# Carvedilol was more effective than metoprolol tartrate for lowering mortality in chronic heart failure

Poole-Wilson PA, Swedberg K, Cleland JG, et al. **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.

## QUESTION

In patients with chronic heart failure (CHF), what is the comparative effectiveness of carvedilol and metoprolol tartrate on morbidity and mortality?

## DESIGN

Randomized {allocation concealed*}†, blinded {patients, health care providers, data collectors, outcome assessors, data analysts, data safety and monitoring committee, and manuscript writers}†,* controlled trial with mean follow-up of 58 months (Carvedilol Or Metoprolol European Trial [COMET]).

## SETTING

341 centers in 15 European countries.

## PATIENTS

3029 patients (mean age 62 y, 80% men, 99% white) with symptomatic CHF and left-ventricular ejection fraction ≤ 0.35. Patients had ≥ 1 cardiovascular admission in the previous 2 years and were on stable heart failure treatment with angiotensin-converting enzyme inhibitors for ≥ 4 weeks and treatment with diuretics for ≥ 2 weeks. Exclusion criteria included a recent change of treatment; requirement for intravenous inotropic therapy; and use of calcium-channel blockers, amiodarone, class-I anti-arrhythmic drugs, and the investigational drug. Follow-up was 100%.

## INTERVENTION

Patients were allocated to twice-daily target doses of carvedilol, 25 mg (*n* = 1511), or metoprolol tartrate, 50 mg (*n* = 1518).

## MAIN OUTCOME MEASURES

All-cause mortality, cardiovascular mortality, the composite endpoint of all-cause mortality or all-cause admission, and adverse events.

## MAIN RESULTS

Analysis was by intention to treat. Patients who received carvedilol had lower risks for all-cause mortality and cardiovascular mortality than did those who received metoprolol tartrate; however, the carvedilol and metoprolol tartrate groups did not differ for the composite endpoint of all-cause mortality or all-cause admission, or for noncardiovascular mortality (Table). Groups did not differ for adverse events.

## CONCLUSION

In patients with chronic heart failure, carvedilol was more effective than metoprolol tartrate for lowering all-cause mortality and cardiovascular mortality.

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*See Glossary.
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### Carvedilol vs metoprolol tartrate in chronic heart failure at mean 58 months‡

| Outcomes | Carvedilol | Metoprolol tartrate | RRR (95% CI) | NNT (CI) |
|---|---|---|---|---|
| All-cause mortality | 34% | 40% | 14% (5 to 21) | 19 (12 to 46) |
| Cardiovascular mortality | 29% | 35% | 17% (8 to 26) | 15 (10 to 31) |
| All-cause mortality or all-cause admission | 74% | 76% | 3% (−0.9 to 7) | Not significant |
| | | | RRI (CI) | NNH |
| Noncardiovascular mortality | 5% | 4% | 6% (−19 to 34) | Not significant |

‡Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article using Cox proportional-hazards model.

## COMMENTARY

Thanks to the remarkable successes in drug development, a variety of effective treatments are available for most medical conditions. The new challenge is often how to select the optimal therapy. For approval purposes, regulatory agencies require placebo-controlled rather than active-comparison trials. The federally funded ALLHAT represents an important comparative trial of antihypertensives (1). A recently introduced congressional bill calls for more ALLHAT-like comparative trials (2). The financial implications are enormous.

The treatment of CHF is a crowded field with multiple choices, both between and within drug classes. In placebo-controlled trials in heart-failure patients, carvedilol and metoprolol controlled release/extended release (CR/XL) reduce mortality to a similar extent. Thus, an indirect comparison suggests little or no difference between drugs.

The findings of COMET, sponsored by the manufacturer of carvedilol, contradict this expectation, and the investigators conclude that carvedilol extends survival more so than metoprolol. Alternative explanations are possible. The target dose for carvedilol in COMET was the U.S. Food and Drug Administration recommended dose of 25 mg twice daily. The investigators used metoprolol tartrate, 50 mg twice daily, which is not approved for heart failure. The metoprolol dose in COMET was also less than the approved long-acting formulation, metoprolol CR/XL 200 mg daily (equivalent to 130 mg metoprolol tartrate). Mean reductions in heart rate and systolic blood pressure in COMET support the view that the β-blocking effect of the metoprolol dose was less pronounced than that of the carvedilol dose. An editorial by Dargie (3) raised the issue of comparable β-blockade. These and other inconsistencies suggest that the results of COMET are not definitive.

Proper trial design is essential to interpretation of comparative trials. Independence from pharmaceutical sponsors may be important to avoid suboptimal comparators, suboptimal doses, or suboptimal formulations.

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### References

1. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002;288:2981-97.
2. Comparing prescription drugs. New York Times, 27 August 2003. www.nytimes.com/2003/08/27/opinion/27WED3.html.
3. **Dargie HJ.** Beta blockers in heart failure. Lancet. 2003;362:2-3.