Nonselective Versus Selective ß-Blockers in the Management of Chronic Heart Failure: Clinical Implications of the Carvedilol or Metoprolol European Trial

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The abundance of evidence supporting ß-blocker therapy has resulted in the widespread acceptance of these drugs in the treatment of heart-failure patients. However, ß-blockers are not a homogeneous class of drugs, and important differences in efficacy have been noted between different members of the class. Thus, practicing physicians are faced with a choice when selecting a particular ß-blocker for treating heart failure. One of the considerations is whether to choose a selective or a nonselective ß-blocker. The results of the Carvedilol or Metoprolol European Trial indicate that carvedilol, a third-generation, nonselective ß-blocker with additional α-blocking, antioxidant, and other properties, is clearly superior to a $ß_1$-blocking drug, metoprolol tartrate. The choice between these drugs is therefore unambiguously in favor of carvedilol.

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Heart failure is pandemic throughout the industrialized world. In the United States alone, it is estimated that nearly 5 million persons currently have this condition. Moreover, the prevalence of heart failure is likely to double over the next few decades. The reasons for this include the aging of the population, increases in the prevalence of important risk factors, such as obesity and diabetes, and the improved early survival of patients experiencing

an acute myocardial infarction (MI). Heart failure accounts for more than 1 million hospital admissions in the United States each year, and the cost (both personal and economic) to society is considerable. Once heart failure is diagnosed, survival is markedly compromised, with 50% of patients dead within 5 years. The outlook is even worse for those patients with more advanced heart failure. Fortunately, advances in therapy have favorably altered the prognosis of heart-failure patients to the extent that the diagnosis is no longer the "death sentence" it had been in the past.

Although the utility of ß-blockers in treating heart failure is no longer an issue, questions remain as to whether the beneficial effects seen in clinical trials represent a class effect of these agents.

Understanding the critical role of neurohormonal activation in the heart-failure syndrome has greatly altered prevailing concepts of both pathogenesis and treatment.[1] It is now recognized that in response to injury to the left ventricle (LV), neurohormonal systems are activated systemically and within the heart itself.[2,3] Although a variety of conditions, including MI, prolonged pressure or volume overload (as seen with hypertension or valvular lesions), viral infection, or exposure to toxins, can initiate this process by causing damage to the LV, the net long-term effects of structural remodeling and progressive deterioration in cardiac function that result from neurohormonal stimulation are remarkably consistent.[4] The most important neurohormonal systems that are activated in response to myocardial injury are the renin–angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS). Although activation of these systems has some short-term benefits in supporting cardiac function, the long-term effects on cardiac structure are deleterious, and the net effect is progressive deterioration in function. Drugs that block the RAS and SNS have been shown to have highly favorable effects on the clinical course of heart-failure patients, and they now form the cornerstones of the treatment regimen.

Foremost among the advances in treatment of heart failure has been the acceptance of ß-blockers as a standard of therapy for the treatment of all stages of this condition. The concept that ß-blocking agents will improve the clinical course of heart failure patients represents a "reversal of fortune" for these agents, because they were formally contraindicated in this condition for fear that they would worsen the course by depriving the failing ventricle of needed inotropic support. Clinical trial data now confirm that the addition of ß-blocking agents to the standard medical regimen that includes an angiotensin converting enzyme (ACE) inhibitor will reduce mortality by approximately 35%.[5–8] Consequently, the use of ß-blockers in the treatment of heart failure has been widely accepted and codified in major guidelines.[9,10] Although the utility of ß-blockers in treating heart failure is no longer an issue, questions remain as to whether the beneficial effects seen in clinical trials represent a class effect of these agents. A related issue is whether differences in the pharmacologic profile of the ß-blockers translate into differences in clinical effects and, if so, whether understanding this will help the practicing physician to select a ß-blocker for the treatment of heart-failure patients.

