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


QUESTION: In patients with symptomatic chronic heart failure, do controlled and extended release metoprolol succinate (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-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 earlier because interim analysis showed a 34% reduction in mortality. Fewer 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).

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

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.

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Outcomes at mean 1 year

<table>
<thead>
<tr>
<th>Outcomes at mean 1 year</th>
<th>Met</th>
<th>Placebo</th>
<th>RRR (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause death or hospital admission</td>
<td>32%</td>
<td>38%</td>
<td>16% (9 to 23)</td>
<td>17 (12 to 32)</td>
</tr>
<tr>
<td>Admission to hospital for worsening HF</td>
<td>10%</td>
<td>15%</td>
<td>32% (19 to 42)</td>
<td>22 (15 to 39)</td>
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</tbody>
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†Abbreviations defined in glossary; RRR, NNT, and CI calculated from data in article.