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CLINICAL UPDATE

Beta-blockers in severe congestive heart failure

Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651-8.

Background: Earlier trials of β-blockers (carvedilol,[1] metoprolol[2] and bisoprolol[3]) have shown a favourable effect on mortality and hospital admission rates among patients with mild to moderate (New York Heart Association [NYHA] class II or III) congestive heart failure (CHF). Whether this effect extends to patients with severe CHF (NYHA class IV) is unknown.

Question: In patients with severe CHF does carvedilol, a nonselective β-blocker, reduce the risk of hospital admission and death?

Design: This randomized, double-blind, placebo-controlled trial was conducted in 334 centres in 21 countries.[4] Patients were enrolled if they had ischemic or nonischemic cardiomyopathy and met the study's entry criteria for severe CHF: severe systolic dysfunction (left ventricular ejection fraction [LVEF] less than 25%), and dyspnea or fatigue at rest or with minimal exertion for at least 2 months, while receiving optimal therapy (with diuretics and an angiotensin-converting-enzyme inhibitor or an angiotensin II receptor antagonist). Notable exclusion criteria included severe pulmonary, hepatic or renal disease, CHF secondary to valvular disease, recent coronary revascularization or acute myocardial or cerebral ischemic event, recent use of intravenous vasodilating or inotropic agents, systolic blood pressure less than 85 mm Hg, heart rate less than 68 beats/min and any contraindication to β-blockers.

Patients randomly assigned to the carvedilol group received an initial dose of 3.125 mg twice daily, which was doubled every 2 weeks to a target dose of 25 mg twice daily. Treatment with other agents for CHF (digoxin, hydralazine, nitrates, spironolactone) was allowed at the treating physician's discretion. The primary end point was all-cause mortality, and the secondary end point was the combined risk of death or hospital admission for any reason. All analyses were performed on an intention-to-treat basis.

Results: The trial was terminated early because an interim analysis showed a significant survival benefit in the carvedilol arm. Of the 2289 patients enrolled, 1156 received carvedilol and 1133 placebo. Most (80%) of the subjects were men, and the mean age was 63 years. Ischemic cardiomyopathy was the underlying cause of the CHF in 67% of the patients; the mean LVEF was 20%.

Patients were followed for a mean of 10.4 months, during which all mortality data were captured. In all, 130 patients in the carvedilol group and 190 in the placebo group died, for a relative risk reduction of 35% (95% confidence interval [CI] 19%–48%, $p = 0.00013$). As for the secondary end point, 425 patients in the carvedilol group and 507 taking placebo died or were admitted to hospital, for a relative risk reduction of 24% (95% CI 13%–33%, $p < 0.001$). The favourable effect of carvedilol extended to a prespecified subset of patients judged to be at highest risk and to other subgroups defined by age, sex, LVEF, recent hospital admission and underlying cause of the CHF. Carvedilol was well tolerated, with 65.1% of the patients reaching the target dose by 4 months. The withdrawal rate was significantly lower in the carvedilol group than in the placebo group (14.8% v. 18.5%, $p = 0.02$).

Commentary: Failure of a recent trial of another nonselective β-blocker (bucindolol[5]) to demonstrate benefit in patients with severe CHF raises the possibility that carvedilol's non-β-blocking properties (α-blockade, and antioxidant and anti-endothelin effects) are especially important in patients with severe CHF. Whether these properties render carvedilol superior to other β-blockers should be known once a European trial currently comparing carvedilol and metoprolol in CHF is completed.

Practice implications: The nonselective β-blocker carvedilol is safe, well-tolerated and effective in reducing mortality and hospital admission rates among patients with severe CHF caused by systolic dysfunction. The effect of β-blockers in patients with CHF caused by diastolic dysfunction (normal LVEF) is unknown. — *Donald Farquhar*

The Clinical Update section is edited by Dr. Donald Farquhar, head of the Division of Internal Medicine, Queen's University, Kingston, Ont. The updates are written by members of the division.

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