The role of renin-angiotensin system blockade therapy in the prevention of atrial fibrillation: a meta-analysis of randomized controlled trials


CRD summary
The review concluded that there was a significant effect of renin-angiotensin-aldosterone system blockade on the prevention of atrial fibrillation, but there was substantial variation across included trials. This variation among trials, along with their uncertain quality, means that caution is warranted when interpreting the authors’ conclusions.

Authors’ objectives
To evaluate the effect of renin-angiotensin-aldosterone system blockade therapy (angiotensin-converting enzyme inhibitors and/or angiotensin-receptor blockers) on the prevention of atrial fibrillation.

Searching
EMBASE, MEDLINE, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to December 2009 for articles published in English or Chinese. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) of patients treated with an angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers for at least 24 weeks were eligible for inclusion. Control groups could receive placebo or another conventional treatment. Trials of more than one angiotensin-receptor blocker or angiotensin-converting enzyme inhibitor or containing co-administration of other drugs were included. Trials had to provide data on the prevention of atrial fibrillation.

In included trials, the angiotensin-converting enzyme inhibitors studied were captopril, enalapril, lisinopril, perindopril, ramipril or trandolapril; angiotensin-receptor blockers included candesartan, irbesartan, losartan, telmisartan or valsartan. Control groups received placebo, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers.

Participants included patients with diagnosed atrial fibrillation and patients without atrial fibrillation. Most trials diagnosed atrial fibrillation by electrocardiograph and/or 24-h holter at specific time points after randomisation; in some trials, participants were required to undergo the assessment at any time they experienced symptoms of atrial fibrillation.

Two reviewers independently performed study selection; disagreements were resolved by consensus or consultation with a third reviewer.

Assessment of study quality
Trial quality was assessed using the Cochrane risk of bias assessment tool, which assessed blinding, allocation concealment, randomisation, selective reporting, incomplete outcome data, and other biases.

The authors did not state how many reviewers were involved in quality assessment.

Data extraction
Data were extracted on risk of atrial fibrillation and used to calculate odds ratios (ORs), with 95% confidence intervals (CIs). Analyses were conducted on an intention-to-treat basis.

The authors did not state how many reviewers were involved in data extraction.

Methods of synthesis
A random-effects meta-analysis was undertaken to calculate pooled odds ratios, and 95% confidence intervals. Statistical heterogeneity was assessed using $X_\text{2}$ and $I^2$.
Subgroup analysis was assessed on the basis of drug. Post hoc analyses were performed on the basis of atrial fibrillation population, use of amiodarone, and left ventricular ejection fraction. Sensitivity analyses were performed by excluding one trial at a time, and excluding smaller trials. Bayesian meta-analysis was used to assess the effects of angiotensin-receptor blockers versus angiotensin-converting enzyme inhibitors.

Publication bias was assessed using funnel plot and Egger's regression.

**Results of the review**

Twenty-eight trials were included in the review (n=102,365 participants). Twenty-five trials compared patients using angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker with those who did not (n=80,524 patients). Five trials compared patients using angiotensin-converting enzyme inhibitors with patients using angiotensin-receptor blockers (n=21,841 patients). Quality assessment indicated that all of the trials were randomised, and over half were double blind. In most trials, atrial fibrillation was measured using a defined diagnostic tool.

There was a statistically significant lower risk of atrial fibrillation in patients who used angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker users (OR 0.65, 95% CI 0.55 to 0.76; I²=78%; 23 RCTs) compared with patients who did not use these drugs. Subgroup analysis revealed that results were still statistically significant for trials of patients who used angiotensin-receptor blockers alone and angiotensin-converting enzyme inhibitors alone.

Bayesian meta-analysis of trials of angiotensin-converting enzyme inhibitors versus angiotensin-receptor blockers indicated that there was no statistically significant difference between the two for the risk of atrial fibrillation. Post hoc subgroup analyses revealed that results were most statistically significant in the atrial fibrillation population (OR 0.45, 95% CI 0.31 to 0.65; I²=76%; 12 trials) and with the addition of amiodarone (OR 0.35, 95% CI 0.26 to 0.48; I²=0%; seven trials). Subgroup analyses showed that results were only significant in patients with a left ventricular ejection fraction below 40% (OR 0.60, 95% CI 0.48 to 0.75; I²=0%; two trials); results were not statistically significant in patients with left ventricular ejection fraction over 40%.

Sensitivity analysis revealed similar results.

There was no evidence of publication bias.

**Authors' conclusions**

There was a significant effect of renin-angiotensin-aldosterone system blockade on the prevention of atrial fibrillation, but there was significant heterogeneity across included trials.

**CRD commentary**

Inclusion criteria for the review were clearly defined. Several relevant data sources were searched. There was the potential for language bias, as only English and Chinese language articles were included. Publication bias was assessed and was not detected. Attempts were made to reduce reviewer error and bias during study selection, but it was not clear if such methods were used for data extraction and quality assessment.

Quality assessment was undertaken using a standard tool, although full details were not presented, which made it difficult to determine the quality of included trials. Trials were pooled using random-effects meta-analysis and statistical heterogeneity was assessed, which was appropriate. There was evidence of substantial heterogeneity in many of the analyses, even when a random-effects analysis was used; this limited the reliability of pooled results.

Substantial heterogeneity and uncertainties regarding trial quality means that caution is warranted when interpreting the authors’ conclusions.

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

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

**Research:** The authors stated that there is a need for further randomised controlled trials to confirm the results of this
meta-analysis.

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