Controlled and extended release metoprolol reduced death, hospital admissions, and symptoms in chronic heart failure

Hjalmarson A, Goldstein S, Fagerberg B, et al, for the MERIT-HF Study Group. ***Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF).*** *JAMA 2000 Mar 8;**283**:1295–1302.*

QUESTION: In patients with symptomatic chronic heart failure, do controlled and extended release metoprolol succinate (a β-blocker) reduce mortality, hospital admissions, and symptoms?

Design

Randomised (allocation concealed*), blinded (outcome assessor, {patients, and clinicians}†),* placebo controlled trial with a mean follow up of 1 year.

Setting

313 investigational sites in the US and 13 European countries.

Patients

3991 patients (mean age 64 y, 78% men) who had had symptomatic heart failure (New York Heart Association [NYHA] class II to IV) for ≥3 months, a decreased ejection fraction (≤ 0.40), and a resting heart rate ≥68 beats/minute and had received optimal treatment for ≥2 weeks before randomisation. Exclusion criteria included acute myocardial infarction or unstable angina pectoris ≤ 28 days before randomisation, indication or contraindication for β_1-blockers, severe decompensated heart failure, or supine systolic blood pressure <100 mm Hg. Patients with an ejection fraction between 0.36 and 0.40 were excluded if they exceeded 500 yards in a 6 minute walk test. All patients were included in the analysis.

Intervention

Patients were allocated to metoprolol (n=1990) or placebo (n=2001). The dose was started at 25 mg/day (12.5 mg/d for patients with NYHA class III or IV) and doubled every 2 weeks until the target dose of 200 mg/day was reached.

Main outcome measures

All cause mortality or any hospital admission, admission to hospital for worsening heart failure, and change in NYHA class.

Main results

Analysis was by intention to treat. The study was stopped early because interim analysis showed a 34% reduction in mortality. Fewer patients in the metoprolol group than in the placebo group died or were admitted to hospital ($p<0.001$) or were admitted to hospital for worsening heart failure ($p<0.001$) (table). Patients in the metoprolol group were more likely to improve by 1 NYHA class (26% *v* 24%) or 2 NYHA classes (2.6% *v* 1.5%) and were less likely to deteriorate in NYHA class than were patients in the placebo group ($p=0.003$ for trend).

Controlled and extended release metoprolol (Met) v placebo for symptomatic chronic heart failure (HF)‡

Outcomes at mean 1 year	Met	Placebo	RRR (95% CI)	NNT (CI)
All cause death or hospital admission	32%	38%	16% (9 to 23)	17 (12 to 32)
Admission to hospital for worsening HF	10%	15%	32% (19 to 42)	22 (15 to 39)

‡Abbreviations defined in glossary; RRR, NNT, and CI calculated from data in article.

Conclusion

In patients with symptomatic chronic heart failure, controlled and extended release metoprolol reduced mortality, hospital admissions, and symptoms.

*See glossary.

†Information provided by authors.

COMMENTARY

Our understanding of systolic heart failure in the past decade has evolved through a series of models, from cardiorenal (diuretics), to haemodynamic (inotropic and vasodilator treatment), to the more recent neurohormonal model. The earlier models all achieved the basic clinical need of symptomatic relief, but only the neurohormonal model has addressed morbidity and survival benefits. The earlier conceptual models labeled β-blockade as counterintuitive treatment, but β-blockers are now mandated in conjunction with angiotensin converting enzyme (ACE) inhibitors in patients who have chronic heart failure with systolic dysfunction.

Even in the face of overwhelming data supporting the use of β-blockers, it is important to apply clinical caution: β-blockade *must not* be begun in the presence of overtly decompensated heart failure; a "start low and go slow" regimen should be followed; close clinical follow up for signs of decompensation during titration must be maintained; and severe class IV heart failure is usually still a contraindication for β-blockade because of little supportive evidence.

Unlike ACE inhibitors for which a class effect has been shown, different β-blockers still appear to evoke some heterogeneity in their responses. The most validated adrenergic blockers in heart failure include carvedilol, metoprolol CR/XL, and bisoprolol. Little evidence exists for the benefit of other β-blockers in chronic heart failure.

Mandeep R Mehra, MD
Ochsner Medical Institution
New Orleans, Louisiana, USA

Source of funding:
AstraZeneca.

For correspondence:
Dr B Fagerberg,
Wallenberg Laboratory for Cardiovascular Research, Sahlgren-ska University Hospital,
SE-413 45
Gothenburg, Sweden.
Fax +46 31 885747.