Systematic review of combined angiotensin-converting enzyme inhibition and angiotensin receptor blockade in hypertension

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CRD summary
This review assessed the effects of combining angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers for people with hypertension. The authors concluded that combination therapy has little clinical benefit, compared with the use of individual drugs, except possibly in people who also have chronic renal disease and diabetes. Given the available evidence and some limitations with the review, this conclusion is suitably conservative.

Authors' objectives
To assess the effects of combining angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) in the treatment of hypertension.

Searching
MEDLINE (1966 to July 2004), EMBASE (1988 to July 2004) and the Cochrane Library (1995 to 2004) were searched; the search terms were given. The reference lists of identified articles were also checked. The search was limited to articles reported in the English language.

Study selection

Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. Both parallel-group and crossover trials were included in the review.

Specific interventions included in the review
Studies that compared the effects of combined ARBs and ACEIs with either class of drug given as monotherapy were eligible for inclusion. Studies where significant alterations in the use or dose of concomitant medications were allowed were excluded. The drugs used in the included studies were enalapril, irbesartan, benazepril, valsartan, lisinopril, candesartan, losartan, fosinopril, captopril, ramipril, quinalapril and trandolapril. In some studies placebo was used as part of the comparator treatment. The duration of treatment generally ranged from 4 to 12 weeks; the exception was one study that lasted 2.9 years.

Participants included in the review
Studies on people with hypertension or using antihypertensive drugs were sought. Hypertensive was defined as a clinical sitting systolic blood-pressure (BP) of 140 mmHg or above, and/or a diastolic BP of 90 mmHg or above; or a mean ambulatory systolic BP 130 mmHg or above, or ambulatory diastolic BP 85 mmHg or above. In the included studies, the mean ages ranged from 42 to 76 years and 71% of the participants were men. Some participants had diabetes or chronic renal failure. Baseline BP (some measured on medication) ranged from 128/79 to 163/96 (systolic/diastolic).

Outcomes assessed in the review
Studies where the change in BP was a primary or significant secondary outcome were sought. The outcomes reported included 24-hour ambulatory BP and clinic BP (sitting or supine). For subgroup analyses, the outcomes were a combination of these (i.e. combining ambulatory results with clinic results where ambulatory results were unavailable), proteinuria (including albuminuria, proteinuria or urinary albumin creatinine ratio) and safety data (changes in serum potassium, changes in haemoglobin, deterioration in renal function, hyperkalaemia and withdrawal from study). Compliance with medication was also discussed.

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
The authors did not state that they assessed validity.

Data extraction
Two reviewers independently extracted the data using a standard form. The treatment effects were calculated: i.e., in parallel studies the difference in change in BP between the two groups, and in crossover studies the difference between the end of the single drug phase and the combined drug phase. Percentage changes in proteinuria were calculated. The variance in the treatment effect was calculated from standard deviations or standard errors of paired differences between baseline and end of follow-up in parallel studies and between the treatment periods in the crossover studies. Where this was not possible, calculations were based on confidence intervals (CIs), exact t or P-values. Where necessary, values were imputed.

Methods of synthesis
How were the studies combined?
Mean effect sizes, and 95% CIs were calculated using a random-effects model. Funnel plots were used to assess publication bias.

How were differences between studies investigated?
Subgroup analyses were conducted. These were based on participants with essential or isolated systolic hypertension, diabetes or chronic renal failure. The authors also considered differences in dosages in different studies.

Results of the review
Fourteen RCTs (903 participants) were included: four of parallel design (718 participants) and ten of crossover design (185 participants).

A combination of ARBs and ACEIs reduced 24-hour ambulatory BP (systolic/diastolic) by 4.7/3.0 mmHg (95% CI systolic/diastolic: 2.9, 6.5 / 1.6, 4.3) compared with ACEI monotherapy (10 trials) and by 3.8/2.9 mmHg (95% CI: 2.4, 5.3 / 0.4, 5.4) compared with ARB monotherapy (4 trials).

Clinic BP was reduced by 3.8/2.7 mmHg (95% CI: 0.9, 6.7 / 0.8, 4.6) compared with ACEI monotherapy (7 trials) and by 3.7/2.3 mmHg (95% CI: 0.4, 6.9 / 0.2, 4.4) compared with ARB monotherapy (6 trials).

The authors stated that the majority of studies used submaximal doses or once daily short-acting doses of ACEIs. There was no additive effect of combined treatment in the one study that used a longer acting ACEI.

In subgroup analyses, compared with ACEI monotherapy, combination therapy reduced BP by 4.0/2.3 mmHg (95% CI: 1.9, 6.0 / 0.2, 4.4; 3 trials) in those with essential or isolated systolic hypertension and by 6.8/4.7 mmHg (95% CI: 4.4, 9.2 / 3.3, 6.0; 3 trials) in diabetics. There was no reduction in those with chronic renal failure (0.7/0.4 mmHg. 95% CI: -0.6, 1.3 / -1.2, 2.7; 1 trial). Only a small number of studies in each subgroup compared combination therapy with ARB monotherapy, so the results were not calculated.

Eight trials reported on proteinuria. Combination therapy reduced proteinuria by 30% (95% CI: 23, 37) compared with ACEI monotherapy and by 39% (95% CI: 31, 48) compared with ARB monotherapy.

In terms of safety, the majority of studies showed no significant change in serum potassium or haemoglobin. One case of deterioration in renal function was reported. Further details of adverse event data were reported. Nine studies reported on compliance: in 7 studies it was generally above 90%, while in 2 studies it was assessed but details were not given.

The funnel plots suggested that studies showing no effect of combination therapy were under-reported.

Authors' conclusions
There was a small additive effect on BP with combination therapy, although this was of questionable clinical significance and may be a result of individual study design rather than a true effect. Combination therapy produced a clinically significant reduction in proteinuria in those with chronic renal disease and diabetes.

**CRD commentary**
The aims and inclusion criteria for this review were clearly stated. Several relevant databases were searched, but the search was restricted to English language articles and no attempt was made to identify unpublished studies. Consequently, studies might have been missed, as suggested by tests for publication bias, and this could have affected the results of the review. The methods used to select studies were not described, thus making it difficult to assess the potential for error or bias. There was no mention of any quality assessment of the included studies, so any potential effect of study quality on the results cannot be assessed. Given these limitations of the review, and that the available evidence came from short-term studies, the authors conclusions, recommending further research, are suitably conservative.

**Implications of the review for practice and research**
*Practice:* On the basis of available evidence, the use of combination therapy is not recommended for essential hypertension. However, it may be useful for those with hypertension and chronic renal failure, as long as renal function and electrolyte balance is carefully monitored.

*Research:* Further studies are needed to compare combination therapy with maximal licenced doses of monotherapy drugs. In addition, long-term studies are needed to assess whether short-term reductions in proteinuria affect clinical end points.

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