Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158,998 patients

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CRD summary
The review concluded that treatment with angiotensin-converting enzyme inhibitors resulted in a significant further reduction in all-cause mortality in patients with hypertension. The authors’ conclusions were based on the evidence and seem reliable but the unclear quality of the evidence base should be considered when interpreting the review.

Authors’ objectives
To determine the effects of renin-angiotensin-aldosterone system inhibitors, angiotensin-converting enzyme inhibitors and AT1 receptor blockers on all-cause mortality in patients with hypertension.

Searching
MEDLINE and Web of Science were searched between January 2000 and March 2011 for articles published in English. Search terms were reported. Abstract listings of six conferences, including the American Heart Association and the American College of Cardiology, were searched. Reference lists of relevant articles were searched.

Study selection
Randomised controlled trials (RCTs) of renin-angiotensin-aldosterone system inhibitors, angiotensin-converting enzyme inhibitors or AT1 (angiotensin II type 1) receptor blockers versus control in patients with hypertension were eligible for inclusion. Controls could include active control, usual care or placebo. The primary end-point was all-cause mortality. Trials in which patients were selected because of a specific disease (such as heart failure, acute coronary syndromes, acute stroke, haemodialysis, atrial fibrillation) or post-cardiac surgery were excluded. Trials with fewer than 100 patients or a low incidence (less than 10 events) of all-cause mortality were excluded.

The included trials studied various drugs including losartan, irbesartan, lisinopril, enalapril, candesartan, valsartan, eprosartan and telmisartan. Control groups also varied widely and included placebo, amlodipine, nifedipine, atenolol and diuretic. The proportion of patients with hypertension ranged from 68.7% to 100% (mean 91%). Baseline systolic blood pressure ranged from 135 to 182 mmHg (mean 153 mmHg). The mean age of patients ranged from 58.9 to 83.8 years. The proportion of male patients varied from 35.5% to 80.2%. Trials were published between 2001 and 2010.

Two reviewers undertook study selection.

Assessment of study quality
The authors did not state whether they assessed trial quality.

Data extraction
Two reviewers independently extracted data on all-cause mortality and cardiovascular mortality and used these data to calculate hazard ratios (HR) and 95% confidence intervals (CI).

Methods of synthesis
Random-effects meta-analysis was used to calculate pooled hazard ratios and 95% CI. Statistical heterogeneity was assessed using I² and Cochran Q statistics. Publication bias was assessed using funnel plots and Egger’s test. Subgroup analysis was undertaken on the basis of class of drug. Meta-regression was used to assess the influence of patient and study characteristics on outcomes.

Results of the review
Twenty RCTs were included in the review (158,998 patients, range 1,283 to 33,357). Mean length of follow-up ranged from 1.12 to 6.10 years.
Compared with control, renin-angiotensin-aldosterone system blockade was associated with a statistically significant decrease in all-cause mortality (HR 0.95, 95% CI 0.91 to 1.00; 20 RCTs; I²=15%) and cardiovascular mortality (HR 0.93, 95% CI 0.88 to 0.99; 16 RCTs; I²=23%).

Subgroup analysis indicated that angiotensin converting enzyme inhibitors were associated with statistically significantly lower all-cause mortality (HR 0.90, 95% CI 0.84 to 0.97; seven RCTs) and cardiovascular mortality (HR 0.88, 95% CI 0.77 to 1.00; seven RCTs) compared with control. AT1 receptor blockers were not associated with a statistically significant difference in all-cause mortality or cardiovascular mortality.

Meta-regression indicated a significant difference in outcomes on the basis of baseline systolic blood pressure between trials and in terms of blood pressure between intervention and control group. There was no evidence of publication bias.

Authors’ conclusions
Treatment with angiotensin-converting enzyme inhibitors resulted in a significant further reduction in all-cause mortality in patients with hypertension.

CRD commentary
Inclusion criteria for the review were defined and several relevant data source were searched. There was potential for language bias as only articles in English were included. There was no evidence of publication bias. Attempts were made to reduce reviewer error and bias throughout the review.

It was unclear whether any form of quality assessment was undertaken and this made it difficult to interpret the reliability of the evidence base. Appropriate statistical techniques were used to pool data. Statistical heterogeneity was reported. The authors acknowledged differences between trials for interventions and patient characteristics and explored these in subgroup analyses and meta-regression. The authors noted that there may have been differences between individual drugs within drug classifications that were not explored in the meta-analysis (statistical tests did not identify any substantial differences).

The authors’ conclusions were based on the evidence and seem reliable but the unclear quality of the evidence base should be considered when interpreting the review.

Implications of the review for practice and research
Practice: The authors stated that the widespread use of angiotensin-converting enzyme inhibitors may result in an important gain in lives saved because of the high prevalence of hypertension.

Research: The authors did not state any implications for research.

Funding
Department of Cardiology, Thoraxcenter, Erasmus, The Netherlands.

Bibliographic details

PubMedID
22511654

DOI
10.1093/eurheartj/ehs075

Original Paper URL
http://eurheartj.oxfordjournals.org/content/33/16/2088.abstract
Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Aged, 80 and over; Angiotensin-Converting Enzyme Inhibitors /therapeutic use; Antihypertensive Agents /therapeutic use; Cause of Death; Female; Humans; Hypertension /drug therapy /mortality; Male; Middle Aged; Randomized Controlled Trials as Topic; Renin-Angiotensin System /drug effects

AccessionNumber
12012041853

Date bibliographic record published
02/01/2013

Date abstract record published
09/04/2013

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.