerated doses, were reached. If side effects developed that could be related to beta-blockers, increments in doses were delayed or doses were decreased. Before beginning treatment (evaluation 1) and after at least 12 months of treatment (evaluation 2), LVEF was determined by RNV. Furthermore, LV end-diastolic diameter (EDD) and end-systolic diameter (ESD) and fractional shortening were determined by transthoracic echocardiography. New York Heart Association functional class was assessed by medical history and physical examination. Of the 80 patients, four patients on metoprolol and three on carvedilol underwent cardiac transplantation. Four patients on metoprolol and one on carvedilol died before evaluation 2. Of the remaining 68 patients, 24 patients on carvedilol and 20 on metoprolol

---

**Abbreviations and Acronyms**

- betaARK1 = beta-adrenergic receptor kinase 1
- COMET = Carvedilol Or Metoprolol European Trial
- DSE = dobutamine stress echocardiography
- EDD = end-diastolic diameter
- ESD = end-systolic diameter
- HF = heart failure
- LV = left ventricle or left ventricular
- LVEF = left ventricular ejection fraction
- NYHA = New York Heart Association
- PCR = polymerase chain reaction
- RNV = radionuclide ventriculography
- $V_{sc}$ = heart rate corrected velocity of circumferential shortening

---

**Figure 1.** Study flow chart. DSE = dobutamine stress echocardiography.
who had improved in terms of LVEF and NYHA class were switched to the respective other beta-blocker. Inclusion criteria for the crossover were a stable medication with a minimum dose of 100 mg of metoprolol or 25 mg of carvedilol. The crossover was performed within one day, with the first dose of the new beta-blocker given in the morning under continuous monitoring of hemodynamics in our outpatient clinics. A dose of 25 mg of carvedilol was regarded as equivalent to 100 mg of metoprolol. Since the first patients that were switched from carvedilol to metoprolol frequently experienced hypotension or bradycardia, treatment was modified by reducing the first doses of metoprolol to 50 mg of metoprolol, equivalent to 25 mg of carvedilol. After two weeks, the dose was doubled and titrated to the respective maximum dose. Before (evaluation 2) and six months after crossover (evaluation 3), patients underwent RNV, transthoracic echocardiography and physical examination. Eight patients who were switched from carvedilol to metoprolol and six who were switched from metoprolol to carvedilol underwent DSE before and six months after crossover. The RNV, echocardiography and DSE were assessed by physicians who were blinded to the study medication of the patient. After the crossover of beta-blocker treatment, five patients who received metoprolol after carvedilol and six patients from the other group discontinued study medication for different reasons (see Results section).

Echocardiography and DSE. Methods for transthoracic echocardiography have been described previously (11–13). All echocardiographic recordings were made by the same investigator (M.C.) and were evaluated independently by two principal investigators (K.L. and G.N.) from the echocardiography laboratory. To obtain a parameter of contractility that is not confounded by the influence of heart rate, we calculated heart rate corrected velocity of circumferential fiber shortening (V_cfc) by the formula $V_{cfc} = FS \times \sqrt{HR/ET}$, where $FS$ is fractional shortening, $HR$ is heart rate, and $ET$ is ejection time.