Catecholamines, Adrenergic Receptors, and ß-Blockers

As background to this discussion, it is worth reviewing the various adrenergic receptors that interact with catecholamines in the heart and in the periphery, to review the changes in the density of these receptors that take place in the failing heart, and to highlight some of the substantial differences in the pharmacology of the ß-blockers that are currently available on the market. In patients with heart failure, circulating levels of catecholamines (along with other neurohormones) are elevated.[3] In general, the levels measured in blood tend to rise in parallel with the degree of functional impairment. Serum catecholamine levels have been demonstrated to be an important independent prognostic factor in heart-failure patients.[11] Of particular interest, though, is the fact that increases in catecholamine levels can be detected in the blood of patients with LV systolic dysfunction even before symptoms of heart failure are present.[3] This latter finding is consistent with the aspect of the neurohormonal hypothesis that considers catecholamine stimulation to be an important factor in promoting progression of disease.

As outlined in Figure 1, catecholamines interact with receptors on the cell surface that mediate their response. For our purposes, there are three relevant receptor subtypes, which have been termed $ß_1$-, $ß_2$-, and α_1-receptors. All three receptor subtypes have been identified on cardiac myocytes. α_1 Receptors mediate vasoconstriction in peripheral blood vessels, and they help regulate blood flow to the kidney. $ß_1$-Receptors

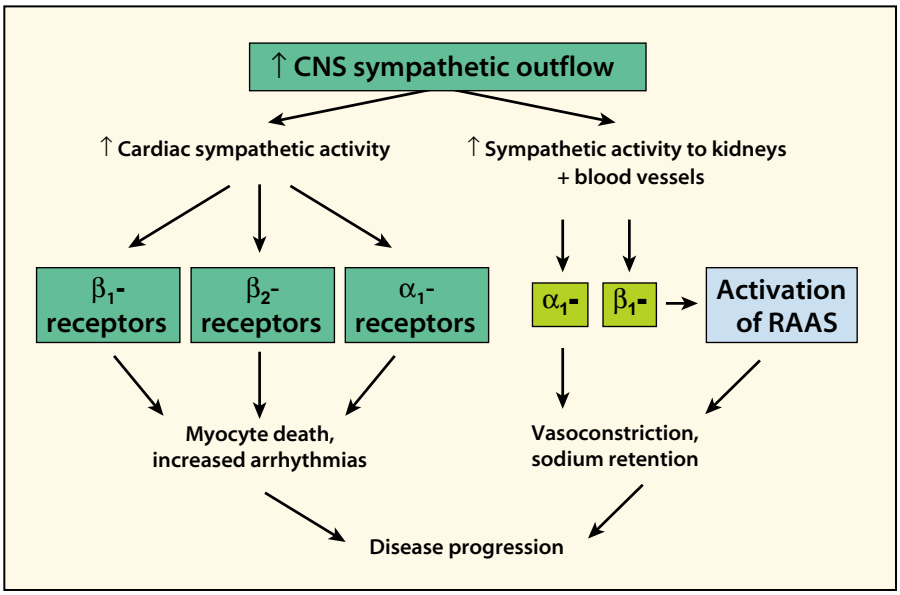

Figure 1. *Overview of the adrenergic receptor subtypes and some of their effects that are relevant in heart failure. CNS, central nervous system; RAAS, renin–angiotensin-aldosterone system.*

present on the juxtaglomerular cells of the kidney play an important role in regulating the release of plasma renin activity, a key enzyme in the activation of the RAAS. In the normal human heart, approximately 70% of the adrenergic receptors are of the $ß_1$ subtype.[12] Thus, in health, most adrenergic trafficking is mediated though the $ß_1$-receptor. $ß_2$- and α_1-receptors are relatively scarce compared with the $ß_1$-receptor density. As mentioned above, catecholamine stimulation of the heart increases in patients with heart failure. Although it had been known for many years that increased exposure to catecholamines resulted in down-regulation of the ß-receptor population, it was only relatively recently that it was learned that this effect is selective for the $ß_1$-receptor. In heart failure, the number of $ß_2$-receptors on cardiac myocytes is essentially unchanged (and there is a small increase in α_1-receptors). Thus, as shown in Figure 2, in heart failure patients there is a relative redistribution of adrenergic receptors, such that the proportion of $ß_1$- receptors is decreased, whereas the proportion of $ß_2$- and α_1-receptors is increased.[12]

