Are beta-blockers efficacious as first-line therapy for hypertension in the elderly: a systematic review
Messerli F H, Grossman E, Goldbourt U

Authors' objectives
To assess the antihypertensive efficacy of beta-blockers and their effect on cardiovascular morbidity and mortality, and all-cause mortality in elderly patients with hypertension, compared with diuretics.

Searching
MEDLINE was searched from January 1966 to January 1998 using the following terms: 'hypertension (drug therapy)' and 'elderly', 'aged' or 'geriatric', and 'cerebrovascular' or 'cardiovascular diseases', and 'morbidity' or 'mortality'. In addition, CARDLINE was searched from 1986 to 1997, and the bibliographies of retrieved papers were examined. The search was limited to articles published in the English language.

Study selection
Study designs of evaluations included in the review
The included studies were randomised controlled trials (RCTs) with a duration of at least one year, which evaluated diuretics and beta-blockers as primary treatment strategies, with outcomes reported per study arm.

Specific interventions included in the review
The diuretics studied were thiazide, chlorthalidone, hydrochlorothiazide, triamterene and amiloride hydrochloride. The beta-blockers studied were atenolol, metoprolol and pindolol. The regimens for the control participants were not explicitly described; however, it appears that in some of the diuretics trials, comparison was made with an alternative diuretic, and in other trials, the control groups may have received a placebo. In one trial there was a direct comparison between beta-blockers (atenolol, metoprolol and pindolol) and diuretics (hydrochlorothiazide or amiloride hydrochloride).

Participants included in the review
People aged at least 60 years with hypertension were included. Trials also evaluating treatment in younger participants were included if separate results were available for those patients aged at least 60 years. Trials that limited the selection of participants to those who had previously had a stroke were excluded.

Outcomes assessed in the review
The outcomes assessed were the rate of blood-pressure response to treatment, defined as the percentage of patients that remained on the initial monotherapy throughout the trial, and the rates of morbidity and mortality. Coronary heart disease (CHD) included fatal and nonfatal myocardial infarction, and sudden or rapid cardiac death. Cerebrovascular events included fatal and nonfatal stroke, and transient ischaemic attacks. Cardiovascular mortality included CHD and cerebrovascular mortality, aneurysms, and congestive heart failure. In some studies, part of the information was not assessed or not reported.

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

Assessment of study quality
The authors do not state that they assessed quality.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction. The odds ratios (ORs) were calculated on an intention to treat basis for each trial for the outcomes of cerebrovascular events, stroke mortality, CHD, cardiovascular mortality and all-cause mortality.

Methods of synthesis

How were the studies combined?

Measures of association were combined across the trials using the Mantel-Haenszel pooled chi-square statistic for test of association, as described by Cochran (see Other Publications of Related Interest no.1), with and without the Yates correction for continuity. The associated 90, 95 and 99% confidence intervals (CIs) were calculated according to the method of Mehta et al. (see Other Publications of Related Interest no.2). The ORs were pooled for the outcomes of cerebrovascular events, stroke mortality, CHD, cardiovascular mortality and all-cause mortality. A random-effects model was used to pool the ORs in the case of significant heterogeneity at the 0.10 level.

To evaluate the response rates to treatment, the authors appear to have averaged the rates across the relevant study arms, in order to make an indirect comparison between beta-blockers and diuretics. The latter also appears to be the case for the analysis of measures of association.

How were differences between studies investigated?

Heterogeneity for measures of association was assessed using a test based on the Cornfield-Gart procedure (see Other Publications of Related Interest no.3). Subgroup analyses according to specific diuretics were also undertaken.

Results of the review

Ten RCTs were included. The overall number of participants was 16,164, with 6,152 patients receiving diuretics, 2,065 receiving beta-blockers, and 7,947 receiving placebo.

