Renin-angiotensin system modulators modestly reduce vascular risk in persons with prior stroke

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CRD summary
This review found that treatment with renin-angiotensin system modulators had significant but modest effects on the risk of future stroke events in patients with prior strokes. The review was well conducted and the authors' conclusions are likely to be reliable.

Authors' objectives
To evaluate the efficacy of the renin-angiotensin system modulators angiotensin-converting enzyme inhibitors and angiotensin receptor blockers to reduce future vascular events for patients with prior stroke.

Searching
PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) were searched without language restriction to March 2011 for relevant studies; search terms were reported. The reference lists of relevant trials and recent review articles were checked for additional studies.

Study selection
Randomised controlled trials of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with a prior stroke or transient ischaemic attack were eligible for inclusion. Eligible trials were required to have a follow-up duration of at least six months and have the total patients and the number of future vascular events or recurrent stroke reported separately for the intervention and control groups. Studies that examined the efficacy of the interventions within 48 hours of an acute initial stroke, or if either of the interventions under study were used in the control groups were excluded from the review.

Some included patients presented with hypertension, cardiovascular disease and a prior stroke. The mean age of the patients ranged from 63.9 years to 76.4 years, and the time period from the initial stroke to enrolment in the trials ranged from three to 60 months. Comparisons were also made between the renin-angiotensin system modulators under study and calcium channel blockers. The primary outcomes was risk of major vascular events (a composite of death from cardiovascular causes, non-fatal stroke, and non-fatal myocardial infarction), and the risk of recurrent ischaemic or haemorrhagic stroke. Secondary outcomes were the risks of major coronary events, total deaths, deaths from cardiovascular causes and hypotension.

Two reviewers performed study selection.

Assessment of study quality
Methodological quality was assessed using the Jadad five-points scale in terms of randomisation, blinding, reporting of losses to follow-up and withdrawals.

The authors did not state how many reviewers assessed methodological quality.

Data extraction
Data were extracted to calculate relative risks for the outcomes with 95% confidence intervals for the estimates. Study authors were contacted for information on subgroups of patients with prior stroke when necessary.

Data were extracted by two independent reviewers; any discrepancies between the reviewers were resolved by a third reviewer.

Methods of synthesis
Pooled relative risks and 95% confidence intervals for the summary estimates were calculated using a Mantel-Haenszel fixed-effect model. The presence of statistical heterogeneity was assessed using $\chi^2$ and $I^2$, where $I^2$ results of less than
40% were regarded as not significant, and $I^2$ scores of more than 74% were indicative of significant statistical heterogeneity. Sensitivity analyses were undertaken to explore the strength of the findings and subgroup analyses were conducted to explore the effects of clinical characteristics including study population, active treatment agent, comparator agent mean age at entry and the presence of hypertension at study entry. The potential for publication bias was assessed using visual appraisals of funnel plots.

**Results of the review**

Eight randomised controlled trials (29,667 patients, range 194 to 20,332) were included in the review. Five studies were allocated Jadad scores of five points, one study was given a score of four points and two studies received Jadad scores of three points.

Treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was associated with statistically significant reductions of the risk of future major vascular events (RR 0.91, 95% CI 0.87 to 0.97; seven trials; $I^2=61\%$) and recurrent stroke (RR 0.93, 95% CI 0.86 to 0.99; eight trials; $I^2=6\%$). Exclusion of the smallest study from the analysis of future major vascular events continued to show a significant result indicating benefits of the intervention (RR 0.92, 95% CI 0.87 to 0.97), but statistical heterogeneity was not significant ($I^2=41\%$). A borderline significant benefit was also observed with renin-angiotensin system modulators compared to calcium channel blockers in reducing the risk of major vascular events (RR 0.89, 95% CI 0.80 to 1.00, three trials; $I^2=58\%$), but there were no differences between the interventions and calcium channel blockers for recurrent strokes.

Treatment with renin-angiotensin system modulators was associated with a statistically significant higher risk of hypotension (RR 1.87, 95% CI 1.61 to 2.17; two trials). There were no significant differences between treatment groups angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and the comparator groups in major coronary events (five trials), death from cardiovascular causes (one trial) and total death (two trials).

The results of the subgroup analyses showed similar patterns of results to the main findings for the primary outcomes of risk of major vascular events and recurrent stroke.

The results from the visual appraisals of the funnel plots showed no evidence of publication bias.

**Authors’ conclusions**

Treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers had clear effects of reducing vascular risks in patients with prior strokes; however the effects observed were modest.

**CRD commentary**

The review addressed a clear question and criteria for the inclusion of studies were stipulated. Two appropriate databases were searched for relevant studies without language restrictions and some attempt was made to identify unpublished studies. The potential for publication bias was examined, but there were not enough studies to studies to validate the tests. Steps were taken to minimise reviewer error and bias for the selection of studies and data extraction, but were not reported for the assessment of methodological quality.

The authors’ decision to combine the results in a meta-analysis appeared justified and potential sources of heterogeneity were explored using appropriate sensitivity and subgroup analyses. Some limitations of the review were acknowledged by the authors including the use of subgroups of patients from some studies, and the lack of generalisation of the results to patients with acute stroke.

In general, the review was well conducted and the authors’ conclusions are likely to be reliable.

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

**Practice:** The authors stated that treatment with renin-angiotensin system modulators could be a reasonable add-on therapy in the sub-acute or chronic stage after a stroke if there were no contraindications for treatment.

**Research:** The authors stated that more randomised controlled trials that enrolled solely patients with a history of stroke were required, and that patient-level pooled analysis may determine the effects of the interventions on lowering blood pressure in particular subgroups according to smoking status, sex, race and time from stroke to use of renin-angiotensin system modulators.
Funding
None.

Bibliographic details

PubMedID
22052520

DOI
10.1161/STROKEAHA.111.632596

Original Paper URL
http://stroke.ahajournals.org/content/43/1/113.abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Angiotensin Receptor Antagonists /therapeutic use; Angiotensin-Converting Enzyme Inhibitors /therapeutic use; Cardiovascular Diseases /drug therapy /prevention & control; Humans; Randomized Controlled Trials as Topic; Renin-Angiotensin System /drug effects; Secondary Prevention; Stroke /drug therapy /prevention & control

AccessionNumber
12012002075

Date bibliographic record published
21/11/2012

Date abstract record published
12/04/2013

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.