ß-Blockers have been used in the treatment of cardiovascular disease for more than 40 years. Various ß-blocking agents have been developed over this period, and many have distinct pharmacologic properties. Several of the most important of these differences are outlined in Table 1. The first generation of ß-blockers were nonspecific agents that blocked both $ß_1$- and $ß_2$-adrenergic receptors. Propranolol is the prototypic nonspecific ß-blocker. Second-generation ß-blockers were designed to be selective for the $ß_1$-adrenergic receptor. Metoprolol and bisoprolol are examples of $ß_1$-selective agents. Third-generation ß-blockers have cardiovascular effects in addition to their ß-blocking properties. Carvedilol, a nonselective ß-blocker with additional α-blocking, antioxidant, and other properties, is a third-generation ß-blocker.

There is evidence that the pharmacologic profile of a particular ß-blocker might make it more or less suitable for use in patients with heart failure. For instance, nonselective ß-blockers, such as propranolol, that have no additional properties, are more likely to adversely affect cardiac function than either a $ß_1$-selective agent or a nonselective agent with α-blocking properties, such as carvedilol.[13] This difference likely accounts for the problems

Figure 2. *Alterations (mean and standard deviation) in distribution of adrenergic receptors in failing human myocardium. *P < .05 vs normal function. Adapted from Bristow MR. Changes in myocardial and vascular receptors in heart failure.* J Am Coll Cardiol. *1993;22(4 suppl A):61A–71A.*

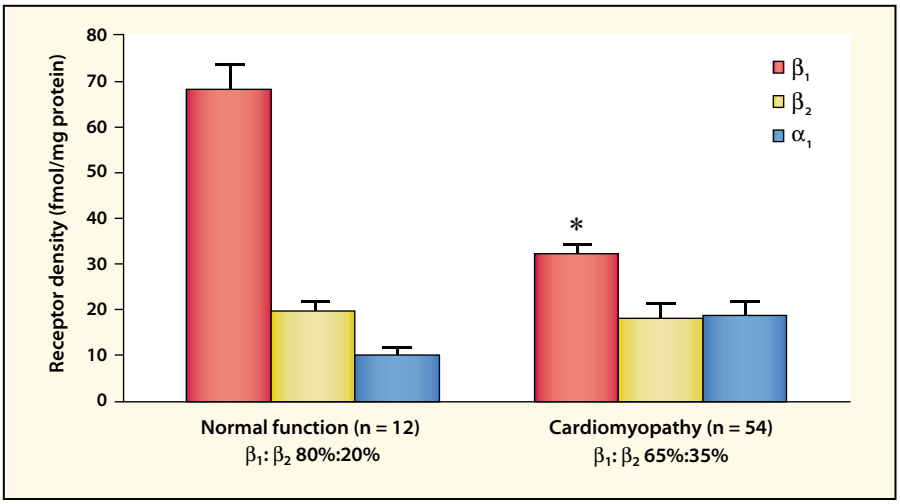

Table 1
Pharmacologic Differences Among ß-Blockers

- Selective vs nonselective
- α-Adrenergic blocking properties
- Additional properties (eg, antioxidant)
- Intrinsic sympathomimetic activity
- Inverse agonism
- Receptor up-regulation
- Effects on catecholamine levels

with worsening heart failure that have been seen with propranol but that are relatively uncommon with either metoprolol or carvedilol. ß-Blocking agents with intrinsic sympathomimetic activity that stimulates the myocardium are particularly unsuited for use in the heart-failure population. In clinical trials, these agents have been shown to increase mortality in heart-failure patients.[14]