Based on data from 6 trials (n=4,595) among patients receiving a diuretic as a first drug, approximately 66% were well controlled on monotherapy, and the remaining third required an additional agent. Among 2,040 patients who received beta-blockers as a first drug, less than a third were controlled on monotherapy and about two thirds required a diuretic as a supplement.

Both diuretics and beta-blockers reduced the incidence of cerebrovascular events. Diuretic treatment reduced the odds for cerebrovascular events by 39% (OR 0.61, 95% CI: 0.51, 0.72) and beta-blockers reduced the odds by 26% (OR 0.74, 95% CI: 0.57, 0.98). The odds for stroke mortality were reduced by 33% with diuretics (OR 0.67, 95% CI: 0.49, 0.90) and 24% with beta-blockers (OR 0.76, 95% CI: 0.48, 1.22). The odds for CHD were reduced by 26% with diuretics (OR 0.74, 95% CI: 0.64, 0.85); however, there was no reduction with beta-blockers (OR 1.01, 95% CI: 0.80, 1.29). Diuretic treatment reduced the odds for cardiovascular mortality by 25% (OR 0.75, 95% CI: 0.64, 0.87), whilst there was no reduction with beta-blockers (OR 0.98, 95% CI: 0.78, 1.23). All-cause mortality was reduced by diuretic therapy (OR 0.86, 95%: CI 0.77, 0.96) but not by beta-blockers (OR 1.05, 95% CI: 0.88, 1.25).

Subgroup analyses for all-cause mortality, based on the comparison between beta-blockers and specific diuretics, showed the following:

for comparison with thiazides only (30 deaths among 661 patients), the OR was 0.89 (95% CI: 0.42, 1.89); for comparison with thiazides with potassium-sparing diuretics, the OR was 0.86 (95% CI: 0.73, 1.03); and for comparison with chlorthalidone, the OR was 0.85 (95% CI: 0.74, 0.99).

Authors’ conclusions

In contrast to diuretics, which remain the standard first-line therapy, beta-blockers should no longer be considered appropriate first-line therapy of uncomplicated hypertension in the elderly hypertensive patient, until proven otherwise.
The research question, and the selection criteria for the primary studies, were described clearly. The search strategy was limited to two databases and scrutiny of retrieved bibliographies. It is possible that further relevant material may have been identified if other databases had been accessed, relevant journals handsearched, and other experts or researchers in the field contacted. There was no attempt to identify unpublished literature, or to assess the impact of publication bias. There was no reported assessment of the methodological quality of the primary studies.

Some details of the primary studies were tabulated. However, more information would have been useful, particularly relating to the participants' characteristics, the drug dose and regimens, and the treatment of the control groups. The methods used to pool the data were described, but since the authors appear to have used indirect comparisons across the trials, findings from this type of analysis should be interpreted with caution. No details were provided of the review process, i.e. how many reviewers were involved, how decisions about selection were made, and how disagreements were resolved.

The authors' conclusions appear to follow on from the evidence presented, although there was no acknowledgement of the impact of the methodological limitations of this review.

**Implications of the review for practice and research**
The authors did not state any implications for further research.

**Bibliographic details**

**PubMedID**
9634263

**Original Paper URL**
http://jama.ama-assn.org/

**Other publications of related interest**

These additional published commentaries may also be of interest. Carruthers SG. Review: diuretics are more efficacious than b-blockers as first-line therapy for elderly patients with hypertension. Evid Based Med 1998;3:174. Carruthers SG. Review: diuretics are more efficacious than B-blockers as first-line therapy for elderly patients with hypertension. ACP J Club 1998;129:60.

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adrenergic beta-Antagonists /therapeutic use; Aged; Antihypertensive Agents /therapeutic use; Cardiovascular Diseases /mortality /prevention & control; Diuretics /therapeutic use; Humans; Hypertension /drug therapy /mortality; Models, Statistical; Morbidity; Randomized Controlled Trials as Topic

**AccessionNumber**
11998008721
Date bibliographic record published
31/10/1999

Date abstract record published
31/10/1999

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.