Table 1. Effect of Beta-Blockers Before Crossover of Treatment

<table>
<thead>
<tr>
<th></th>
<th>Carvedilol (n = 34)</th>
<th>After Treatment</th>
<th>Metoprolol (n = 34)</th>
<th>After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>57 ± 2</td>
<td>60 ± 1</td>
<td>31/3</td>
<td>29/5</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>15/19</td>
<td>16/18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA I/II/III</td>
<td>4/10/20</td>
<td>4/12/18</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hemodynamics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>93.7 ± 3.3</td>
<td>67.7 ± 1.6†</td>
<td>85.3 ± 3.8</td>
<td>66.9 ± 1.9†</td>
</tr>
<tr>
<td>LVEF</td>
<td>25.2 ± 2.9</td>
<td>36.0 ± 3.9*</td>
<td>25.2 ± 3.9</td>
<td>33.1 ± 5.1*</td>
</tr>
<tr>
<td>EDD</td>
<td>66.2 ± 1.9</td>
<td>63.5 ± 1.5</td>
<td>66.8 ± 1.9</td>
<td>62.6 ± 1.6*</td>
</tr>
<tr>
<td>FS</td>
<td>12.8 ± 2.1</td>
<td>20.2 ± 1.8*</td>
<td>17.4 ± 3.9</td>
<td>26.9 ± 4.4*</td>
</tr>
<tr>
<td>NYHA</td>
<td>2.7 ± 0.2</td>
<td>1.7 ± 0.1†</td>
<td>2.7 ± 0.1</td>
<td>1.9 ± 0.1†</td>
</tr>
</tbody>
</table>

*p < 0.05 vs. baseline; †p < 0.001 vs. baseline.

DCM = dilated idiopathic cardiomyopathy; EDD = left ventricular end-diastolic dimension; FS = fractional shortening; HR = heart rate; ICM = ischemic cardiomyopathy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association functional class.

except that, after determination of baseline hemodynamics at rest, increasing concentrations of dobutamine (10, 20, 30 and 40 µg/kg body weight/min) were administered intravenously. After 5 min, contractility and hemodynamic parameters were determined.

**Cytochrome P450 2D6 (CYP2D6) genotype determination.** The CYP2D6 genotype was determined with an improved polymerase chain reaction–restriction fragment length polymorphism method suited for routine diagnostics (14). DNA extraction from ethylenediaminetetraacetic acid-blood, two first-round polymerase chain reactions (PCR) covering the entire coding sequence with no cross reactivity with the known CYP2D6 pseudogenes, four second-round PCR reactions covering polymorphic sites on the first-round products, and seven restriction enzyme digestions of the second-round PCR products were performed. The method allows >98% prediction of the poor metabolizer phenotype in the Caucasian population.

**Statistical analysis.** Values are given as means ± standard error of the mean. Statistical analysis was performed by Mann-Whitney U test or Wilcoxon rank-sum test. A p value <0.05 was considered significant.

**RESULTS**

Sixty-eight patients with chronic HF were investigated (Fig. 1). Thirty-four patients received metoprolol, and 34 patients received carvedilol for at least one year. Baseline characteristics of these patients are given in Table 1. There were no differences regarding demographics, etiology of HF, NYHA functional class and LVEF. Treatment with either beta-blocker resulted in a decrease of heart rate, an increase of LVEF and an improvement of NYHA functional class (Table 1). The EDD decreased significantly only after metoprolol but not after carvedilol treatment.

Of these patients, 24 on carvedilol and 20 on metoprolol were switched to the respective other beta-blocker. Baseline characteristics of both groups before the crossover of beta-
blocker treatment are listed in Table 2. There were no significant differences in demographics, etiology of HF and NYHA functional class.

Patients received 47 ± 3 mg carvedilol or 182 ± 15 mg metoprolol before and 48 ± 3 mg carvedilol or 180 ± 10 mg metoprolol after crossover, respectively. The change from metoprolol to carvedilol treatment was tolerated well. Nevertheless, six patients discontinued carvedilol treatment and wished to be put back on metoprolol, although none of these patients experienced hypotension, bradycardia or worsening of symptoms. Patients discontinued due to inconvenient tablet size or due to the referral of their general physician, respectively. Despite lower initial dose of metoprolol (50 mg metoprolol equivalent to every 25 mg of carvedilol), five patients who were switched from carvedilol to metoprolol did not tolerate metoprolol treatment due to hypotension or bradycardia. Cytochrome P4502D6 (CYP2D6) is responsible for the metabolism of metoprolol. Mutations of CYP2D6 may lead to inactivation of this enzyme with subsequently higher plasma levels of metoprolol (15). Thus, the five patients who did not tolerate metoprolol were genotyped for CYP2D6 polymorphism and were put back on carvedilol. Of these five patients, three patients had two functional alleles (extensive metabolizer); one patient had one functional and one nonfunctional allele (heterozygous individual), and one patient had two nonfunctional alleles (poor metabolizer).