ß-Blockers for the Treatment of Heart Failure

There is now incontrovertible evidence that ß-blockers improve the clinical course of heart-failure patients. Large-scale clinical trials have shown that when these agents are added to ACE inhibitors, there is an additional mortality reduction of approximately 35%.[5–8] Hospitalizations are also shown to be decreased, and New York Heart Association (NYHA) functional class improves. ß-Blockers are effective in patients with ischemic and nonischemic etiology of their heart failure and across a broad range of severity. Recent evidence from the COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) trial demonstrated that even patients with advanced heart failure who were treated with carvedilol experience highly significant reductions in mortality and showed evidence of clinical improvement.[8] On the other hand, the CAPRICORN (Carvedilol Post-Infarct Survival Controlled Evaluation) study reported beneficial effects, including reduced mortality with ß-blockade in the treatment of MI survivors with evidence of LV dysfunction.[15] Although the mechanisms responsible for these beneficial effects have not been precisely identified, inhibition (and reversal) of adverse cardiac remodeling is believed to play a pivotal role.[16] On the basis of these findings, ß-blockers have been strongly recommended for the treatment of heart failure in all guidelines for treatment of this condition. Although the results in clinical trials with ß-blockers have been strongly positive in most cases, not all studies have shown a favorable effect. The BEST study (Beta-Blocker Evaluation of Survival Trial), in which bucindolol was given to patients with advanced heart failure, demonstrated only insignificant effects on mortality.[17] The reason for the discrepancy between the results of the BEST trial and the positive results of other trials is not known with certainty, but differences in the pharmacologic profile of bucindolol and the drugs used in the other successful trials is a much more likely explanation than differences in the patient populations that were studied.

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Nonselective Versus Selective ß-Blockers

The abundance of evidence supporting ß-blocker therapy has resulted in the widespread acceptance of these drugs in the treatment of heart-failure patients. As noted above, however, the ß-blockers are not a homogeneous class of drugs, and important differences in efficacy have been noted between different members of the class. Thus, practicing physicians are faced with a choice when selecting a particular ß-blocker for treating heart failure. One of the considerations is whether to choose a selective or a nonselective ß-blocker. The latter, of course, would involve the use of a drug with additional properties, such as α_1-blockade, because the prototypic first generation nonselective ß-blocker, propranolol, has been shown to be poorly tolerated in heart-failure patients. Following is an overview of the studies comparing metoprolol, a $ß_1$-selective agent, with carvedilol, a nonselective ß-blocker with additional properties, including α_1-blocking, antioxidant, antiapoptotic, and anti-ischemic properties.

Metra and colleagues[18] compared the effects of carvedilol with metoprolol tartrate in 122 heart-failure patients who underwent hemodynamic evaluation before and after 13 to 15 months of therapy. All patients were receiving standard therapies, including an ACE inhibitor at the time of randomization into the trial. The results (depicted in Figure 3) show that whereas both agents increased LV ejection fraction from the baseline level, the magnitude of change was significantly greater with carvedilol than with metoprolol. A trend toward greater reductions in end-diastolic and end-systolic volumes (eg, reverse remodeling) was also seen with carvedilol. Di Lenarda and coworkers[19] evaluated the effects of switching from metoprolol to carvedilol in heart-failure

patients who demonstrated a persistently low ejection fraction despite being treated with metoprolol. As shown in Figure 4, the 16 patients who continued on metoprolol (mean dose, 142 mg daily) experienced no increase in ejection fraction or reduction in end-diastolic volume over the 12-month follow-up period. In contrast, the 14 patients treated with carvedilol (mean dose, 74 mg) had increased ejection fraction and tended to have a reduction in end-diastolic volume. Moreover, the differences between the 2 groups favored carvedilol. A meta-analysis by Packer and colleagues,[20] which included these two studies as well as two additional studies in which carvedilol and metoprolol were directly compared, demonstrated highly significant differences in the increase in LV ejection fraction and a strong trend in reduction in LV end-diastolic volume that favored carvedilol.

COMET

The Carvedilol or Metoprolol European Trial (COMET) was designed to compare carvedilol with metoprolol tartrate in a head-to-head fashion.[21] The primary endpoint was all-cause mortality. The study enrolled 3029 patients with symptomatic heart failure (NYHA functional class II–IV) and evidence of systolic dysfunction. Patients were receiving standard medical therapy, including an ACE inhibitor, at the time of randomization. Both agents were started at a low dose (3.125 mg and 5 mg twice daily for carvedilol and metoprolol, respectively) and titrated up to a target of 25 mg carvedilol and 50 mg metoprolol twice daily. These regimens were generally well tolerated, as evidenced by the maximum total dose achieved of 42 mg of carvedilol and 85 mg of metoprolol daily.

