Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension

CRD summary
The authors concluded that angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers seemed to achieve a comparable long-term effect on blood-pressure control, with similar benefits on cardiovascular risk factors. ACE inhibitors appear associated with higher rates of cough. The authors’ conclusions seem supported by the evidence presented, although poor reporting of review methodology and the clinical variability between the studies need consideration.

Authors’ objectives
To compare the efficacy and safety of angiotensin-converting enzyme (ACE) inhibitors versus angiotensin II receptor blockers (ARBs) for treating essential hypertension in adults.

Searching
MEDLINE (1966 to 2007) and the Cochrane CENTRAL Register (Issue 2, 2006) were searched. A register of systematic reviews underway in the Cochrane Hypertension Review Group was also searched. Only studies published in the English language after 1988 were included. The search terms were reported in the Agency for Healthcare Research and Quality (AHRQ) report (see Other Publications of Related Interest). The bibliographies submitted by pharmaceutical companies to the Scientific Resource Center for the AHRQ's Effective Health Care Program and reference lists of relevant reviews or articles were checked for additional papers.

Study selection
Study designs of evaluations included in the review
Comparative clinical studies of any design, including RCTs and non-RCTs, prospective and retrospective cohorts, and case–control studies, were eligible.

Specific interventions included in the review
Studies evaluating the efficacy of ACE inhibitors versus ARBs at 12 weeks or more after the initial intervention were eligible for inclusion. Studies were considered if they compared a single ACE inhibitor and a single ARB, or if they ‘grouped’ comparisons such as a specific ARB versus ACE inhibitors or unspecified ARBs versus unspecified ACE inhibitors. The most frequently evaluated drugs were enalapril for ACE inhibitors and losartan for ARBs. The doses of study drug varied largely across the studies. Other concomitant antihypertensive medications were permitted if provided in a similar fashion to both study groups. Randomised controlled trials (RCTs) of ARBs or ACE inhibitors versus other non–ACE inhibitor or non-ARB comparators were considered when too few direct head-to-head trials were identified for the outcomes of interest and if the comparator was evaluated in at least 3 trials. Three common comparators were identified: atenolol, amlodipine and placebo.

Participants included in the review
Studies of at least 20 patients aged 18 years or older with essential hypertension were eligible. Most of the studies included in the review excluded patients with secondary causes of hypertension, as well as those with recent acute cardiovascular or cerebrovascular events.

Outcomes assessed in the review
The primary outcomes evaluated were blood-pressure control, mortality, morbidity (i.e. major cardiovascular events and quality of life), serious and overall adverse events, adherence to study regimen, and rate of use of a single antihypertensive for blood-pressure control. The secondary outcomes were lipid levels and glucose control, left ventricular mass or function, serum creatinine level, glomerular filtration rate and proteinuria.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.
Assessment of study quality
Quality criteria adapted from those of the U.S. Preventive Services Task Force and the Centre for Reviews and Dissemination were used to score individual studies as good, fair, or poor. The strength of the evidence for each key question was scored as high, moderate, low, or very low based on the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework. More details of the quality assessment were given in the AHRQ report.

Data extraction
One author extracted the data from each study and another author confirmed the extraction.

Methods of synthesis
How were the studies combined?
Pooled odds ratios (ORs) and risk differences (RDs), and their 95% confidence intervals (CIs), were calculated by a random-effects model for the primary analysis and a fixed-effect model for the sensitivity analysis. The data were pooled when at least four clinically and relatively similar studies assessed the same outcome. The analysis was stratified by study design. Peto’s method was used to analyse data on cough and withdrawals due to adverse events.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the I-squared statistic and the Q statistic.

Results of the review
Sixty-one studies were included: 47 RCTs, 1 non-RCT, 9 retrospective and 2 prospective cohort studies, 1 cross-sectional cohort study and 1 case–control study.

Blood-pressure control.
Fifty studies were identified: 47 RCTs (most scoring fair to good quality), 1 non-RCT, 1 retrospective cohort and 1 case-control study. Most of the studies showed similar long-term blood-pressure control, while some favoured one treatment over the other. The authors stated that there was substantial clinical heterogeneity across the studies. The average proportion of patients who achieved successful blood-pressure control with a single agent was about 55% for both study groups (RD 1.3%, 95% CI: -1.0, 3.5, p=0.26).

Other efficacy outcomes.
No significant differences were observed for death and major cardiovascular events (9 studies), quality of life (4 studies), rate of single antihypertensive agent use, lipid (12 studies), glucose level control or progression to diabetes (13 studies), left ventricular mass or function (8 studies), and creatinine level, glomerular filtration rate or urinary protein or albumin excretion (19 studies).

Adverse events.
The overall rate of adverse events was comparable, although ACE inhibitors were associated with a greater risk for cough (OR 0.32, 95% CI: 0.29, 0.36, p=0.000; 29 studies); there was evidence of statistical heterogeneity (Q statistic 57.5, I-squared 51.3%). This corresponded to an absolute RD of 6.7% in RCTs and 1.1% in cohort studies. There were fewer withdrawals due to adverse events (24 studies) and greater persistence with therapy for ARBs (OR 0.51, 95% CI: 0.38, 0.70; 17 studies); there was modest statistical heterogeneity between the studies (Q statistic 36.0, I-squared 36.2%).

Other outcomes including adherence to medication were also reported.

There were no subgroups benefiting more from one agent over the other.

Authors' conclusions
ACE inhibitors and ARBs appear to have similar long-term blood-pressure control and comparable effects on
cardiovascular risk factors. ACE inhibitors are associated with higher rates of cough.

CRD commentary
This review addressed a well-defined question in terms of the patients, interventions, outcomes and study design. One database and trial registers were searched and further efforts were made to find published and unpublished studies. Only studies in English were considered, which might have introduced language bias. Publication bias was not evaluated in the report. It is not clear whether the study selection, validity assessment and data extraction processes were performed by independent reviewers, which might have introduced bias and error. The assessment of validity used appropriate criteria. The presence and sources of statistical heterogeneity were explored. The decision to employ meta-analysis in pre-specified circumstances appears appropriate. The authors’ conclusions seem supported by the evidence presented, although poor reporting of review methodology and clinical heterogeneity between the included studies might represent a limitation to the applicability of these conclusions.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further studies with pragmatic designs and long-term follow-up should compare these antihypertensive therapies, with special attention given to subgroups at risk.

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Other publications of related interest

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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.