Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials

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CRD summary
The authors concluded that compared with monotherapy, combination blockade of the renin-angiotensin system had some beneficial effects, but it did not reduce mortality and significantly compromised safety. Despite some limitations in the review, there were a lot of trials, and larger trials tended to find similar effects, which suggests that the authors’ conclusions are likely to be reliable.

Authors’ objectives
To compare the long-term efficacy and safety of individual versus combined blockade of the renin-angiotensin system, for patients with various disorders.

Searching
PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for peer-reviewed articles from January 1990 to August 2012. Search terms were reported and no language restrictions were applied. Reference lists of relevant studies were manually searched.

Study selection
Eligible for inclusion were randomised controlled trials (RCTs) that compared the long-term efficacy (one year or more) and safety (four weeks or more) of individual versus combined blockade of the renin-angiotensin system. Combined blockade could include any two angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers, or aliskiren (a direct renin inhibitor). Eligible trials had to include at least 50 participants.

The included trials were of patients with varying conditions, including hypertension, diabetes, microalbuminuria, heart failure, kidney disease, or myocardial infarction. Where reported, the mean age of patients ranged from 50 to 67 years, and the percentage of men ranged from 40 to 100. A range of treatments was used and the regimens were not reported; combination therapy included the comparison treatment used as monotherapy. The included trials reported efficacy (all-cause mortality, cardiovascular mortality, or admission to hospital for heart failure) and safety events (hyperkalaemia or hypotension – defined in the review, renal failure, or withdrawal due to drug-related adverse events).

Two reviewers independently screened studies for inclusion; disagreements were resolved through consensus.

Assessment of study quality
Trial quality was assessed according to the criteria recommended by the Cochrane Collaboration, covering allocation generation and concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. Those trials that were at high or unclear risk of bias for allocation generation and concealment, and blinding were rated as low quality.

The authors did not state how many reviewers assessed quality.

Data extraction
The efficacy and safety events were extracted, on an intention-to-treat basis, to calculate risk ratios and 95% confidence intervals. The authors did not state how many reviewers extracted the data.

Methods of synthesis
A Mantel-Haenszel random-effects model was used to combine the risk ratios and 95% confidence intervals, for relevant outcomes, and by type of treatment. Statistical heterogeneity was assessed using I², where under 25% was low and over 75% was high.

For efficacy, subgroup analyses were undertaken for patients with and without heart failure. For safety, subgroup
analyses were undertaken for patients with and without heart failure, low and high risk of bias, duration of follow-up (less than one year versus one year or more), and number of patients (less than 500 versus 500 or more). The interaction between the estimates for each pair of subgroups was assessed, using published methods.

Publication bias was assessed, using funnel plots or the Begg and Egger tests. Where there was evidence of bias, the trim-and-fill method was used to adjust the results of the meta-analysis.

Results of the review

Thirty-three trials, with 68,405 patients, were included in the review. Fifteen trials were at high risk of bias and 18 were at low risk of bias; 18 trials reported adequate allocation generation and concealment, and 24 reported adequate blinding. Follow-up ranged from four to 243 weeks. There was no evidence of publication bias.

Efficacy: In meta-analysis of seven trials, with 56,824 patients, there was no statistically significant difference between individual and combined therapy for all-cause mortality ($I^2=69\%$), and in six trials there was no difference in cardiovascular mortality ($I^2=59\%$). There were discrepancies between the all-cause mortality results reported in the text and those in the forest plots for the subgroups; the forest plots indicated that there were no statistically significant differences in either patient subgroup.

There was a statistically significant reduction in the number of hospital admissions for heart failure in patients receiving combination therapy, compared with individual therapy (RR 0.82, 95% CI 0.74 to 0.92; $I^2=68\%$; five RCTs). Subgroup analyses showed the significant differences were due to a benefit in patients with heart failure.

Safety: In meta-analyses, using 33 trials, combined treatment statistically significantly increased the risk of hyperkalaemia (RR 1.55, 95% CI 1.32 to 1.82; $I^2=50\%$; 23 RCTs), hypotension (RR 1.66, 95% CI 1.38 to 1.98; $I^2=66\%$; 18 RCTs), and renal failure (RR 1.41, 95% CI 1.09 to 1.84; $I^2=83\%$; 20 RCTs). There were statistically significantly more withdrawals due to drug-related adverse events, in patients receiving combination treatment (RR 1.27, 95% CI 1.21 to 1.32; $I^2=2\%$; 26 RCTs).

Subgroup analyses indicated no differences between patients with and without heart failure, for hyperkalaemia, hypotension, and withdrawals. The risk of renal failure was significantly increased in patients with heart failure, but not in patients without heart failure.

Authors' conclusions

Compared with monotherapy, combination blockade of the renin-angiotensin system had some beneficial effects, but did not reduce mortality and significantly increased the risks of adverse events. The risks outweighed the benefits of dual therapy.

CRD commentary

The review question was clearly stated and was supported by appropriate inclusion criteria, but the outcome criteria were broad. The literature search was adequate and no language restrictions were applied, but it did not appear that unpublished data were sought. Formal assessment of publication bias did not find evidence of it. Appropriate quality assessment was performed, but just under half the trials were at a high risk of bias, which questions the reliability of their findings. Study selection was performed in duplicate, but it was unclear whether this was true for quality assessment and data extraction, which means that reviewer error and bias cannot be ruled out.

The authors acknowledged the clinical and methodological differences between trials and went some way to account for this in their analysis. There was evidence of statistical heterogeneity for most outcomes and the authors investigated this. They highlighted issues around using surrogate end points, and they acknowledged that the analysis of safety events was prone to bias due to the nature of the data.

Despite the potential for bias and questionable trial quality, there were a lot of trials and several had very large samples. These large trials tended to have similar results for each outcome, which suggests that the authors' conclusions are likely to be reliable.

Implications of the review for practice and research

Practice: The authors stated that the addition of an angiotensin-receptor blocker to an ACE inhibitor, in patients with
heart failure, should be restricted to patients who continued to have symptoms, while on monotherapy, and could not
tolerate mineralocorticoid antagonists.

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

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