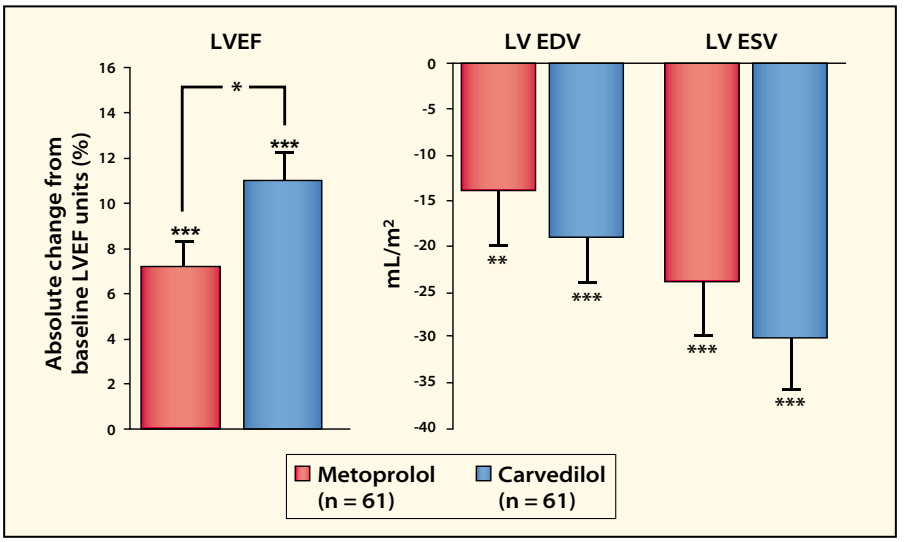
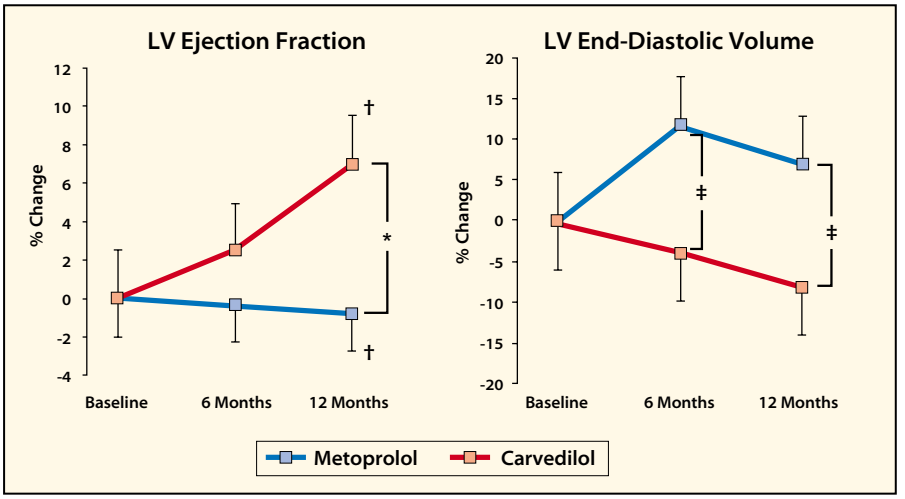


Figure 3. *Comparison of carvedilol and metoprolol tartrate on left ventricular ejection fraction (LVEF) and end-diastolic volume (EDV) in heart failure patients. A total of 150 heart-failure patients receiving diuretics and angiotensin-converting enzyme inhibitors, with or without digoxin, were randomized to double-blind treatment; 122 had ejection fraction/hemodynamic assessments at baseline and after 13 to 15 months of treatment. ESV, end-systolic volume. *P < .05; **P < .01; ***P < .001. Reproduced with permission from Metra et al.*[18]

