Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors or angiotensin II-receptor blockers for ischemic heart disease


CRD summary
The authors concluded that ACE inhibitors can improve rates of mortality and myocardial infarctions in patients with stable ischaemic heart disease and preserve left ventricular function. Combination therapy was no better than ACE inhibitor therapy alone, and can increase harms. The conclusion appeared to underestimate the reported harms associated with ACE inhibitors, therefore, its reliability in practice is unclear.

Authors' objectives
To compare the benefits and harms of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II-receptor blockers (ARBs) or combination therapy in adults with stable ischaemic heart disease and preserved ventricular function.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched. Search dates spanned from 1966 to July 2009. Search terms were reported. There were no language restrictions. Manual searches were performed using trials or reviews and major cardiology meeting abstracts (American Heart Association, American College of Cardiology and European Society of Cardiology) from June 2006 to July 2009. Clinical trial registry websites were searched to identify ongoing and unpublished trials.

Study selection
Randomised controlled trials (RCTs) of standard medical therapy with added ACE inhibitor or ARB therapy compared with placebo or active control, or with added combination ACE inhibitor and ARB therapy with either agent alone, were eligible for inclusion in the review. The eligible population comprised at least 75 patients with stable ischaemic heart disease and preserved left ventricular function (average ejection fraction in the experimental group of >0.40 or no systematic evaluation of left ventricular ejection fraction but exclusion of patients with signs or symptoms of heart failure). Follow-up had to be at least six months. Trials needed to report at least one of the following outcomes: total mortality; cardiovascular mortality; nonfatal myocardial infarction; stroke; or a composite measure of cardiovascular mortality, nonfatal myocardial infarction and stroke. RCTs that evaluated harms were included if the above criteria were met and replaced the eligible outcomes with withdrawals due to adverse events, hypotension, syncope or cough. Observational studies of at least 1,000 patients were included if they met the inclusion criteria for interventions and patient characteristics and reported the outcomes that related to harms (stated above).

Where reported, mean age range of included patients was between 57 and 67 years. More than half of patients were men. All participants had some history of diabetes, hypertension, peripheral vascular disease, previous stroke or transient ischaemic attack. The included ACE inhibitors were enalapril, perindopril, ramipril, trandolapril, and zofenopril. The included ARB was telmisartan. Baseline medical therapy varied between trials.

Two independent reviewers selected studies for inclusion.

Assessment of study quality
Two independent reviewers performed the validity assessment. Trials were assessed for adequacy of randomisation, allocation concealment, blinding and use of intention to treat data. Disagreements were resolved through discussion.

Data extraction
Two independent reviewers extracted data to estimate relative risks (RR) and 95% confidence intervals (CI). Disagreements were resolved through discussion. Authors were contacted for additional data (where necessary).

Methods of synthesis
A random-effects meta analysis was conducted where two or more RCTs provided sufficient data for pooling. Analyses involved both pooling results from ACE inhibitor studies with ARB studies and pooling treatments individually. Subgroup analyses were conducted according to type of baseline medical therapy and coronary revascularisation status. Heterogeneity was assessed using the $I^2$ statistic. Publication bias was explored using funnel plots and the Egger test.

**Results of the review**

Forty-four studies were included in the review, including nine RCTs used in the meta-analysis reported below. For the analysis of benefits of ACE inhibitors, most RCTs had adequate randomisation and double blinding and used intention to treat data. The authors stated that it was not possible to assess publication bias.

**Benefits of ACE inhibitors or ARBs:** Pooled analysis showed that when compared to placebo, ACE inhibitors produced a statistically significant reduced risk for total mortality (RR 0.87, 95% CI 0.81 to 0.94, $I^2=0\%$; seven RCTs), cardiovascular mortality (RR 0.83, 95% CI 0.70 to 0.98, $I^2=46\%$; six RCTs), nonfatal myocardial infarction (RR 0.83, 95% CI 0.73 to 0.94, $I^2=31\%$; six RCTs), stroke (RR 0.78, 95% CI 0.63 to 0.97, $I^2=38\%$; seven RCTs) and the composite measure (RR 0.85, 95% CI 0.72 to 1.01; two RCTs). A single RCT of the ARB showed no effect on the risk for total mortality or cardiovascular mortality, but reduced risks for stroke (RR 0.83, 95% CI 0.65 to 1.06) and for the composite measure (RR 0.88, 95% CI 0.77 to 1.00) were observed.

**Harms from ACE inhibitors or ARBs:** Pooled analysis from trials of ACE inhibitors showed that the intervention groups were more likely to withdraw due to adverse events than those in the placebo group (RR 2.30, 95% CI 1.34 to 3.95, $I^2=87\%$; three RCTs). ACE inhibitors also produced an increased risk for syncope (RR 1.24, 95% CI 1.02 to 1.52; two RCTs) and cough (RR 1.67, 95% CI 1.22 to 2.29, $I^2=60\%$; three trials). There was no statistically significant effect of ACE inhibitors on hypotension risk (three RCTs).

**Benefits and harms from combination therapy:** When combination therapy (telmisartan and ramipril) was compared with the ACE inhibitor (ramipril) alone (one RCT), no statistically significant differences were reported for total mortality, cardiovascular mortality, total myocardial infarctions, stroke or the composite measure. Combination therapy was associated with a higher rate of study discontinuation (p<0.001) and discontinuation due to hypotension (p<0.001) and syncope (p<0.03).

Subgroup analyses revealed a positive effect of ACE inhibitors in terms of more reduced event rates in those who did not receive antiplatelet therapy (p<0.003) and in those without previous coronary revascularisation (p=0.078).

**Authors’ conclusions**

Adding an ACE inhibitor to standard medical therapy improved outcomes, including mortality and myocardial infarctions, in some patients with stable ischaemic heart disease and preserved left ventricular function. Combination therapy was no better than ACE inhibitor therapy alone, and can increase harms. Data were insufficient to adequately assess the benefits of ARBs.

**CRD commentary**

The review addressed a clear question and was supported by detailed inclusion criteria. The search strategy included some relevant sources. Attempts were made to minimise the effects of language and publication biases. The processes of study selection, data extraction and validity assessment were conducted with adequate attempts to minimise reviewer error and bias. The applied validity assessment criteria were appropriate for the included study design; however, the results of this appeared to be reported sporadically. The chosen method of synthesis appeared to be suitable in the presence of statistical heterogeneity, although this variation was not explored further. This was a largely well-conducted review and the authors conclusion reflected the evidence in terms of the efficacy of ACE inhibitors, but appeared to underestimate the associated harms, so the extent to which the conclusion should be relied upon in practice is unclear.

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

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

**Research:** The authors stated that further trials were needed to define the role of ARBs in adults with stable ischaemic heart disease and preserved ventricular function.
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