Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis

CRD summary
This review assessed angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers for the prevention of atrial fibrillation. The authors concluded that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers appear to reduce atrial fibrillation, but the results differed amongst studies. An inadequate validity assessment and the combining of studies using different comparator treatments limits the robustness of the evidence.

Authors' objectives
To assess angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) for the prevention of atrial fibrillation (AF), and to identify which subgroups of patients are most likely to benefit.

Searching
MEDLINE and EMBASE were searched from 1980 using the reported search terms. The reference lists of identified papers and published reviews were screened. Abstracts from meetings of four named associations or societies over the past 4 years were also scanned. Only studies reported in the English language were eligible.

Study selection
Study designs of evaluations included in the review
Parallel-group randomised controlled trials (RCTs) were eligible for inclusion. The mean duration of follow-up ranged from 42 days to 6.1 years.

Specific interventions included in the review
Studies that compared ACEIs or ARBs with an alternative treatment were eligible for inclusion. The included studies of ACEIs used lisinopril, enalapril, trandolapril and captopril; the included studies of ARBs used candesartan, irbesartan, valsartan and losarten. The control interventions appeared to include beta-blockers, diuretics, calcium-channel blockers and placebos.

Participants included in the review
Inclusion criteria were not defined in terms of the participants. The included studies were in individuals with hypertension, post myocardial infarction (MI) with and without left ventricular (LV) dysfunction, heart failure, and following cardioversion for AF. In the included studies, the LV ejection fraction (LVEF) ranged from 27 to 64 (reported in 6 studies) and the rate of AF in the control groups ranged from 2 to 64%.

Outcomes assessed in the review
Studies that assessed new or recurrent AF were eligible for inclusion. The included studies used different definitions of AF and different methods to diagnose AF: the methods ranged from an electrocardiogram once a year to extensive investigations, including daily event recording using Holter for 24 hours at 1, 6 and 12 months.

How were decisions on the relevance of primary studies made?
Two reviewers independently evaluated titles and two blinded reviewers independently selected studies. Any disagreements were resolved by consensus.

Assessment of study quality
The studies appear to have been assessed for blinding of the outcome assessment. The authors did not state how the validity assessment was performed.
**Data extraction**

The data were independently extracted in duplicate and any disagreements were resolved through consensus. For each treatment arm in each study, the numbers of patients with AF were extracted. Data were extracted for all patients in factorial studies. The authors of studies of ACEIs and ARBs that did not report data for AF were contacted for this information.

**Methods of synthesis**

How were the studies combined?

Pooled relative risk reductions (RRRs) with 95% confidence intervals (CIs) were calculated using a random-effects model (DerSimonian and Laird); the studies were weighted by the sample size. For the main meta-analysis, single-centre data for the occurrence of AF were used from one study that also reported results for hospitalisations due to AF. The potential for publication bias was assessed by considering the effect size in relation to the sample size.

How were differences between studies investigated?

Statistical heterogeneity was assessed using the chi-squared test. Separate meta-analyses were performed for ACEIs and ARBs separately, and for subgroups of studies of patients with different medical conditions (heart failure, hypertension, AF and post MI). The meta-analysis was repeated using data for hospitalisations due to AF for one study that also reported results for AF. Differences between the studies, with respect to duration of follow-up, study size and methods used to document AF, were also considered.

**Results of the review**

Eleven RCTs with a total of 56,308 patients were included.

In terms of study quality, in 7 studies the outcomes were assessed by blinded investigators; some other studies assessed outcomes by events committees.

ACEIs and ARBs significantly reduced the relative risk of developing AF compared with control by 28% (95% CI: 15, 40, p=0.0002). Statistically significant heterogeneity was found (p=0.0002).

ACEIs and ARBs reduced AF by a similar amount: 28% (95% CI: 7, 44, p=0.01) for ACEIs and 29% (95% CI: 16, 40, p=0.0002) for ARBs. Statistically significant heterogeneity was found for both meta-analyses (both p<0.00001).

Treatment effects by medical condition.

Post MI (2 studies): the results were mixed. One study of patients with LV dysfunction found a significant reduction in AF with trandolapril for up to 4 years (RRR 0.52, 95% CI: 0.31, 0.87). The larger study, in patients with no heart failure, found no significant reduction in the risk of AF with 6 weeks of lisinopril compared with control (RRR 0.92, 95% CI: 0.83, 1.02).

Heart failure (4 studies): in patients with heart failure, ACEIs and ARBs significantly reduced the risk of AF by 44% (95% CI: 15, 63, p=0.007). All studies showed a significant reduction in AF but statistically significant heterogeneity was found (p=0.002).

In 3 studies the RRR appeared to increase with the severity of LV dysfunction: the RRR was 78% for 1 study of patients with severely impaired LV function (mean LVEF 26.7%), 23% for 1 study with mean LVEF 28%, and 18% for 1 study with mean LVEF 39%. The other study found a similar RRR in AF in patients with normal and impaired LV function.

Hypertension (3 studies): there was no significant reduction in AF with ACEIs and ARBs in patients with hypertension (RR 0.88, 95% CI: 0.66, 1.19, p=0.4). Statistically significant heterogeneity was found (p=0.001). Only the study of ARBs in patients with LV hypertrophy showed a significant reduction in the risk of AF.

Secondary prevention of AF after cardioversion (2 studies): most patients had hypertension and unimpaired LV function. There was a significantly reduction in AF with AECIs and ARBs in patients following cardioversion (RRR
48%, 95% CI: 21, 65). Neither study was placebo controlled.

Publication bias: the 5 smallest studies found the largest effect sizes but no negative small studies were found; this suggested the possibility of publication bias.

**Authors' conclusions**
ACEIs and ARBs appeared to produce a clinically significant reduction in AF, but the results differed amongst studies. Reductions appeared to be present only for patients with systolic LV dysfunction or LV hypertrophy. Further research to assess the potential benefits following cardioversion is required.

**CRD commentary**
This review addressed a clear question that was defined in terms of the intervention, outcomes and study design; inclusion criteria for the participants were not defined. Several relevant sources were searched and attempts were made to locate unpublished studies, thus limiting the possibility of publication bias; the authors also discussed the possibility of publication bias. No attempts were made to minimise language bias. Methods were used to minimise reviewer errors and bias in the study selection and data extraction processes. The validity assessment appears to have been restricted to an assessment of blinding of the outcome assessment. Any synthesis based on studies with an inadequate validity assessment may not be reliable. There was some information on the included studies, but the control interventions used in individual studies were not described clearly. Statistical heterogeneity was assessed but the studies were pooled regardless of the comparator treatment; the authors acknowledged that this might have influenced the results, but meta-analyses for active drugs compared with placebo were not reported. Some potential sources of heterogeneity were examined. Overall, the authors' cautious conclusions appear to be supported by the review.

**Implications of the review for practice and research**
Practice: The authors stated that it is too early to recommend ACEIs or ARBs solely for the prevention or treatment of AF.

Research: The authors stated that the need for further research to assess the effects of ACEIs and ARBs in patients with AF, and to determine how these drugs reduce AF recurrent and cardiovascular events. They also recommended further research to assess the potential benefits following cardioversion. The authors stated that further information may become available when the results of 4 ongoing trials are reported.

**Bibliographic details**

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Other publications of related interest
This additional published commentary may also be of interest. Karthikeyan VJ, Lip GY. Review: angiotensin converting enzyme inhibitors and angiotensin receptor blockers prevent atrial fibrillation. Evid Based Med 2006;11:15.
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MeSH
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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.