The primary endpoint results of COMET are shown in Figure 5. For all-cause mortality, carvedilol treatment was associated with a 17% reduction (95% confidence interval [CI] 0.74-0.93, *P* = .0017) compared with metoprolol. Carvedilol was also shown to reduce cardiovascular death by 20% (*P* = .004). Subgroup analysis, shown in Figure 6, demonstrates that the mortality benefits of carvedilol compared with metoprolol were manifest across virtually all predefined patient groupings. These data show that the superiority of carvedilol to metoprolol in the mor-

Figure 4. *Long-term effects of carvedilol in patients with persistent left ventricular (LV) dysfunction despite chronic metoprolol tartrate administration. The metoprolol group (n = 16) was continued on metoprolol tartrate (mean dose, 142 mg); the carvedilol group (n = 14) was switched to carvedilol (mean dose, 74 mg). *P < .05, Δ 12 months carvedilol vs metoprolol; †P < .05, Δ 12 months vs baseline carvedilol or metoprolol; ‡P < .10, Δ 6 or Δ 12 months carvedilol vs metoprolol. Reproduced from Di Lenarda et al.*[19]



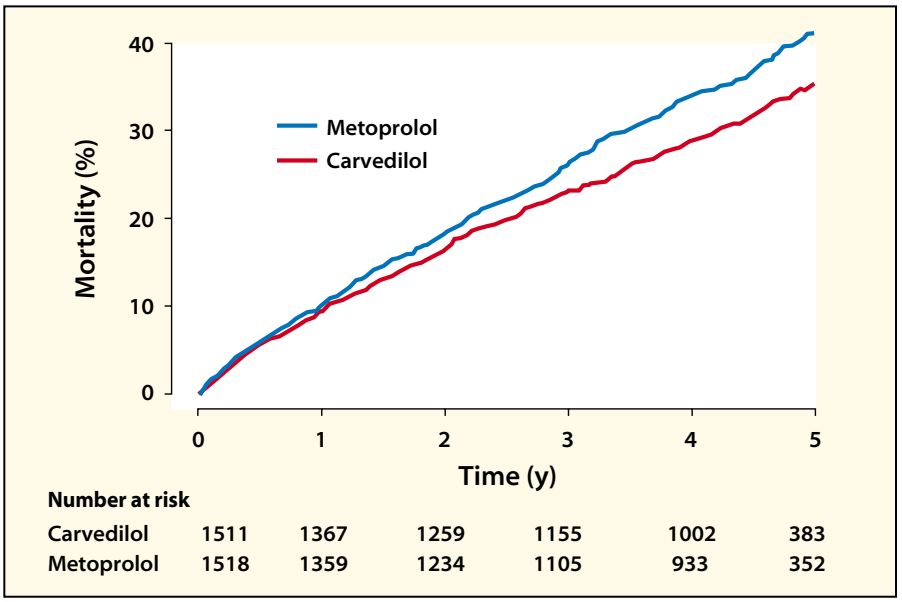


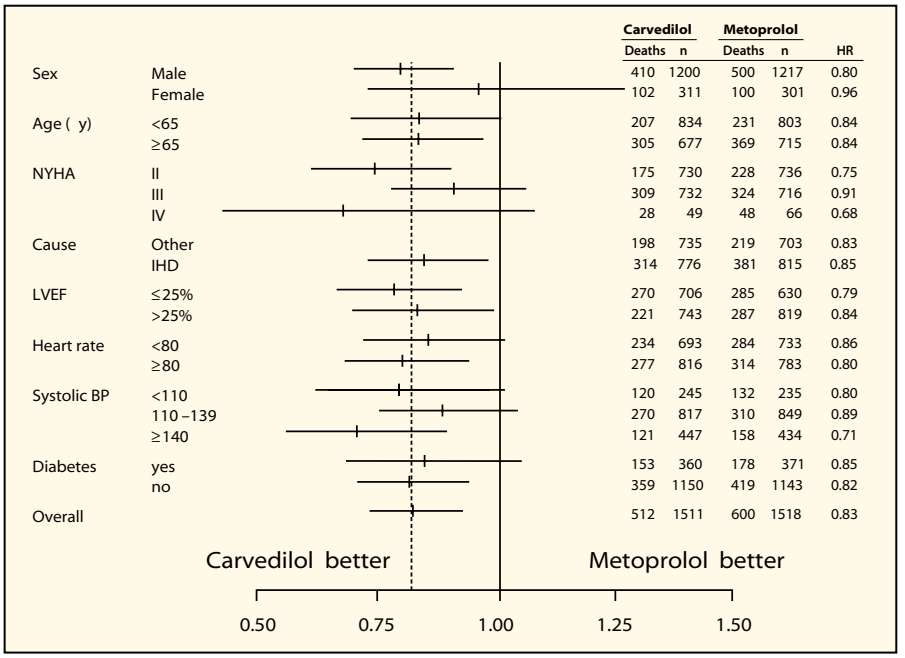
Figure 5. *Primary endpoint results of the Carvedilol or Metoprolol European Trial. The primary endpoint of the trial was all-cause mortality. Hazard ratio = 0.83 (95% confidence interval, 0.74-0.93;* P *= .0017). Reproduced with permission from Poole-Wilson.*[21]

