Controlled- and extended-release metoprolol reduced mortality in congestive heart failure

MERIT-HF Study Group. **Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF).** Lancet. 1999 Jun 12;353:2001-7.

Question

In patients with symptomatic congestive heart failure (CHF), does controlled- and extended-release (CR-XL) metoprolol used with standard therapy reduce mortality?

Design

Randomized (allocation concealed*), blinded (patients, clinicians, and outcome assessors),* placebo-controlled trial with planned interim analyses.

Setting

313 centers in 13 European countries and the United States.

Patients

3991 patients (mean age 64 y, 77% men) with stable symptomatic CHF for ≥ 3 months (New York Heart Association [NYHA] class II to IV) who were receiving optimal standard therapy. Patients were also required to have had an ejection fraction ≤ 40% within 3 months and heart rate ≥ 68 beats/min. Exclusion criteria were recent myocardial infarction or unstable angina; recent use of, need for, or contraindications to β-blockers; CHF secondary to systemic disease or alcohol abuse; recent or scheduled cardiac surgery; second- or third-degree heart block; hypertension; or use of amiodarone or calcium antagonists, such as diltiazem or verapamil. Other calcium-channel blockers that do not decrease heart rate were allowed. Follow-up was 100%.

Intervention

After a 2-week run-in period, patients were allocated to CR-XL metoprolol (n = 1990) or placebo (n = 2001). Metoprolol was started at 12.5 or 25 mg once per day depending on severity of CHF; it was titrated up to 200 mg once per day in 2-week intervals.

Main outcome measures

All-cause mortality alone or combined with hospitalization.

Main results

The study was stopped early (mean follow-up 1 y vs planned follow-up of 2.4 y) because of reduced mortality at the second interim analysis. Patients in the metoprolol group had lower rates of all-cause mortality (P < 0.001) and mortality from cardiovascular events (P < 0.001), sudden death (P = 0.001), and worsening CHF (P = 0.002) (Table) than did patients in the placebo group. The groups did not differ for the rate of patients who stopped taking study medication (14% for metoprolol vs 15% for placebo, P = 0.4).

Conclusion

Controlled- and extended-release metoprolol reduced mortality at 1 year in patients with congestive heart failure.

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For correspondence: Dr. B. Fagerberg, Wallenberg Laboratory for Cardiovascular Research, Göteborg University, Sahlgrenska University Hospital, SE 413 45 Göteborg, Sweden. FAX 46 31 82 53 30. ■

*See Glossary.

Controlled- and extended-release metoprolol vs placebo for patients with symptomatic congestive heart failure (CHF)†

Mortality at mean 1 y	Metoprolol	Placebo	RRR (95% CI)	NNT (CI)
All-cause	7.2%	10.9%	33.5% (19 to 46)	28 (19 to 54)
Cardiovascular	6.4%	10.2%	37.3% (23 to 49)	27 (19 to 48)
Sudden death	3.9%	6.6%	40.5% (22 to 55)	38 (25 to 77)
Worsening CHF	1.5%	2.6%	42.6% (11 to 63)	90 (50 to 419)

†Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

Commentary

The Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) is the second published trial in the past year that has assessed β-blockade in patients with CHF. The 34% reduction in all-cause mortality in this large trial was consistent with a recent meta-analysis (1) and the Cardiac Insufficiency Bisoprolol Study II (CIBIS- II) (2). The incremental benefits of β-blockade were shown because 90% of patients were also taking angiotension-converting enzyme inhibitors. Patients were mainly in NYHA functional class II or III (96%). CR-XL metoprolol was well tolerated. When titrated up, the mean daily dose was 159 mg, with most patients receiving ≥ 100 mg (87%) and 64% receiving 200 mg. A predefined subgroup analysis according to baseline characteristics showed a consistent reduction in mortality in all groups. The reduction in death from worsening CHF extends the findings of the CIBIS-II trial (2).

Substantial data support the routine use of β-blockers in patients with NYHA class II or III disease. These data come mainly from studies of β_1-selective antagonists (metoprolol or bisoprolol) or nonselective antagonists with α_1-receptor blocker and antioxidant properties (carvedilol). No large trials of patients with CHF have examined the effects of a pure nonselective β-receptor antagonist. Because of the possibility of a difference in effect on mortality between selective and nonselective β-blockers, further studies are needed before a general effect on mortality can be assumed for all β-blockers. Other studies of β-blockade in patients with CHF are also required for those in NYHA class IV or those with preserved left ventricle ejection function.

Robert S. McKelvie, MSc, MD, PhD
Hamilton Health Sciences Corporation
Hamilton, Ontario, Canada

References

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2. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353:9-13.