Perindopril: do randomised, controlled trials support an ACE inhibitor class effect: a meta-analysis of clinical trials

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CRD summary
The review found that perindopril alone or in combination therapy had a significantly larger effect than other angiotensin-converting enzyme inhibitors in reducing risk of myocardial infarction, stroke and all-cause mortality. The review had numerous methodological flaws and the authors' conclusions are unlikely to be reliable.

Authors' objectives
To determine whether perindopril produces a greater reduction in adverse outcomes compared to other angiotensin-converting enzyme (ACE) inhibitors.

Searching
MEDLINE and The Cochrane Library were searched. Retrieved articles, reviews and commentaries were cross-checked. Search terms and dates were not reported.

Study selection
Randomised controlled trials (RCTs) of ACE inhibitor therapy, irrespective of drug combinations, compared to placebo or other active therapy with a minimum of six months duration were eligible for inclusion. The prespecified outcomes were: all-cause mortality, stroke, cardiovascular events, mortality due to cardiovascular events and myocardial infarction.

Most of the included studies had composite outcomes. Studies were of varying doses of perindopril, captopril, enalapril, lisinopril, quinapril, ramipril and trandolapril. Most studies were placebo-controlled. ACE inhibitor dosage details were not reported for some studies. Some studies used ACE inhibitors in combination with other drugs. Details of the many other drugs used in the studies were provided. The range of duration of follow-up for the included studies was six months to 11.1 years (mean 3.6 years).

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Methodological quality characteristics such as blinding, randomisation, completeness of follow-up and measurement methods for outcome events were checked, but no relevant data was provided.

The authors reported neither how the validity assessment was performed nor how many reviewers were involved.

Data extraction
The number of events for each outcome were extracted in order to calculate odds ratios (OR) and 95% confidence intervals (95% CI), and p values.

The authors reported neither how data was extracted for the review nor how many reviewers performed the extraction.

Methods of synthesis
An analysis was performed using the primary outcome of the trials, irrespective of differences. Wherever possible, especially in three-arm treatment design trials, both comparators were included in order to provide the maximum possible benefit of effect for each ACE inhibitor. Pooled odds ratios and 95% confidence intervals were calculated using a fixed-effect model. Logistic regression was used to examine the effects of other variables. The influence of the
perindopril studies on the pooled effect sizes was assessed by excluding these studies. The number-needed-to-treat (NNT) was calculated.

Results of the review
Thirty relevant RCTs were identified (n=202,157).

Combined outcomes: There was a lower risk of any event in the angiotensin-converting enzyme (ACE) inhibitor group versus comparator or placebo (OR 0.91, 95% CI 0.88 to 0.94). The effect was greater for perindopril alone (OR 0.82, 95% CI 0.77 to 0.88; five RCTs) than for the other studies excluding perindopril (OR 0.95, 95% CI 0.91 to 0.98; 11 RCTs).

Myocardial infarction: (18 studies) The effect was greater for perindopril alone (OR 0.78, 95% CI 0.72 to 0.85; three RCTs) than for studies excluding perindopril (OR 0.86, 95% CI 0.80 to 0.91).

Stroke: There was a reduction in risk for pooled ACE inhibitors (OR, 0.96, p=0.05). There was a greater reduction in risk for perindopril alone (OR 0.79, 95% CI 0.72 to 0.86). Studies excluding perindopril (17 RCTs) showed no significant effect.

All-cause mortality: The effect was greater for perindopril alone, which had a significant reduction versus placebo or other drugs (OR 0.89, 95% CI 0.84 to 0.95; six RCTs) than for studies excluding perindopril (OR 0.95, 95% CI 0.92 to 0.98; 23 RCTs). This absolute risk difference correlated to a NNT of 210 for other ACE inhibitors versus 127 for perindopril (p<0.0001).

Further results were reported including a comparison between results for enalapril/lisinopril and perindopril.

Authors' conclusions
Perindopril had a significantly larger effect than other ACE inhibitors in reducing risk of myocardial infarction, stroke and mortality. One cannot assume a class effect for all ACEIs in the presence of robust RCTs for perindopril.

CRD commentary
The review addressed a well-defined question and used appropriate inclusion criteria. Search terms and dates were not reported, so it was not possible to determine how appropriate the search was. Relevant databases were searched, but apparently only for studies published in English. It appeared that unpublished studies were not considered and so some relevant studies may have been missed. It was unclear whether efforts were made to reduce error and bias in the review process (such as by use of independent duplicate study selection). Little information on the study participants was provided, which made it difficult to assess the generalisability of the results. Some study quality criteria were assessed, but no resulting details were reported; this lack of quality assessment results made it impossible to assess the strength of the evidence. The authors did not assess heterogeneity; visual assessment of heterogeneity was only possible for some analyses (presented as forest plots). The fixed-effects model used for the meta-analyses was questionable, since the data appeared to be clinically very heterogeneous. Pooling all the results for ACE inhibitors other than perindopril without also presenting pooled results by individual drug was also questionable. The review had numerous methodological flaws, so the authors' conclusions are not likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that perindopril alone or as part of combination therapy may deliver better outcomes than other ACE inhibitors. The dosage of ACE inhibitors used influences their clinical efficacy. Therefore, using the appropriate dosage was of paramount importance to achieve full benefits of treatment. The proven clinically effective dosage of specific ACE inhibitors should be used.

Research: The authors presumed that head-to-head studies comparing the individual effects of different ACEIs were unlikely to occur due to the cost of such studies.

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