tality results was not related to a disproportionate effect in some patients but rather that all patients seem to benefit. For the second primary endpoint of all-cause death or hospitalizations, there was an insignificant 6% reduction (95% CI 0.85-1.02, *P* = .122).

Similar reductions were observed in the risk for sudden death and progressive heart failure deaths with carvedilol (Figure 7). The COMET trial also showed that there was greater vascular protection with carvedilol relative to metoprolol, including a 67% reduction in death from stroke (95% CI 0.18-0.62, *P* = .006) and a 29% reduction in fatal and nonfatal MI (95% CI 0.52-0.97, *P* = .03). The risk of new-onset diabetes was also reduced by 22% with carvedilol relative to metoprolol.

Interpretation of the results of COMET has been controversial because of the dose of drugs given and the formulation of metoprolol that was used. The debate regarding dose has focused on the adequacy of the dose of metoprolol and whether it was equal to the dose of carvedilol in achieving blockade of the $ß_1$-receptor. Although reduction in heart rate with carvedilol was slightly greater during the first year, the differences were small, representing approximately 10% of the bradycardic effect that was seen. These findings indicate the relative equality of the doses of the drugs in blocking the $ß_1$-receptor, although the duration of blockade with metoprolol has been an additional concern. Perhaps even more importantly, regarding the dose of metoprolol, is the fact that 50 mg (or less) is commonly used in clinical practice to treat heart-failure patients. Little can be said with respect to the issue of whether a longer-acting preparation of metoprolol would have fared better compared with carvedilol. Although metoprolol succinate at a target dose of 200 mg daily (achieved dose of 159 mg daily) was shown in the MERIT-HF (Metoprolol Cr/XL Randomized Intervention Trial in Congestive Heart Failure) trial to effectively reduce mortality and improve the clinical course of heart failure patients,[7] there is no information available to establish whether

Figure 6. *Subgroup mortality analyses in the Carvedilol or Metoprolol European Trial. HR, heart rate; NYHA, New York Heart Association; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; BP, blood pressure. Reproduced with permission from Poole-Wilson.*[21]



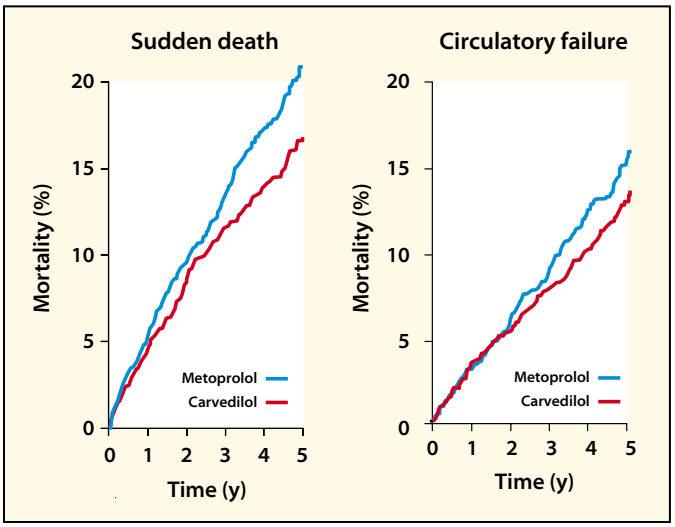


Figure 7. *Sudden deaths and deaths from circulatory failure in the Carvedilol or Metoprolol European Trial. Sudden death: hazard ratio = 0.81 (95% CI 0.677-0.97, P = .0216); circulatory failure: hazard ratio = 0.827 (95% CI 0.673-1.016, P = .0702).*

this agent would be as effective as carvedilol.

