Bisoprolol: a review of its use in chronic heart failure

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Authors' objectives
To discuss the use of oral bisoprolol in patients with chronic heart failure (CHF) associated with systolic dysfunction. This abstract summarises the sections on therapeutic efficacy and tolerability only, although pharmacokinetic data were also given in the review.

Searching
MEDLINE and EMBASE were searched from 1980 to October 2002; AdisBase, a proprietary database of Adis International, was also searched. The terms used were 'bisoprolol', 'heart failure' and 'chronic heart failure'. The bibliographies of identified articles were also checked. Additional data were requested from the company that developed bisoprolol.

Study selection
Study designs of evaluations included in the review
Randomised, double-blind placebo-controlled trials were included.

Specific interventions included in the review
Patients who were given bisoprolol were eligible for inclusion. The included studies had patients given a starting dose of 1.25 mg/day, titrated to 5 or 10 mg/day. In the controlled studies, the controls were given placebo. In these studies the patients continued to use standard treatment (diuretics and angiotensin-converting enzyme inhibitors) during the trials.

Participants included in the review
The inclusion criterion was patients with CHF. The participants in the included studies had heart failure classified as New York Heart Association class III or IV. The participants were both male and female, although the majority were male. The mean ages ranged from 59.6 to 60.9 years.

Outcomes assessed in the review
No criteria for inclusion were stated. The main outcome assessed in the review was all-cause mortality. The secondary end points were hospital admissions, cardiovascular (CV) mortality and adverse events.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity, only that large well-controlled trials with appropriate statistical methodology were preferred.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
A narrative synthesis of the studies was undertaken. For all-cause mortality, the authors cited pooled data from a published meta-analysis of the two included studies.
How were differences between studies investigated?
Differences between the studies were discussed in the text.

**Results of the review**
Two randomised controlled trials (RCT; 3,288 patients) and a published meta-analysis of these two RCTs (see Other Publications of Related Interest) were included.

Bisoprolol reduced all-cause mortality by 29% (P=0.00003) in the published meta-analysis of two trials; no confidence intervals (CIs) were given. The results from the individual trials both showed a beneficial effect, which reached statistical significance in one trial (hazard ratio, HR=0.66, 95% CI: 0.54, 0.81, n=2,647) but not in the other (HR 0.80, 95% CI: 0.56, 1.15, n=641).

One trial reported fewer CV deaths (9% versus 12%) and hospitalisations (33% versus 39%), and a significant reduction in the combined outcome of CV death or CV hospitalisation in patients on bisoprolol compared with placebo. In the meta-analysis of the two trials, no excess of strokes was seen in patients treated with bisoprolol, but the results from the individual studies were inconsistent.

In terms of adverse events, based on one trial, patients on bisoprolol had a higher incidence of bradycardia (15.2% versus 4.5%), dizziness (13.3% versus 9.5%), hypotension (11.4% versus 7.3%) and fatigue (9.3% versus 7.1%). On both trials, treatment withdrawal between the bisoprolol and placebo groups was similar.

**Cost information**
Cost-minimisation and cost-effectiveness models have been developed based on the two large clinical trials. The authors reported that the addition of bisoprolol to standard treatment is a cost-effective option for treating patients with CHF, both from a health service and a societal perspective.

**Authors' conclusions**
The addition of bisoprolol to a treatment regime that contains an angiotensin-converting enzyme inhibitor and a diuretic significantly improves survival and reduces the need for hospitalisation in patients with stable CHF. The authors also concluded that bisoprolol is well tolerated and cost-effective.

**CRD commentary**
This review did not report its methods in sufficient detail for adequate critique. The research question was vague. It is possible that the authors' search missed some papers, as the search terms were very restricted. It is not apparent whether any attempt was made to search unpublished literature, or whether studies in all languages or only English were eligible for inclusion. Furthermore, the authors' stated preference for large well-controlled trials with appropriate statistical methodology implies that the search strategy and selection might not have been systematic.

The reporting of the results did not aid their interpretation, and there was no attempt to quantitatively synthesise the results. In instances where references were made to the published meta-analysis, the results were not always reported with CIs, as would be expected.

The authors' conclusions should be interpreted with caution since, given the methodological limitations of this review, we cannot be sure whether this is a comprehensive review of the literature.

**Implications of the review for practice and research**
Practice: The authors recommended that bisoprolol should be considered a standard treatment when selecting a beta-blocker for use in conjunction with angiotensin-converting enzyme inhibitors and diuretics in patients with stable, moderate to severe CHF.

The authors did not state any implications for further research.
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Other publications of related interest

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.