Efficacy of angiotensin II receptor antagonists in preventing headache: a systematic overview and meta-analysis
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Authors' objectives
To determine whether angiotensin II receptor antagonists (AIIRAs) reduce the incidence of headaches, and to explore a dose-response relationship.

Searching
MEDLINE, EMBASE, the Cochrane Library, and International Pharmaceutical Abstracts were searched using the following terms: 'candesartan', 'eprosartan', 'irbesartan', 'losartan', 'tasosartan', 'telmisartan' or 'valsartan' for the intervention, and 'headache' 'headache disorders', cluster headaches', 'tension headaches' and 'migraine' to identify trials that had measured headache. The authors do not state the years over which the searches were conducted. The reference lists of the retrieved articles were examined for additional studies, and pharmaceutical manufacturers were contacted for any data that may have been missed.

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

Specific interventions included in the review
Comparisons of any AIIRA with a placebo were included in the review. The included drugs were candesartan (n=1,508), eprosartan (n=695), irbesartan (n=2,843), losartan (n=1,429), tasosartan (n=2,090), telmisartan (n=522) or valsartan (n=3,023). With the exception of losartan 50 mg, which was later chosen as the baseline because it is commonly prescribed, full details of the regimens were not provided.

Participants included in the review
Hypertension and headache. The participants eligible for inclusion were receiving AIIRA treatment for either hypertension or headache and were taking no other antihypertensive agent. No other details of the participants, such as age, gender and disease status, were provided. All the studies included in the review were of patients being treated for mild-to-moderate hypertension.

Outcomes assessed in the review
The incidence of headache was assessed, either as the primary outcome or as an adverse event.

How were decisions on the relevance of primary studies made?
All potential trials were independently reviewed by two of the study authors, and any disagreements were resolved by consensus.

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

Data extraction
The authors stated in the study abstract that two reviewers independently extracted the data from the studies and that any discrepancies were resolved by discussion, although no details on the data extraction methods were provided in the text of the study. The following data were extracted: study; the number of participants; drug used; the length of the study (weeks); and the relative risk (presented as 95% confidence intervals for headache prevention).
**Methods of synthesis**

**How were the studies combined?**

The data were pooled in a meta-analysis. The summary relative risk (RR) and relative risk reduction were calculated using the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest no.1), with the participants classified according to the placebo or treatment group. To examine the dose-response relationship, all the doses for each drug were converted to equipotent doses of losartan 50 mg. The dose equivalency (to losartan) for each drug was then estimated using data from placebo-controlled trials involving each drug. A Bayesian random-effects logistic regression model was fitted to estimate the odds ratio for headache per equivalent dose of losartan. A summary slope was taken to be the mean of the population, from which the study-specific slopes are a random sample. No methods for assessing publication bias were reported.

**How were differences between studies investigated?**

Heterogeneity between study-specific estimates was tested for using the Q statistic, while heterogeneity was examined using the L'Abbe plot (see Other Publications of Related Interest no.2). These analyses were performed using HepiMA software.

**Results of the review**

Twenty-seven RCTs (n=12,110) were eligible for inclusion in the review.

There was a 31% reduction in the risk of headache in patients taking AIIRAs, compared with those taking placebo (RR 0.69, 95% confidence interval, CI: 0.62, 0.76); the test of heterogeneity was negative (p=0.2). The odds ratio for headache per unit dose of losartan was 0.81 (95% CI: 0.68, 0.93).

**Authors' conclusions**

The results of the meta-analysis indicated that AIIRAs reduce the frequency of headache.

**CRD commentary**

The review question and the study selection criteria were clear. The literature search seems reasonably comprehensive, with sources additional to electronic databases being searched. However, it was unclear whether any language restrictions were applied, and the authors neglected to provide the dates over which the search was conducted. The authors did not provide information on whether, or how, validity assessments were carried out. The range of statistical tests employed seemed appropriate, but it was not mentioned whether publication bias was assessed.

It was stated in the study objectives that a dose-response relationship was explored, but the results from this were not included in the study findings. Details of the different drug regimens were not supplied, apart from the stated use of losartan 50 mg as the baseline.

A major limitation of the review is that it is entirely of studies in which AIIRAs were being used to treat hypertension, not headache. In such studies, the definition and reporting of headache are likely to have been inconsistent and incomplete. Therefore, any conclusions drawn about the effectiveness of AIIRAs in the treatment of headache can only be used as a basis for studies in the indication of interest.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors state that a randomised placebo-controlled trial of an AIIRA in patients with migraine is warranted.

**Bibliographic details**

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headache: a systematic overview and meta-analysis. American Journal of Medicine 2002; 112(8): 642-646

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**Other publications of related interest**

This additional published commentary may also be of interest. Bronson DL. Review: angiotensin II receptor antagonists prevent headache in patients with mild-to-moderate hypertension. ACP J Club 2003;138:12.

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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.