Should beta blockers remain first choice in the treatment of primary hypertension: a meta-analysis

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CRD summary
This review assessed the use of beta-blockers for treating hypertension. It concluded that beta-blockers lead to an increased risk of stroke compared with other anti-hypertensive drugs and a decreased risk of stroke compared with placebo. Poor reporting of the review process, a limited search, and the lack of a quality assessment make it difficult to assess the reliability of the authors' conclusions.

Authors' objectives
To enlarge the data on atenolol and to analyse the effect of different beta-blockers on stroke, myocardial infarction (MI) and all-cause mortality.

Searching
The Cochrane Library and PubMed were searched for systematic reviews and meta-analyses, which were used as a source of RCTs. PubMed was also searched for additional RCTs. The search terms were reported.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
The included studies were required to use a beta-blocker as a first-line antihypertensive drug in at least 50% of the patients in one treatment group. The beta-blockers included were atenolol, metoprolol, propranolol and oxprenolol. The comparators were other antihypertensive drugs, placebo or no treatment.

Participants included in the review
The inclusion criteria specified that patients should have primary hypertension. The average age of the included patients ranged from 46 to 76 years, and the baseline blood-pressure ranged from 150/87 to 195/102 mmHg.

Outcomes assessed in the review
The outcomes specified by the inclusion criteria were all-cause mortality and/or cardiovascular morbidity. The follow-up periods of the included studies ranged from 2.1 to 10 years.

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.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The relative risks (RRs) of stroke, MI and all-cause mortality were reported in the review.

Methods of synthesis
How were the studies combined?
Studies comparing beta-blockers with other drugs were analysed separately from those comparing beta-blockers with placebo or no treatment. Data were analysed for all beta-blockers and for three subgroups: atenolol, non-atenolol beta-blockers, and mixed beta-blockers and diuretics. The studies were combined using a random-effects model if the P-value from a statistical test of heterogeneity was less than 0.1.

How were differences between studies investigated?
Heterogeneity was assessed statistically using a chi-squared test.

Results of the review
Eighteen studies (n=127,879) were included. Of these, 13 studies (n=105,591) compared beta-blockers with other drugs, and 7 studies (n=27,433) compared beta-blockers with placebo or no antihypertensive treatment; 2 trials had three treatment arms and were included in both analyses.

The risk of stroke was significantly increased by 16% for beta-blockers compared with other antihypertensive drugs (12 studies; RR 1.16, 95% CI: 1.04, 1.3). The risk of stroke was significantly decreased by 19% for beta-blockers compared with placebo (7 studies; RR 0.81, 95% CI: 0.71, 0.93). There was statistically significant heterogeneity between study results for the comparison with other drugs (P=0.02), but not for the comparison with placebo (P=0.23).

The risk of MI was not statistically significantly different for beta-blockers compared with other antihypertensive drugs (12 studies; RR 1.02, 95% CI: 0.93, 1.12) or with placebo (7 studies; RR 0.93, 95% CI: 0.83, 1.05). There was statistically significant heterogeneity between study results for the comparison with other drugs (P=0.04), but not for the comparison with placebo (P=0.85).

In terms of all-cause mortality, the risk of death was not statistically significantly different for beta-blockers compared with other antihypertensive drugs (13 studies; RR 1.03, 95% CI: 0.99, 1.08) or with placebo (7 studies; RR 0.95, 95% CI: 0.86, 1.04). There was no evidence of significant heterogeneity for either comparison (P=0.2 and P=0.13, respectively).

Subgroup analyses.
For the comparison of atenolol with other antihypertensive drugs, the risk of stroke was significantly increased by 26% (6 studies; RR 1.26, 95% CI: 1.15, 1.38); the risk of death was significantly increased by 8% (6 studies; RR 1.08, 95% CI: 1.02, 1.14); and the results for MI were similar to the primary analysis. For the comparisons of atenolol with placebo, and mixed treatments with other drugs, the results for all outcomes were similar to the primary analysis. There were insufficient data to draw conclusions about non-atenolol beta-blockers.

Authors' conclusions
Beta-blocker treatment of patients with primary hypertension was associated with a substantially higher risk of stroke than treatment with other antihypertensive agents.

CRD commentary
The criteria for including studies in the review were clearly defined with respect to the study design, patients, treatments and outcomes. The literature search was limited to an initial search of two databases to identify systematic reviews, rather than a search for primary studies; reviews identified were then used as a source of primary studies. It is therefore difficult to judge the likely yield of the search strategy, as this will primarily depend upon the quality of searching employed by the systematic reviews. One database (PubMed) was then searched to identify any primary studies that had not been identified from the reviews. There were also no details of the search dates and whether any language restrictions were applied, further factors which may limit the yield of searching. Although one additional recently published trial was included, it should be noted that one of the review authors was a coordinator for this trial. It was not reported whether any further attempts were made to locate unpublished results, and publication bias was not assessed. The quality of the included studies was not assessed and details of the methods used to select studies and extract the data were not reported.
There was no information on the doses of the drugs used in the individual studies, or other existing medical conditions which might have affected a patient's risk of cardiovascular events. The analytical methods used in the meta-analyses seemed appropriate. However, poor reporting of the review process, a limited search, and the lack of a quality assessment make it difficult to assess the reliability of the authors' conclusions.

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

Practice: The authors stated that beta-blockers should not remain the first choice in the treatment of primary hypertension.

Research: The authors stated that beta-blockers should not be used as reference drugs in future RCTs of primary hypertension.

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**Other publications of related interest**
These additional published commentaries may also be of interest. Rudd P. Review: beta blockers are less effective than other antihypertensive drugs for reducing risk of stroke in primary hypertension. Evid Based Med 2006;11:85. Rudd P. Review: beta-blockers are less effective than other antihypertensive drugs for reducing risk for stroke in primary hypertension. ACP J Club 2006;144:67.

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the reliability of the review and the conclusions drawn.