Authors' objectives
The authors' aim appears to have been to conduct a meta-analysis of randomised trials of beta-blockers versus placebo, to quantify the effects on mortality and morbidity.

Searching
MEDLINE was searched from 1966 to July 2000 using the keywords 'adrenergic beta-antagonists', 'congestive heart failure' and 'trial'; the authors then handsearched the retrieved articles. The bibliographies of four published meta-analyses were examined. The authors state that the Cochrane Library and Web of Science databases were also searched, but no details of the search strategy or years included in the search were given.

Study selection
Study designs of evaluations included in the review
Randomised trials of beta-blockers compared with placebo were included. Trials were excluded if they involved crossover designs or had a follow-up of less than 3 months.

Specific interventions included in the review
Beta-blockers. The intervention group received beta-blockers including metoprolol or bucindolol (up to 200 mg/day), nebivelol, carvedilol (up to 25 mg twice daily), and bisoprolol with or without additional therapy, which could include digitalis, diuretics or angiotensin-converting enzyme inhibitors (with or without an angiotensin-receptor blocker). The control groups received placebo. Trials were excluded if they involved beta-blockers with intrinsic sympathomimetic activity.

Participants included in the review
The study selection required that the included participants had chronic stable congestive heart failure (CHF). Trials were excluded if they included patients admitted with acute myocardial infarction. The participants in the included trials had non-ischaemic cardiomyopathy (4,127 patients) and ischaemic cardiomyopathy (6,005 patients). The trials included 78% men and the mean age ranged from 48 to 67 years. The trial samples typically had less than 5% patients with New York Heart Association (NYHA) class IV disease. Most of the patients were receiving triple therapy for CHF. Trials excluded patients with acute cardiac decompensation, CHF immediately after myocardial infarction, those with contraindications to beta-blockers, or advanced renal or hepatic dysfunction.

Outcomes assessed in the review
The outcomes assessed in the review were overall mortality and hospitalisations for CHF.

How were decisions on the relevance of primary studies made?
The authors do not state who, or how many of the reviewers selected the studies.

Assessment of study quality
The authors appear to have assessed blinding, and the procedure and adequacy of the description of the randomisation process. However, details of what criteria were used are not given. The authors do not state how judgements of validity were made, nor how many of the reviewers performed the validity assessment.

Data extraction
The authors extracted the following data: patient characteristics; beta-blocker used; additional therapy; duration of follow-up; use of a run-in phase and adverse events during this run-in phase; overall mortality and hospitalisations for CHF. The authors do not state how many of the reviewers performed the data extraction.
Methods of synthesis
How were the studies combined?
A Bayesian hierarchical (random-effects) meta-analytic model was used to combine the data. Probability distributions of differences in survival rates were calculated. To estimate the contemporary annual baseline mortality rate among placebo recipients, a separate Bayesian analysis was performed using the three most recent and largest trials. Funnel plots were used to assess publication bias.

How were differences between studies investigated?
The authors compared the numbers of participants recruited by year of publication. Sensitivity analyses were conducted for type of beta-blocker (selective agents versus nonselective agents), to test the effect of adding an unpublished trial, to compare probability density curves for trials published pre- and post-1999, and to assess the effect of adding further unfavourable future or unpublished (hypothetical) trials.

Results of the review
Twenty-two randomised controlled trials with 10,135 patients were included.

The combined odds ratio (OR) for total mortality was 0.65 (95% confidence interval, CI: 0.53, 0.80). Assuming a mortality rate among placebo recipients of 12%, 3.8 lives are saved per 100 patients treated (95% CI: 2.1, 5.3) in the first year of treatment. The probability density curve showed a 99% probability that beta-blockers save at least 2 lives per 100 patients, and an 85% probability that 3 or more lives are saved per 100 patients. Selective agents (predominantly metoprolol and bisoprolol) and nonselective agents (predominantly carvedilol) were associated with reduced mortality: the ORs were 0.67 (95% CI: 0.57, 0.79) and OR 0.52 (95% CI: 0.28, 0.89), respectively.

The OR for hospitalisations for heart failure was 0.64 (95% CI: 0.53, 0.79). Recent trials showed the weighted average of placebo recipients who were hospitalised in the first year of follow-up was 14%. Given this assumption, beta-blockers reduce hospitalisations by 4 patients per 100 treated (95% CI: 2.4, 5.6).

When the results of an unpublished trial of bucindolol (n=2,708) were incorporated, the accumulative mortality OR was 0.72 (95% CI: 0.61, 0.84). Funnel plots did not suggest any publication bias. Adding further (hypothetical trials) involving 2,000 patients with mortality rates of 20 and 10% in the beta-blocker and placebo groups, respectively, beta-blockers would still reduce the OR by 16% (OR 0.84, 95% CI: 0.74, 0.94).

Cost information
None. The authors state that while the cost-effectiveness has not been analysed formally, large treatment benefits and the low cost of beta-blockers indicate that it would be cost-attractive.

Authors' conclusions
Beta-blockers have large beneficial effects on mortality (3.8 lives saved per 100 patients treated) and morbidity (4 fewer hospitalisations per 100 patients treated) in stable patients with NYHA class II or III CHF. This benefit is statistically and clinically significant, and is obtained with selective and nonselective beta-blockers. The role of beta-blockers in patients with NYHA class IV disease is uncertain as evidence is limited. Beta-blockers should be offered to most stable patients with mild to moderate CHF.

CRD commentary
The purpose of the review was clearly presented, as was the search strategy used. Three electronic databases and bibliographies were searched, although details of the search strategy were insufficient to determine whether it was comprehensive. The authors did not state whether they searched for non-English language studies or unpublished material, although an unpublished study was discussed. They did, however, perform a funnel plot analysis and found no suggestion of publication bias.
A validity assessment appears to have been made, although details of this assessment were not given and its results were not used in the discussion. Details of the primary data, data pooling and sensitivity analyses were well presented. The authors noted in the 'Results' section that the average age of the patients included in the trials was younger than is generally seen in routine clinical practice, but they did not mention that this may affect the generalisability of the results to clinical practice. The authors discussed other patient characteristics (e.g. disease severity) and aspects of patients care (e.g. slow titration of beta-blockers) in relation to the difficulty of incorporating these results into clinical practice.

This review appears to have added relevant and useful evidence for the effectiveness of beta-blockers for the treatment of most stable patients with mild to moderate CHF. However, given the difference in age between the patients included in the trials and those seen in usual practice, the authors’ conclusions appear too strong.

**Implications of the review for practice and research**

Practice: Beta-blockers are associated with clinically meaningful reductions in mortality and morbidity in patients with stable CHF, and should be offered to most stable patients with mild to moderate CHF. The role of beta-blockers for NYHA class IV patients is uncertain.

Research: Further randomised trials comparing different beta-blockers are justifiable, but a very large mega-trial is needed to detect clinically significant differences. Meta-analyses using individual patient data may be important.

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