Tolerability of angiotensin-receptor blockers in patients with intolerance to angiotensin-converting enzyme inhibitors: a systematic review and meta-analysis

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CRD summary
This review concluded that in patients with angiotensin-converting enzyme inhibitor intolerance, angiotensin receptor blockers had similar rates of discontinuation, cough and angioedema compared with placebo and diuretics. However, significantly higher incidences of hypotension, renal dysfunction and hyperkalaemia were associated with angiotensin receptor blockers when compared to placebo. These conclusions reflect the evidence presented and are likely to be reliable.

Authors' objectives
To assess the tolerability of angiotensin receptor blockers in patients with intolerance to angiotensin-converting enzyme inhibitors (ACE inhibitors).

Searching
PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Knowledge were searched up to March 2011 without language restrictions. Search terms were reported in a supplemental file. Reference lists of retrieved publications were screened.

Study selection
Randomised controlled trials (RCTs) that compared angiotensin receptor blockers with alternative angiotensin receptor blockers, different doses of an angiotensin receptor blocker, another active drug or placebo in patients with intolerance to ACE inhibitors were eligible for inclusion. Outcomes of interest were cough, discontinuation due to adverse events, angioedema, hypotension, renal dysfunction and hyperkalaemia.

Most of the included studies compared angiotensin receptor blockers with ACE inhibitors, diuretics or placebo. Only one study compared high-dose with low-dose of an angiotensin receptor blocker. Some studies recruited only patients with ACE inhibitor-induced cough; in other studies that recruited patients with all causes of intolerance the baseline event rate for cough was over 60%. The mean age of patients across studies ranged from 53.6 to 73 years. Follow-up ranged from six weeks to a median follow-up of 4.7 years.

Two reviewers assessed studies for inclusion.

Assessment of study quality
Study quality was assessed using the Jadad scale, a five-point scale of randomisation, allocation concealment and withdrawals/drop-outs.

The authors did not state how many reviewers performed quality assessment.

Data extraction
Data were extracted on event rates for intervention and control groups to enable the calculation of relative risks (RRs) and 95% confidence intervals (CIs). Where cells with a value of zero were present in one arm, 0.5 was added to each cell to perform calculations.

It appeared that two reviewers performed data extraction. Data entry was double checked. Any disagreements were resolved by consensus.

Methods of synthesis
The studies were combined in a meta-analysis. Pooled risk ratios (RRs) with 95% CIs were calculated using a random-effects model. Statistical heterogeneity was assessed using the $X^2$ and $I^2$ statistics. Subgroup analyses were conducted on the basis of patients with different conditions (such as arterial hypertension and heart failure).
Results of the review

Twelve RCTs were included in the review (12,632 participants, range 84 to 5,296). Eight RCTs had a Jadad score of 3 and four RCTs had a Jadad score of at least 4.

Angiotensin receptor blockers were associated with a significant reduction in the rate of cough compared with ACE inhibitors (RR 0.37, 95% CI 0.28 to 0.48; seven RCTs). There were no significant differences in the rate of cough when comparing angiotensin receptor blockers versus placebo or placebo/diuretics.

Compared with placebo, angiotensin receptor blockers were significantly associated with an increased rate of hypotension (RR 2.59, 95% CI 1.48 to 4.55; four RCTs), renal dysfunction (RR 2.07, 95% CI 1.45 to 2.95; three RCTs) and hyperkalaemia (RR 3.37, 95% CI 1.60 to 7.11; two RCTs). There was no significant difference in the rate of angioedema between angiotensin receptor blockers and placebo. There were no significant differences in the rate of drug discontinuation due to adverse events between angiotensin receptor blockers and one of the controls (placebo, diuretics or ACE inhibitors).

No significant heterogeneity was observed in these outcomes. Other results were reported.

Authors’ conclusions

In patients with ACE inhibitor intolerance, angiotensin receptor blockers were well tolerated with discontinuation rates, incidence of cough and angioedema risk similar to those with placebo and diuretics. However, significantly higher incidences of hypotension, renal dysfunction and hyperkalaemia were associated with angiotensin receptor blockers when compared to placebo.

CRD commentary

This review's inclusion criteria were clear. Several relevant databases were searched. Limited attempts were made to find unpublished studies, which increased the risk of publication bias. No language restriction was applied in the searches, which reduced the risk of language bias. Steps were made to minimise errors and biases during data extraction and study selection; it was unclear whether quality assessment was also performed in duplicate. Appropriate criteria were used to assess study quality.

The authors acknowledged that there was a degree of clinical heterogeneity across included studies for definitions of adverse events and some study characteristics. Statistical heterogeneity was assessed and appropriate methods were used to pool the results.

The authors’ conclusions reflect the evidence presented and are likely to be reliable.

Implications of the review for practice and research

Practice: The authors stated that ACE inhibitor rechallenge should be discouraged in patients with previous ACE inhibitor-induced cough.

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

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