Risk of pneumonia associated with use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers: systematic review and meta-analysis

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CRD summary
The authors suggested an important role for angiotensin-converting enzyme inhibitors, but not angiotensin receptor blockers, in reducing pneumonia. Evidence was weaker for pneumonia-related mortality. This was a generally well-conducted review, but the primary evidence was limited. Very few studies were developed to assess pneumonia and some results were conflicting, so the authors' conclusions may not be reliable.

Authors’ objectives
To assess the effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on risk of pneumonia.

Searching
PubMed and Web of Science were searched from inception to June 2011 with no language restrictions. Reference lists of identified articles, and relevant systematic reviews and meta-analyses were manually searched. The Food and Drug Administration website was searched for unpublished data.

Study selection
Eligible for inclusion were randomised controlled trials (RCTs) with parallel design, cohort studies, and case-control studies. Studies in any population were eligible if they compared the effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers with each other, with placebo, or with any other active drug. The primary outcome of interest was incidence of pneumonia, whether reported as a predefined outcome or adverse event. Lower respiratory tract infections and admissions to hospital due to lower respiratory tract infections were also considered. The other outcome of interest was pneumonia-related death (including in-hospital death or death within 30 days after onset of pneumonia).

Included studies were conducted worldwide; three were located in the UK. Included patients had various conditions such as heart failure, previous stroke, chronic kidney disease, and type 2 diabetes. The mean age of patients ranged from 44.8 to 82.8 years (where reported). Most RCTs reported pneumonia as an adverse event. The data for incidence of pneumonia and death came from various sources for observational studies, including hospital or pharmacy databases (where reported).

At least two reviewers screened studies for inclusion. Disagreements were resolved by consensus.

Assessment of study quality
Two reviewers assessed study risk of bias (high, unclear, or low) following modified criteria specified by the Cochrane risk of bias tool for RCTs, and STROBE, MOOSE and QATSO (quality assessment tools for systematic reviews) for observational studies.

Data extraction
Two reviewers independently extracted odds ratios and 95% confidence intervals or calculated them from hazard or risk ratios.

Where pneumonia was classified by severity, only the most severe cases were extracted. Drug withdrawals due to pneumonia were extracted where no other estimates on pneumonia incidence were available. Nested case-control studies were treated as cohort studies.

Methods of synthesis
A random-effects model, using the inverse-variance or Peto approach, was used to pool odds ratios (ORs) and 95% confidence intervals (CIs). Pairwise comparisons were undertaken to directly compare angiotensin-converting enzyme inhibitors with angiotensin receptor blockers.
inhibitors and angiotensin receptor blockers versus each control group. Results were stratified by study design. The number needed to treat was calculated, taking into account baseline risk. Statistical heterogeneity was assessed using $I^2$.

Indirect analyses (using the Bucher frequentist method) were performed to compare angiotensin-converting enzyme inhibitors versus controls and angiotensin receptor blockers versus controls. Direct and indirect comparisons were compared using a random-effects model to determine any discrepancy and heterogeneity between the different estimates.

Subgroup analyses were conducted on at-risk patients (those with previous conditions such as stroke) and by ethnicity (Asian versus non-Asian populations).

Publication bias was assessed through visual inspection of funnel plots.

**Results of the review**

Thirty-seven studies were included in the review. The quality of the RCTs was considered good, but there was high risk of bias in selective reporting. The quality of observational studies was adequate; there was high risk of bias in adjusting for patient characteristics and other adjustments. Mean follow-up ranged from 0.2 to 14 years.

**Incidence of pneumonia**

Overall, angiotensin-converting enzyme inhibitors significantly reduced risk of pneumonia compared with controls (OR 0.66, 95% CI 0.55 to 0.80; five RCTs, 14 observational studies). The number needed to treat for two years was 65. There was substantial heterogeneity ($I^2=79\%$). Similar results were reported for different study designs except heterogeneity was no longer significant for RCTs.

There were no statistically significant differences in risk of pneumonia between angiotensin receptor blockers and controls for overall estimates or estimates by study design (nine RCTs and two observational studies). There was no significant heterogeneity.

Direct comparison between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers showed no statistically significant difference in risk of pneumonia (one RCT, one observational study). There was evidence of substantial heterogeneity ($I^2=78\%$).

**Pneumonia-related mortality**

Angiotensin-converting enzyme inhibitors were associated with a statistically significant reduction in pneumonia-related mortality compared with controls (OR 0.73, 95% CI 0.58 to 0.92; three RCTs, four observational studies). There was evidence of moderate heterogeneity ($I^2=51\%$). However, stratification including only RCTs showed no statistically significant difference.

One RCT reported a borderline effect with angiotensin receptor blockers compared with controls (OR 0.63, 95% CI 0.40 to 1.00).

Subgroup analyses, indirect comparisons and other results were reported in the review.

Funnel plots did not show evidence of publication bias.

**Authors' conclusions**

The results suggested an important role for angiotensin-converting enzyme inhibitors, but not angiotensin receptor blockers, in reducing the risk of pneumonia. Angiotensin-converting enzyme inhibitors also lowered the risk of pneumonia-related mortality, particularly in patients with established disease, but the evidence was weaker.

**CRD commentary**

The review question and inclusion criteria were clearly specified. A comprehensive search of the literature was conducted to identify published and unpublished data. Each step of the review process was performed in duplicate, which reduced potential reviewer error and bias.
Study quality was assessed; some areas were at high risk of bias. The authors acknowledged that very few studies were primarily developed to assess pneumonia as an outcome.

Statistical methods seemed appropriate for direct analyses. Indirect comparisons should not be thought of as definitive (acknowledged by the authors). The reliability of the sources of data for observational studies was unclear; these gave most weight to the overall outcome estimates. Stratification by study design highlighted some conflicting results. There was also substantial heterogeneity among studies (as acknowledged by the authors). Subgroup analyses generally included very few studies and some had wide confidence intervals.

This was a generally well-conducted review, but given the limitations of the primary evidence, the authors’ conclusions should be interpreted with caution as they may not be reliable.

Implications of the review for practice and research

Practice: The authors stated that the evidence may discourage the withdrawal of angiotensin-converting enzyme inhibitors in some patients with tolerable adverse events who are at particularly high risk of pneumonia.

Research: The authors stated that randomised controlled trials specifically designed to assess pneumonia were needed to establish definitive conclusions. Further research was also needed to explore the differences in ethnic groups to better define those who benefit most.

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