News and Views from the Literature

Heart Failure

Carvedilol Is Superior to Metoprolol for Mortality Reduction in Heart Failure

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Comparison of Carvedilol and Metoprolol on Clinical Outcomes in Patients with Chronic Heart Failure in the Carvedilol Or Metoprolol European Trial (COMET): Randomised Controlled Trial.

Poole-Wilson PA, Swedberg K, Cleland JG, et al.
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Randomized clinical trials have demonstrated that treatment with angiotensin-converting enzyme (ACE) inhibitors reduces hospitalizations and decreases the risk of mortality in patients with chronic heart failure due to systolic dysfunction by 20%–25%.[1] The addition of ß-blocker therapy further reduces mortality by 24%–65%.[1] National guidelines call for all patients with heart failure due to systolic dysfunction to be treated with ß-blocker therapy, in the absence of contraindications or intolerance.[1] Beta-blockers have different pharmacological profiles, which may lead to different clinical outcomes. Metoprolol, bisoprolol, and carvedilol reduced mortality in heart failure, whereas bucindolol had no mortality benefit, and xamoterol increased mortality.[2-6] Metoprolol and bisoprolol have a high specificity for the ß-1 adrenergic receptor. Carvedilol blocks ß-1, ß-2, and α-1 adrenergic receptors. Several small studies have suggested that carvedilol is more effective than metoprolol in reversing ventricular remodeling, increasing left-ventricular systolic function, and decreasing cardiac sympathetic drive.[7] Whether these differences would translate into differences in survival in patients with chronic heart failure was not known.

The Carvedilol Or Metoprolol European Trial (COMET) was designed to compare directly the effects of carvedilol and metoprolol on mortality and morbidity in patients with mild to severe chronic heart failure.[8] The study was conducted in 341 centers in 15 European countries and enrolled 3029 patients with class II to IV heart failure. Patients were randomized to carvedilol (target dose 25 mg twice daily) or metoprolol tartrate (target dose 50 mg twice daily). These doses were chosen because it was expected that they would produce a comparable degree of ß-1 adrenergic blockade in both groups. Mean left-ventricular ejection fraction was 0.26 at baseline; 99% of patients were already taking diuretics and 98% ACE inhibitors or angiotensin-receptor antagonists, with 59% also on digoxin and 11% on spironolactone. The average daily dose of carvedilol in the trial was 42 mg and the average daily dose of metoprolol was 85 mg. Similar reductions from baseline in resting heart rates and blood pressure were observed over the duration of the trial, except for very mild differences in the first few months.

A co-primary endpoint of the trial, all-cause mortality, showed a 17% relative risk reduction with carvedilol rel-

ative to metoprolol. Mortality was reduced from 39.5% with metoprolol to 33.9% with carvedilol (OR, 0.87; 95% CI, 0.74-0.93; P <.0017). The annual mortality rate was reduced from 10% in the metoprolol group to 8.3% in the carvedilol group. The survival advantage with carvedilol translated to a prolongation of median survival by an extra 1.4 years. The co-primary, composite endpoint of all-cause mortality or all-cause hospitalization was not statistically different between the 2 medications. Similar reductions were observed in the risk for sudden death and progressive heart failure deaths with carvedilol. There was no significant heterogeneity in response between clinically relevant subgroups of patients, including men and women, those with and without coronary artery disease, and diabetics and nondiabetics.

The favorable outcome with carvedilol could be attributed to blockade of both ß-1 and ß-2 adrenergic receptors, inhibition of α-1 adrenergic receptors, a greater antiischemic effect, inhibition of apoptosis, or an antioxidant action. This trial convincingly demonstrates that carvedilol produces benefits in patients with heart failure beyond those of ß-1 blockade alone. The calculated number of patient-years of treatment to save one life is 59. While it has been suggested that the use of the metoprolol CR/XL preparation at higher doses may have produced different results, this possibility remains speculative and would need to be demonstrated in a prospective, randomized mortality trial. COMET has clearly demonstrated the superiority of carvedilol for the treatment of chronic heart failure. Every effort should be made to translate this significant research finding into routine clinical practice and ensure that patients with systolic-dysfunction heart failure are treated with carvedilol, in the absence of contraindications or intolerance. ■

References

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Cardiomyopathy

Feasibility and Safety of Skeletal Myoblast Transplantation

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Autologous Skeletal Myoblast Transplantation for Severe Postinfarction Left Ventricular Dysfunction

Menashe P, Hagege A, Viliquin JT, et al.

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Menashe and coworkers report the clinical outcome of a phase I study to assess the feasibility and safety of autologous skeletal myoblast transplantation in patients with severe ischemic cardiomyopathy.

Ten patients with left ventricular (LV) systolic dysfunction with an ejection fraction of less than 35% were recruited for the study. The patients all had LV scar documented by the use of low-dose dobutamine and positron emission tomography and were undergoing coronary artery bypass surgery to the non-scar areas.

Ten to 15 g of vastus lateralis muscle was removed and digested using collagenase and trypsin. After a mean period of 16 days of expansion, 871×10^6 cells in 5.7 mL of saline were injected over 37 sites throughout the scar area. Two bypass grafts were done in all but 1 patient. One patient died before cardiopulmonary bypass was initiated. The rest of the patients were followed for an average of 10.9 months (range, 5 to 17.5 months).

The major adverse event was the development of ventricular tachycardia in 4 patients 11 to 22 days after transplantation. All 4 received an automatic implantable cardioverter-defibrillator (AICD). However, the recurrence of AICD-triggered shock was rare after implantation.

LV function improvement can be distinguished in those segments injected with cells and those segments that were bypassed. Fourteen of 22 (63%) transplanted segments improved (6 of 8 patients). Twenty-six noninjected but bypassed segments also improved. The overall ejection fraction improved from 23.8% to 32.1%, and the NYHA class improved from 2.7 to 1.6. One patient died subse-