Implications of COMET

COMET showed that in symptomatic heart-failure patients, carvedilol compared with metoprolol tartrate effectively reduced annual mortality from 10.0% to 8.3%.[21] This resulted in a prolongation of median survival in this population of 1.4 years. Another way to look at this is that one life would be saved for every 60 patients treated with carvedilol as compared with commonly administered doses of metoprolol tartrate. The results of COMET suggest that the effects of carvedilol beyond those of $ß_1$-blockade were responsible for the favorable effect on survival. Although it is not possible to determine which of the additional properties of carvedilol were responsible for this outcome, it seems unlikely that either the α_1-blocking or antioxidant properties of the drug were responsible. α_1-Blockers alone are not effective therapy for heart failure,[22,23] and the role of antioxidant therapy in treating heart failure (though theoretically appealing) has not been supported by convincing clinical trial results. Additional blockade of the $ß_2$-receptor seems the most likely explanation, but confirmation of that possibility awaits the results of further studies.

The body of information regarding the pharmacologic profile of the ß-blockers and the results of COMET provide useful information to guide the practicing physician in the selection of therapy for treating heart-failure patients. It is clear that ß-blockers are a heterogeneous group of drugs, and the results of clinical trials with 1 agent cannot be generalized to other drugs within the class. Thus, selection of a specific ß-blocker must be based on results from well-designed, large-scale clinical trials that demonstrate efficacy in reducing mortality in heart failure. The 3 ß-

Main Points

- Clinical trial data now confirm that, for the treatment of chronic heart failure, the addition of ß-blocking agents to the standard medical regimen that includes an angiotensin converting enzyme inhibitor will reduce mortality by approximately 35%.
- Beta-blockers are not a homogeneous class of drugs, and important differences in efficacy have been noted between different members of the class.
- First-generation ß-blockers (eg, propranolol) blocked both $ß_1$-and $ß_2$-adrenergic receptors; second-generation ß-blockers (eg, metoprolol and bisoprolol) were designed to be selective for the $ß_1$-adrenergic receptor; third-generation ß-blockers (eg, carvedilol) are agents that have cardiovascular effects in addition to their ß-blocking properties.
- A meta-analysis of four studies in which carvedilol and metoprolol were directly compared demonstrated highly significant differences in the increase in left ventricular (LV) ejection fraction and a strong trend in reduction in LV end-diastolic volume that favored carvedilol.
- The Carvedilol or Metoprolol European Trial (COMET) was designed to compare carvedilol with metoprolol tartrate in a head-to-head fashion. For the primary endpoint of all-cause mortality, carvedilol treatment was associated with a 17% reduction compared with metoprolol; carvedilol was also shown to reduce cardiovascular death by 20%.
- Selection of a specific ß-blocker must be based on results from well-designed, large-scale clinical trials that demonstrate efficacy in reducing mortality in heart failure; the results of COMET indicate that carvedilol is clearly superior to a $ß_1$-blocking drug, metoprolol tartrate.

blockers with which this has been seen are bisoprolol (another ß$_1$-selective agent that has not been approved for treating heart failure in the United States), metoprololol succinate, and carvedilol. The results of COMET indicate that carvedilol is clearly superior to a ß$_1$-blocking drug, metoprolol tartrate. The choice between these drugs is therefore unambiguously in favor of carvedilol. As noted above, studies comparing the effects of other longer-acting ß$_1$-selective agents with carvedilol on relevant clinical endpoints are not available, and at present the efficacy of these drugs compared with carvedilol remains speculative. ■

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