Six months after switching from one compound to the other, LVEF had continuously improved in patients who were switched from carvedilol to metoprolol as well as in patients who were switched from metoprolol to carvedilol (Table 2). The relative increase in LVEF was similar in both groups. The EDD and ESD remained constant after crossover. Additionally, heart rate, systolic and diastolic blood pressure and NYHA functional class did not change in either group.

Table 3 and Figure 2 display the results from DSE. The results are given for all patients either during carvedilol or during metoprolol treatment. In metoprolol-treated patients, maximum values (Table 3) as well as the relative increase of heart rate (Fig. 2A) and Vcf during after maximum dobutamine dose were higher than they were in carvedilol-treated patients. The LV EDD (Fig. 2B) and ESD decreased in metoprolol-treated but not in carvedilol-treated patients. The relative increase of LVEF was not significantly different between both treatments (Fig. 2C). Stroke volume increased in carvedilol-treated patients and decreased in metoprolol-treated patients (Fig. 2D). Cardiac output was similar in both treatment groups (Fig. 2E). Interestingly, systolic and median blood pressure increased in carvedilol-treated patients but remained unchanged in metoprolol-treated patients.

**DISCUSSION**

The most important findings of this study are that six months after crossover of beta-blocker treatment, further improvement of ventricular function occurred irrespective of the beta-blocker used. No substantial differences in baseline hemodynamics were observed between carvedilol- or metoprolol-treated patients. Dobutamine stress echocardiography revealed different hemodynamic responses to beta-adrenergic stimulation in patients treated with carvedilol or metoprolol.

**LV function.** Carvedilol and metoprolol improved LVEF six months after crossover. In a recent study, carvedilol improved LVEF in patients with idiopathic dilated cardiomyopathy who were poor responders to metoprolol treatment (7). In contrast with that trial, this investigation was
performed in patients who had responded well to beta-blocker treatment in terms of LVEF and NYHA functional class. Both agents improved LVEF to a similar extent. This is in concert with the studies of Kukin et al. (8) and Sanderson et al. (6) who observed no differences between metoprolol- and carvedilol-treated patients regarding LVEF. Other trials revealed slightly (5) and significantly (9) more pronounced improvements of hemodynamics by carvedilol compared with metoprolol treatment. These studies could influence the clinical decision to switch treatment of patients from one beta-blocker to the other. However, in patients already treated with beta-blockers, this conclusion cannot be drawn since patients included in these comparative studies were naive to beta-blockers before initiating this treatment. Therefore, this study more closely reflects the situation of a sudden switching of therapy. In this investigation patients had already received beta-blockers for more than one year, and, thus, changes in hemodynamics may be smaller than during the first 12 months of treatment. Nevertheless, the data of the study indicate that the time course of improvement of LV function by beta-blockade exceeds 12 months of therapy, irrespective of the beta-blocker used.

In contrast with former studies with metoprolol (16) and carvedilol (17), no further reduction of LV EDD and ESD was observed. The former studies observed a reversal of LV remodeling during the first six (16) and 12 (17) months of beta-blocker treatment. In the study of Doughty et al. (17), carvedilol reduced the LV end-diastolic volume index during the first six months of treatment, whereas, from six to 12 months of treatment, this parameter remained rather unchanged. Thus, it may well be that LV volume reduction decreases in the course of time, and, thus, changes of LV volumes in this study were too small to be detected. The fact that LVEF improved despite minor changes of LV volumes may be due to an improvement of intrinsic contractility of the myocardium. Since carvedilol and metoprolol improved resting ventricular function to a similar extent, the inhibition of norepinephrine-induced maladaptive responses of the myocardium (i.e., apoptosis [18]), rather than changes of beta-adrenergic signal transduction (5), may be responsible for the increase in resting LVEF.

