Risk of angioedema with angiotensin receptor blockers in patients with prior angioedema associated with angiotensin-converting enzyme inhibitors: a meta-analysis

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CRD summary
The review assessed the risk of angioedema with angiotensin-receptor blockers in patients with prior angioedema associated with angiotensin-converting enzyme inhibitors. It concluded that there was limited evidence that angiotensin-receptor blockers could be used if the patient was suitably advised of the risk of recurrent angioedema. Given the small sample sizes and methodological flaws in the review, the conclusion may be overstated.

Authors' objectives
To perform a systematic review to assess the risk of angioedema with angiotensin-receptor blockers in patients with prior angioedema associated with angiotensin-converting enzyme inhibitors.

Searching
MEDLINE, EMBASE, BIOSIS Previews, SciSearch and Current Contents Connect were searched for studies published between January 1990 and May 2007. No language restrictions were applied. Search terms were reported. Reference lists of reviews and retrieved articles were scanned for further relevant studies.

Study selection
Studies were eligible for inclusion if the patient population previously had angioedema after taking an angiotensin-converting enzyme inhibitor and were subsequently given an angiotensin-receptor blocker. To be eligible, studies had to follow up patients for at least one month to assess whether angioedema had developed. Randomised controlled trials, prospective cohorts and retrospective cohorts were eligible for inclusion; case series and case reports were excluded.

In included studies, the mean age of patients was 63 years and the percentage of men ranged from 40 to 68.2%. The percentage of patients who were white ranged from 23 to 88.4% (where reported).

Two authors independently assessed whether studies were eligible for inclusion; differences were resolved by a third author.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Two reviewers independently extracted data on study characteristics and outcomes using a standardised form.

Methods of synthesis
Data from studies were pooled, using an exact-binomial model and inverse-variance method, to estimate the percentage of patients with definite or possible angioedema, with 95% confidence intervals (CIs). The I^2 statistic was used to estimate statistical heterogeneity.

Results of the review
Three studies were included in the review (n=71 patients receiving an angiotensin-receptor blocker, range six to 30). One study was a randomised controlled trial (RCT); the other two studies were retrospective cohorts. The mean or median follow-up times ranged from 11 months to 33.7 months.

The pooled estimate for the risk of possible angioedema cases was 9.4% (95% CI 1.6 to 17). The pooled estimate for the risk of confirmed angioedema cases was 3.5% (95% CI 0.0 to 9.2).

No fatal events due to an angiotensin-receptor blocker-related angioedema were reported.
There was statistically significant heterogeneity between the studies.

**Authors' conclusions**

There was limited evidence to suggest that an angiotensin-receptor blocker could be administered to a patient who had previously experienced angiotensin-converting enzyme inhibitor-induced angioedema, but the patient should be suitably advised of the risk of recurrent angioedema.

**CRD commentary**

This review addressed a clear research question using appropriate study selection criteria. The search appeared comprehensive and appropriate. The data extraction and method of synthesis both appeared broadly appropriate, although lacked a control group, so the increased risk of the treatment could not be known.

No quality assessment was reported, so the possibility of substantial biases in the studies could not be ruled out; two of the three studies used a retrospective cohort design, which has a higher risk of bias than RCTs. Some primary study details were provided, but these mostly related to population and study characteristics, rather than differences in interventions and treatment regimens, so the possibility of clinical heterogeneity could not be ruled out. The results were based on relatively small sample sizes and numbers of events, so may be subject to substantial error.

Given the lack of study quality assessment, limited treatment regimen details, and small sample sizes, the conclusion and implications for practice may be overstated.

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

**Practice:** The authors stated that, in patients taking an angiotensin-converting enzyme inhibitors who subsequently switch to an angiotensin-receptor blocker, the risk of developing persistent angioedema is less than 10%, and the risk of any occurrence of angioedema is from 2 to 17%.

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

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