Adverse effects of combination angiotensin II receptor blockers plus angiotensin-converting enzyme inhibitors for left ventricular dysfunction: a quantitative review of data from randomized clinical trials


CRD summary
This review, which evaluated the safety of combination angiotensin II-receptor blockers (ARBs) plus angiotensin-converting enzyme (ACE) inhibitors in symptomatic left ventricular dysfunction, concluded that ARB plus ACE inhibitor therapy is associated with a significant increase in the risks of medication nonadherence, renal dysfunction and symptomatic hypotension. The authors' conclusions reflect the evidence presented but are based on only four trials.

Authors' objectives
To assess the safety profile of combination angiotensin II-receptor blockers (ARBS) plus angiotensin-converting enzyme (ACE) inhibitors in symptomatic left ventricular dysfunction (LVD).

Searching
MEDLINE (January 1966 to December 2006), EMBASE (January 1980 to December 2006) and the Cochrane Library were searched; the search terms were reported. In addition, the National Institute of Health Clinical Trials and the U.S. Food and Drug Administration website were searched, as were relevant bibliographies. Inclusion was restricted to English language publications.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with a random allocation of 500 or more participants were eligible for inclusion.

Specific interventions included in the review
Studies of combination ARB plus ACE inhibitor or standard therapy were eligible for inclusion. The comparisons in the included studies were: 320 mg valsartan plus captopril versus 150 mg captopril alone; 320 mg valsartan plus a variety of ACE inhibitors versus placebo or a variety of ACE inhibitors; 8 mg candesartan plus enalapril versus placebo or a variety of ACE inhibitors; and 4 or 8 mg candesartan plus enalapril versus 20 mg enalapril.

Participants included in the review
Studies of individuals with LVD were eligible. The participants in the included studies were characterised by chronic stable heart failure (HF) or acute myocardial infarction (AMI) with LVD. The participants were aged from 63 to 65 years, and 69 to 88% were men.

Outcomes assessed in the review
Studies that reported adverse effects with a minimum 3-month follow-up were eligible. Reported outcomes included: medication discontinuation due to adverse effects; worsening renal function (defined as elevations in serum creatinine level of 0.5 mg/dL or higher); hyperkalemia (serum potassium level of 5.5 milliequivalents/L or higher), and symptomatic hypotension. Outcomes for medication discontinuation due to adverse effects were specific to each trial, but there was more consistency across studies for the definition of renal dysfunction, hyperkalemia and symptomatic hypotension.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened studies for relevance, with any differences resolved through discussion.

Assessment of study quality
Two reviewers independently assessed validity according to the Jadad checklist, which includes items on randomisation, blinding and reporting of losses to follow-up.

**Data extraction**

Two reviewers independently extracted the data from the included studies, with any discrepancies resolved through discussion. Adverse events data, according to treatment groups, were extracted through the use of 2x2 tables. Adverse events were converted to relative risks (RRs) and 95% confidence intervals (CIs) based on intention-to-treat data.

**Methods of synthesis**

How were the studies combined?
The RRs were pooled using fixed-effect or random-effects (DerSimonian and Laird) models, depending on the presence of heterogeneity.

How were differences between studies investigated?
Statistical heterogeneity was assessed and studies were stratified by clinical setting, namely chronic HF or AMI with symptomatic LVD.

**Results of the review**

Four RCTs (n=17,337) were included in the review.

The quality of the included studies was high (interquartile range: 3, 5).

Combination ACE inhibitor plus ARB therapy versus control treatment that included ACE inhibitors was associated with a significant increase in medication discontinuation due to adverse effects in chronic HF patients (15.0% versus 11.0%; RR 1.38, 95% CI: 1.22, 1.55; 3 trials) and also in patients with AMI and symptomatic LVD (9.0% versus 7.6%; RR 1.17, 95% CI: 1.03, 1.34; 1 trial). There was no evidence of statistical heterogeneity.

Combination ARB plus ACE inhibitor therapy versus control treatment was associated with significant increases in the risk of symptomatic hypotension in chronic HF (2.4% versus 1.5%; RR 1.50, 95% CI: 1.09, 2.07; 3 trials) and also in patients with AMI and symptomatic LVD (18.1% versus 11.9%; RR 1.48, 95% CI: 1.33, 3.18; 1 trial).

Worsening renal function occurred more often with combination ARB plus ACE inhibitor therapy versus control treatment in patients with chronic HF (3.3% versus 1.5%; RR 2.17, 95% CI: 1.59, 2.97) and in patients with AMI with symptomatic LVD (4.8% versus 3.0%; RR 1.61, 95% CI: 1.31, 1.98).

There was a significant increase in the risk of hyperkalemia in both patient groups (RR 4.87, 95% CI: 2.39, 9.94; 3 trials; RR 1.48, 95% CI: 1.33, 3.18; 1 trial).

**Authors' conclusions**

For individuals with symptomatic LVD, dual angiotensin inhibition with combination ARB plus ACE inhibitor therapy is associated with a significant increase in the risks of medication nonadherence, renal dysfunction and symptomatic hypotension.

**CRD commentary**

The review question was clear and was supported by appropriate inclusion criteria relating to the participants, interventions, outcomes and study designs. Attempts to identify all the relevant literature were undertaken by searching several electronic databases and other sources, though the restriction to publications in English might have introduced publication bias. Validity was assessed according to published criteria, attempts were made to minimise errors and bias at each stage of the review process, and appropriate methods were used to pool the results and investigate statistical heterogeneity. The authors' overall conclusions appear to reflect the evidence presented and are likely to be reliable, but it should be noted that the evidence was based on a small number of trials only.
Implications of the review for practice and research

Practice: The authors stated that knowledge about the potential for adverse effects may facilitate better physician prescribing practices with respect to selective use of combination ARB plus ACE inhibitor therapy as an alternative for selected patients rather than routine application as a standard management approach in HF or AMI with symptomatic LVD. Clinicians should monitor patients for adverse multidrug interactions.

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

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Other publications of related interest
This additional published commentary may also be of interest. Granger CB. Review: angiotensin II receptor blocker plus angiotensin-converting enzyme inhibitor increases risk for adverse effects. ACP J Club 2008;148:35.

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Subject indexing assigned by NLM

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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.