**Beta-adrenergic responsiveness.** Dobutamine stress echocardiography was used to compare the hemodynamic response to beta-adrenergic stimulation in patients treated with either carvedilol or metoprolol. Dobutamine is an alpha- and beta-adrenoceptor agonist that predominantly activates \( \beta_1 \)-, and to a lesser extent \( \alpha_1 \)- and \( \beta_2 \)-adrenoceptors. The different effects of dobutamine on hemodynamics in carvedilol- and metoprolol-treated patients are likely due to the different pharmacological profile of both beta-blockers. Metoprolol is a \( \beta_1 \)-selective (19–21) strong inverse agonist (20,21) that upregulates ventricular beta-adrenoceptor density (5,21), restores postreceptor events (11) and increases cardiac norepinephrine release in patients with HF (5). In contrast, carvedilol is a nonselective weak inverse agonist (19–21) that does not upregulate beta-adrenoceptors (5). Furthermore, carvedilol has alpha-blocking (19) and antioxidant properties (22) and reduces cardiac norepinephrine release (5).

The results from DSE indicate that, in carvedilol- and metoprolol-treated patients, a similar increase of cardiac output in response to beta-adrenergic stimulation is achieved by different mechanisms. In metoprolol-treated patients, the dobutamine-induced increase of cardiac output was maintained by a substantial rise in heart rate. In contrast, in carvedilol-treated patients, an increase of stroke volume appeared to be the relevant mechanism. In a study by Heilbrunn et al. (23) on patients with HF, improvement of contractility in response to dobutamine after metoprolol treatment was related to upregulation of ventricular beta-adrenoceptor density.
In HF, ventricular protein expression and activity of beta-adrenergic receptor kinase 1 (betaARK1) is elevated compared with healthy controls (24). This enzyme is responsible for beta-adrenoceptor desensitization and down-regulation, and its expression and activity have a strong impact on cardiac contractility at baseline and after beta-adrenergic stimulation (25). In vivo experiments on mice revealed downregulation of betaARK1 protein levels and activity by carvedilol, indicating that, despite a lack of receptor upregulation, at least receptor resensitization by carvedilol might contribute to increased cardiac contractility in patients with HF (26). However, the fact that, in carvedilol-treated patients, a similar increase of cardiac output is achieved with a lower increase of heart rate but a more pronounced increase of stroke volume may resemble a novel and possibly more economical mechanism of beta-adrenergic response compared with an increase of heart rate in metoprolol-treated patients.

Since, at the time of examination, both beta-blockers were applied at maximum achievable doses, the response to 40 μg/kg per min of dobutamine may not reflect full beta-adrenergic stimulation. Maximum heart rates of 86 ± 5 beats/min (carvedilol) and 107 ± 6 beats/min (metoprolol) merely reflect submaximal beta-adrenoceptor occupation due to competition with the beta-blockers. Nevertheless, clear-cut differences in response to dobutamine were detected even at this submaximal level of beta-adrenergic stimulation.

In the majority of clinical trials in patients with HF, both metoprolol and carvedilol treatment improved submaximal exercise tolerance (27). The present data indicate that, at a submaximal level of beta-adrenergic stimulation, the increase of cardiac output is comparable in metoprolol- and carvedilol-treated patients. Under submaximal exercise conditions, similar increases of cardiac output may resemble comparable oxygen supply of peripheral organs and muscles and, thus, similar tolerance to exercise. In contrast with submaximal exercise, maximal exercise tolerance is im-

Figure 2. Effects of maximum dose of dobutamine (40 μg/kg per min) on heart rate (HR) (A), end-diastolic diameter (EDD) (B), left ventricular ejection fraction (LVEF) (C), stroke volume (SV) (D) and cardiac output (C.O.) (E). Values are given as the relative increase or decrease from baseline values, respectively.
proved only by metoprolol but not by carvedilol, according to presently available data (27). This may be due to upregulation of beta-adrenergic receptors in metoprolol-treated patients, since an elevation of beta-adrenoceptor density is associated with higher maximum heart rate and oxygen consumption (28). However, such conclusions have to be drawn carefully, since beta-adrenergic stimulation with dobutamine is not a surrogate parameter for exercise performance. Nevertheless, the present data may help the understanding of different effects of both beta-blockers on exercise tolerance in patients with HF.

