Meta-analysis of randomized trials of angioedema as an adverse event of renin-angiotensin system inhibitors

CRD summary
This review found that the risk of angio-oedema with angiotensin-receptor blockers was less than half that with angiotensin-converting enzyme inhibitors, and did not differ significantly from the risk with placebo. Both types of drug increased the risk of angio-oedema for patients with heart failure. Despite some reporting limitations in the review, these findings seem reliable.

Authors' objectives
To assess the risk of angio-oedema with different renin-angiotensin system inhibitors.

Searching
PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE were searched for studies, in any language, published in peer-reviewed journals, from 1980 to October 2011. Search terms were reported and the reference lists of relevant articles and meta-analyses were checked.

Study selection
Eligible studies were randomised controlled trials (RCTs) that compared angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers or direct renin inhibitors versus other antihypertensive drugs, placebo or each other. Trials had to include at least 100 participants, last at least eight weeks, and report angio-oedema as an outcome. Trials in which the intervention drugs were added as second- or third-line agents were excluded.

Participants in the included trials had a mean age of 62 years and most (61%) were men. The proportion of Black participants ranged from none to all. The clinical characteristics of participants varied widely across studies to include those with a high-risk cardiovascular profile, pre-hypertension, hypertension, cardiovascular disease or diabetes with end-organ damage, and heart failure with an ejection fraction of less than 40%. Most of the trials compared ACE inhibitors or angiotensin-receptor blockers versus each other, placebo or a wide range of other antihypertensive drugs. Many of them included a run-in screening phase prior to randomisation.

The authors did not state how many reviewers selected the studies.

Assessment of study quality
Trial quality was assessed with the Cochrane Risk of Bias tool, covering random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting bias, and other sources of bias. Trials that met all seven criteria were rated as at a low risk of bias and those that met fewer than six were rated as at a high risk of bias.

The authors did not state how many reviewers conducted the assessment.

Data extraction
The reviewers extracted the incidence of angio-oedema for each comparison group. These data were extracted independently by two reviewers, resolving disagreements by arbitration with other reviewers. Trial authors were contacted, if necessary, to request extra data.

Methods of synthesis
The pooled incidence for each intervention was calculated by combining the data from each relevant trial group, using inverse variance to weight the trials. The data from trials that made head-to-head comparisons of renin-angiotensin system inhibitors were pooled using a fixed-effect Mantel-Haenszel model to calculate pooled odds ratios, with 95% confidence intervals. Heterogeneity was assessed with $I^2$. 
For incidence data, subgroup analyses were performed by ethnicity (Black versus non-Black), clinical status (heart failure versus no heart failure), ACE inhibitor intolerance (history versus no history), risk of bias, and trial duration (up to one year versus longer). Publication bias was assessed as funnel plots, and the Begg and Egger tests.

**Results of the review**

Forty RCTs were included in the review, with a total of 206,596 participants (range 128 to 33,357). There were 26 trials of ACE inhibitors; 18 were at low risk and eight were at high risk of bias. There were 19 trials of angiotensin-receptor blockers; 14 were at low risk and five were at high risk of bias. The mean trial follow-up was 123 weeks.

The weighted incidence of angio-oedema was: 0.30% (95% CI 0.28 to 0.32) for ACE inhibitors; 0.11% (95% CI 0.09 to 0.13) for angiotensin receptor blockers; 0.13% (95% CI 0.07 to 0.19) for aliskiren (direct renin inhibitor); 1.7% for omapatrilat (antihypertensive); 0.07% for placebo; 0.05% for thiazides; and 0.03% for calcium-channel blockers.

In subgroup analyses, the incidence of angio-oedema with ACE inhibitors was significantly higher in Black participants, participants with heart failure, trials at high risk of bias, and trials that lasted less than one year. The incidence of angio-oedema with angiotensin-receptor blockers was significantly higher in participants with heart failure, trials at high risk of bias, and those that lasted less than one year, but not in participants with ACE inhibitor intolerance.

In head-to-head comparisons, ACE inhibitors were associated with a significantly higher risk of angio-oedema than angiotensin-receptor blockers (OR 2.24, 95% CI 1.50 to 3.34; seven RCTs) or placebo (OR 2.79, 95% CI 1.63 to 4.79; 10 RCTs). There was no significant difference between angiotensin-receptor blockers and placebo (OR 1.18, 95% CI 0.39 to 3.61; seven RCTs). There was no statistical heterogeneity and no evidence of publication bias.

**Authors' conclusions**

This review found that the risks of angio-oedema with angiotensin-receptor blockers and with direct renin inhibitors were less than half that with ACE inhibitors, and were not significantly different from the risk with placebo. ACE inhibitors and angiotensin receptor blockers were associated with a risk of angio-oedema in patients with heart failure.

**CRD commentary**

The objectives and inclusion criteria were clear, and relevant sources were searched for trials in any language. The restriction to published studies meant that there was a risk of publication bias; no evidence of this was found in formal testing, but there too few trials for the tests to be conclusive. Steps were taken to minimise the risk of reviewer bias and error in data extraction, but it was unclear whether this applied to study selection and quality assessment. No details were provided on the risk of bias in individual trials, nor was the overall risk of bias in the trials of direct renin inhibitors reported.

The estimates of angio-oedema incidence by intervention might not have been reliable, since the data were partly from populations with different underlying risks, and not from direct comparisons. These estimates were broadly consistent with the findings of the randomised comparisons. Appropriate methods were used to combine the data from the head-to-head comparisons, and to assess statistical heterogeneity between the trials. As the authors noted, the review was limited by marked clinical and methodological differences between the trials, as well as potential selection bias because participants with a history of ACE inhibitor intolerance were excluded from some trials.

Despite some reporting limitations in the review, the authors' findings appear to be reliable.

**Implications of the review for practice and research**

**Practice**: The authors stated that clinicians should discuss the increased risk of angio-oedema in African Americans, and should consider alternatives to ACE inhibitors as first-line therapy.

**Research**: The authors stated that larger trials were needed to evaluate the risks of angio-oedema with angiotensin-receptor blockers and direct renin inhibitors, in those with a history of angio-oedema with ACE inhibitors.

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