The role of angiotensin receptor blockers and/or angiotensin converting enzyme inhibitors in the prevention of atrial fibrillation in patients with cardiovascular diseases: meta-analysis of randomized controlled clinical trials


CRD summary
This review assessed the effects of angiotensin II type-1 receptor blockers and/or angiotensin-converting enzyme inhibitors in the prevention of atrial fibrillation. The authors concluded that treatment with these drugs markedly reduces the risk of development or recurrence of atrial fibrillation. Since this effect was not consistent across the trials, the authors' conclusions may therefore be somewhat optimistic.

Authors' objectives
To assess the effects of angiotensin II type-1 receptor blockers (ARBs) and/or angiotensin-converting enzyme inhibitors (ACEIs) in the prevention of atrial fibrillation.

Searching
MEDLINE (1980 to November 2003), EMBASE (1980 to November 2003), Biological Abstracts (1980 to November 2003), International Pharmaceutical Abstracts (1970 to November 2003), the Cochrane Controlled Trials Register (up to November 2003) and the Science Citation Index (1993 to November 2003) were searched; the search terms were reported. In addition, the references of original articles, review articles and the identified studies were checked, and content experts were contacted.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included; both blinded and non-blinded trials were considered.

Specific interventions included in the review
Studies that compared ARBs and/or ACEIs with placebo or conventional therapy for a duration of at least 12 weeks were eligible for inclusion. Studies with more than one control arm were also included. Studies that involved the co-administration of other investigational agents were excluded. The specific interventions assessed were captopril, enalapril, trandolapril, lisinopril, irbesartan and valsartan. These were compared with placebo, beta-blockers, calcium-channel blockers, diuretics or no additional treatment. The mean follow-up period varied from 0.7 to 6.1 years across the studies.

Participants included in the review
Studies that included participants with cardiovascular disease, hypertension, heart failure, ischaemic heart disease or diabetes mellitus were eligible for inclusion. The mean age of the participants in the included studies ranged from 52 to 80 years.

Outcomes assessed in the review
Studies that assessed the development of new-onset or recurrence of atrial fibrillation after starting treatment, detected by routine electrocardiograph at the end of the trial, were eligible for inclusion.

How were decisions on the relevance of primary studies made?
Three reviewers assessed studies for inclusion. Any differences were resolved by consensus.

Assessment of study quality
The validity of the primary studies was assessed according to the methods of randomisation, and the descriptions of
withdrawals and drop-outs. Two independent reviewers assessed validity. Any disagreements were resolved by consensus or by the involvement of a third reviewer.

**Data extraction**
Two independent reviewers extracted the data. Any disagreements were resolved by consensus or by the involvement of a third reviewer. The odds ratios (OR) and the associated 95% confidence intervals (CIs) were extracted. For studies with more than one control arm, all controls were combined to form one control arm then compared with the ARBs and ACEIs arm.

**Methods of synthesis**
How were the studies combined?
The studies were combined in a meta-analysis using the random-effects model of DerSimonian and Laird. The studies were weighted by the inverse of the variance. Publication bias was not assessed.

How were differences between studies investigated?
Statistical differences between the trials were assessed using the chi-squared test and I-squared statistic. A subgroup analysis of the trials, including patients who were at higher baseline risk, was undertaken to explore any differences in intervention effects between the patient groups.

**Results of the review**
Seven RCTs with a total of 24,849 participants (11,328 active therapy and 13,521 control) were included.

Three RCTs were placebo-controlled with a double-blind design, and four were open label.

There was a significant difference in the development of atrial fibrillation (new-onset or recurrence post-cardioversion) in favour of treatment with ACEIs or ARBs compared with control (OR 0.57, 95% CI: 0.39, 0.82). There was significant heterogeneity across the studies. A subgroup analysis of studies that included higher risk patients (those with left ventricular dysfunction or previous documented atrial fibrillation; n=7,250) showed that there was a significant benefit of treatment with ACEIs or ARBs compared with control (OR 0.42, 95% CI: 0.27, 0.66). Again, there was significant heterogeneity across the trials.

**Authors' conclusions**
treatment with ACEIs or ARBs markedly reduces the risk of development or recurrence of atrial fibrillation.

**CRD commentary**
The review question was clearly defined in terms of the interventions, participants, outcomes and study designs. Several sources were searched for relevant studies, but it was unclear whether any language restrictions were applied. Efforts were made to minimise reviewer bias and errors in the review process. No details of the primary studies were presented, which makes it impossible for the reader to judge whether the authors' results and conclusions are consistent with the evidence reviewed. The pooling of studies in a meta-analysis might not have been appropriate given the significant differences between the trials. However, some efforts were made to explore these differences in a subgroup analysis that included the trials of patients at higher risk. Overall, there is some evidence that ACEIs or ARBs reduce the risk of development or recurrence of atrial fibrillation, but this effect was not consistent across the trials. The authors' conclusions may therefore be somewhat optimistic.

**Implications of the review for practice and research**
Practice: The authors stated that treatment with ACEIs or ARBs reduces the risk of development or recurrence of atrial fibrillation in patients with cardiovascular disease.
Research: The authors stated that new trials should include the development of atrial fibrillation as an outcome or at least a secondary end point.

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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.