

Does the choice of β -blocker affect outcome in chronic heart failure?

COMET Investigators. 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. *Lancet* 2003;362:7-13.

Background: Along with diuretics and angiotensin-converting-enzyme (ACE) inhibitors, β -blockers reduce mortality among patients with chronic heart failure. A previous meta-analysis has shown carvedilol to be superior to metoprolol in increasing left ventricular ejection fraction,¹ but the effects on clinical outcomes have been unclear.

Question: Among patients with chronic heart failure who are taking diuretics and ACE inhibitors, is there a difference in clinical outcome between treatment with carvedilol and metoprolol?

Design: This multi-centre double-blind randomized parallel group trial compared the effects of carvedilol and metoprolol on mortality and morbidity among patients with chronic heart failure. Doses were titrated to a target of 25 mg twice daily (carvedilol) and 50 mg twice daily (metoprolol). Enrolled subjects were required to have symptomatic heart failure (New York Heart Association class II-IV), previous hospital admission because of cardiovascular disease and a left ventricular ejection fraction of less than 35%, and to be taking diuretics

and ACE inhibitors if tolerated. Exclusion criteria included any recent changes in treatment or clinical status. Primary end points were all-cause mortality and a composite end point of all-cause mortality and all-cause admission.

Results: Of the 3029 enrolled subjects, 1511 were assigned to receive carvedilol and 1518 metoprolol. The mean study duration was 58 months. The baseline characteristics of the 2 study groups were similar. The all-cause mortality was 34% in the carvedilol group and 40% in the metoprolol group (Table 1). The difference persisted after adjustment for known prognostic factors, and the distribution according to cause of death was similar between the 2 groups. Total admissions did not differ between the 2 groups (hazard ratio 0.97, 95% confidence interval [CI] 0.89 to 1.05, $p = 0.45$); thus, the difference in composite end point was mainly a result of mortality reduction in the carvedilol group. The incidence of side effects and discontinuation of treatment were similar between the 2 groups.

Commentary: This is the first large randomized controlled trial to compare carvedilol and metoprolol directly with respect to clinically important outcomes in patients with chronic heart failure. The absolute risk reduction in mortality over 5 years was 5.7% in the carvedilol group. Interestingly, hospital admission rates did not differ significantly between the 2 groups.

The degree of β -blockade achieved with either drug may have played a role in the study's results. At 4 months, the mean reduction in heart rate was 13.3 beats/min in the carvedilol group and 11.7 beats/min in the metoprolol group (difference -1.6 beats/min, 95% CI -2.7 to -0.6); however, the difference did not exist after 16 months. Although the difference in heart rate may have been statistically significant before 16 months, it is difficult to ascribe the large treatment effect to this modest difference. Indeed, in addition to β_1 -adrenergic blockade, carvedilol differs from metoprolol in that it also blocks the β_2 - and α_1 -adrenergic receptors. The additional sites and modes of action of carvedilol are probably responsible for the differences in outcome.

Practice implications: Previous studies have shown carvedilol to be beneficial in the treatment of chronic heart failure, and trials comparing the effect of carvedilol and metoprolol on cardiac performance^{1,2} have shown carvedilol to be superior. Although β -blockers are known to improve mortality among patients with heart failure, the COMET findings help to refine the choice of drug in this class. Improving global cardiac function for long-term survival requires the optimization of various cardiovascular parameters (cardiac preload, cardiac afterload and myocardial oxygen requirements). When combined with a diuretic and an ACE inhibitor, carvedilol seems to help achieve this end.

Sharon K. Bal

Medical Resident

Department of Family Medicine

University of Ottawa, Ottawa, Ont.

References

1. Packer M, Antonopoulos GV, Berlin JA, Chittams J, Konstam MA, Udelsion JE. Comparative effects of carvedilol and metoprolol on left ventricular ejection fraction in heart failure: results of a meta-analysis. *Am Heart J* 2001;141(6):899-907.
2. Metra M, Giubbini R, Nodari S, Boldi E, Modena MG, Dei Cas L. Differential effects of β -blockers in patients with heart failure. *Circulation* 2000;102:546-51.

Table 1: Outcomes of patients given either carvedilol or metoprolol

Outcome	Treatment group; no. (and %) of patients		Hazard ratio (and 95% CI)	<i>p</i> value
	Carvedilol <i>n</i> = 1511	Metoprolol <i>n</i> = 1518		
All deaths	512 (34)	600 (40)	0.83 (0.74-0.93)	0.002
Cardiovascular deaths	438 (29)	534 (35)	0.80 (0.70-0.90)	0.0004
Composite of all deaths and all admissions	1116 (74)	1160 (76)	0.94 (0.86-1.02)	0.122

Note: CI = confidence interval.