Tolerability. In this study, five patients (21%) who were switched from carvedilol to metoprolol experienced acute hypotension or bradycardia at first dose, while none of the patients switching from metoprolol to carvedilol had these adverse effects. These differences were not due to unequal beta-blockade, since after long-term treatment, patients on metoprolol and carvedilol had the same reduction in heart rate, and both agents were uptitrated to the target doses recommended in large multicenter trials (1,3). In one out of five cases, CYP2D6 poor metabolizer status could account for bradycardia or hypotension. But granted the normal (n = 3) or heterozygous (n = 1) state in the other four cases, CYP2D6 genetic polymorphism cannot be the only reason for metoprolol intolerance.

In human failing myocardium, metoprolol exerts more pronounced negative inotropic effects than carvedilol (20). This is probably related to greater inverse agonist activity of metoprolol compared with carvedilol. Inverse agonism of a beta-blocker is its ability to reduce the spontaneous activity of the beta-adrenoceptor. The more intrinsic activity of beta-adrenoceptors is reduced, the lower is cellular cyclic adenosine monophosphate production and, thus, cardiac inotropy and chronotropy. Thus, different inverse agonist activity of carvedilol and metoprolol may be responsible for the different tolerability of these agents. It is suggested that, when initiating beta-blocker treatment in patients with HF, carvedilol may be well tolerated since, after single dose application, this compound maintains cardiac output (29). Less pronounced negative inotropic effects, but also a decrease in pulmonary wedge pressure by carvedilol due to vasodilation may contribute to this favorable hemodynamic effect (29). In contrast, metoprolol reduces cardiac index after a single dose application in patients with HF (30). Moreover, even during long-term treatment of HF patients, cardiac index is decreased at every subsequent dose (31). Thus, when switching the beta-blocker from carvedilol to metoprolol, the initial metoprolol dose should not exceed 50 mg per 25 mg of carvedilol with consecutive uptitratin to the maximum tolerated dose, while a change from metoprolol to carvedilol is well tolerated with 25 mg carvedilol per 100 mg of metoprolol. However, these immediate effects on tolerance may not justify the formulation of conclusions about long-term tolerability.

Conclusions. Despite different pharmacological profiles of carvedilol and metoprolol, after switching from one compound to the other, both beta-blockers further improve baseline LV function. This effect is not different between both beta-blockers. Thus, circumstantial evidence for differences in surrogate parameters obtained in studies comparing beta-blockers in patients previously naive to this treatment does not justify switching patients from one compound to the other. Nevertheless, the differences obtained in contractile response to dobutamine provide evidence for a functional significance of the differential effects on beta-adrenergic signaling and might explain different effects on submaximal and maximal exercise tolerance. Final comparative conclusions on the long-term effects will not be available before termination of the COMET trial.

Acknowledgment
The authors gratefully acknowledge fellow author Dr. Thomas Elter for allowing parts of his doctoral thesis to be used in this manuscript.

Reprint requests and correspondence: Dr. Christoph Maack, Medizinische Klinik und Poliklinik, Innere Medizin III, Universität des Saarlandes, 66421 Homburg/Saar, Germany. E-mail: maack@med-in.uni-saarland.de.

REFERENCES
12. von Scheidt W, Böh M, Schneider B, Autenrieth G, Erdmann E. Cholinergic baroreflex vasodilation: defect in heart transplant recip-