Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in peritoneal dialysis: systematic review and meta-analysis of randomized controlled trials

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CRD summary
This review concluded that there was insufficient evidence to determine the effects of angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers on mortality or cardiovascular events in people on peritoneal dialysis; limited evidence may show some positive effect on renal function. The review was well conducted and the conclusions were appropriate given the limited amount of available data from small studies.

Authors' objectives
To assess the effects of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in people on peritoneal dialysis.

Searching
MEDLINE (1950 to February 2007), EMBASE (1980 to February 2007) and Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 1 2007) were searched. Search terms were reported. Reference lists of identified studies and reviews and abstracts of the American and Canadian Societies of Nephrology (2004 to 2006) were checked. CRD databases, ClinicalTrials.gov and controlled-trials.com were searched (January 2007). Investigators in the field were contacted. Published or unpublished studies were eligible. Studies that did not have a title or abstract in English were excluded.

Study selection
Randomised controlled trials (RCTs) that compared ACE inhibitors or ARBs to placebo or other antihypertensive agents in adults on peritoneal dialysis and reported on relevant outcomes were eligible for inclusion. Primary outcomes of interest were mortality and cardiovascular events (defined as myocardial infarction, new onset angina, congestive heart failure, cerebrovascular accident, transient ischaemic attack or coronary revascularisation). Secondary outcomes were renal function at 12 months, change in proteinuria at 12 months, incidence of hyperkalaemia (potassium concentration >5.5 mmol/L) and change in erythropoietin requirements at three months.

In the included studies mean ages ranged from 56 to 64 years. Studies included both men and women. All participants underwent continuous ambulatory peritoneal dialysis. Mean duration of dialysis before randomisation was from three to 10.3 months. Causes of renal failure were diabetes (0 to 46%), hypertension (0 to 9%), polycystic kidney disease (0 to 6%), glomerulonephritis (30% to 78%) or other (14% to 33%). Where reported, baseline proteinuria ranged from 1g to 2.3g per day (reported by groups). Mean systolic hypertension ranged from 151mmHg to 166mmHg, diastolic from 83mmHg to 92mmHg (reported by groups). ACE inhibitors used were ramipril, benazepril, enalapril. ARBs were valsartan or candesartan. Controls were placebo and amlodipine. Follow-up ranged from 12 to 24 months. Studies were conducted in Japan and Hong Kong.

Two reviewers independently selected studies for inclusion. Disagreements were resolved by discussion with a third reviewer.

Assessment of study quality
Delphi list criteria were used to assess quality. These were based on items such as allocation concealment, blinding, similarity of groups at baseline, prespecification of eligibility criteria, appropriate reporting of outcome measures, intention-to-treat analysis and completeness of follow-up. Items were marked yes, no or unclear.

Quality was assessed by two reviewers independently.

Data extraction
Where necessary, data were extracted from tables and graphs. Authors were contacted for additional data. For continuous data, means and standard deviations (SD) were calculated. For dichotomous outcomes, odds ratio (OR) and 95% confidence intervals (CI) were calculated.

Data were extracted by two reviewers independently.

**Methods of synthesis**
A random-effects model was used to calculate weighed mean difference (WMD) and 95% CI. Where insufficient studies were available for meta-analysis, results were reported in narrative. Heterogeneity was assessed clinically and statistically ($I^2$ statistic).

**Results of the review**
Four RCTs (154 participants) were included.

Two studies reported adequate allocation concealment. Two studies were unclear or were unreported. Two studies were double blinded.

Three trials reported on death or cardiovascular events: two studies reported no events; in a third study there was no statistical difference between groups for death or cardiovascular events.

At 12 months, use of ACE inhibitors or ARBs was associated with a higher glomerular filtration rate (WMD 0.9mL/min/1.73m$^2$, 95% CI 0.14 to 1.68, $I^2$=0%; two trials); at 24 months one study reported no difference.

One study reported results that suggested ACE inhibitors and ARBs were associated with erythropoietin resistance; however, the review authors stated that they considered there were errors in this calculation. No other adverse events were reported.

**Authors’ conclusions**
There was insufficient evidence to determine the effects of ACE inhibitors or ARBs on mortality and cardiovascular events in people on peritoneal dialysis. Limited data suggested that ACE inhibitors and ARBs may slow the loss of residual renal function.

**CRD commentary**
The aims of the review in terms of inclusion criteria for participants, treatment and study design were clearly defined. The search covered a number of relevant sources and looked for unpublished studies, which was likely to have reduced any possible affect of publication bias. Studies that did not report a title or abstract in English were excluded; it was possible that language bias may have affected the review. The methods of study selection, quality assessment and data extraction were aimed at reducing reviewer error or bias. Limited use of meta-analysis and a descriptive discussion of the results were appropriate given the small amount of available data. The authors commented that three of the included studies were conducted at the same institution and this may have had implications for generalisability of any results. Overall the review was well conducted and the authors’ conclusions are suitably conservative given the limited amount of available data.

**Implications of the review for practice and research**
The authors do not state any implications for practice.

**Research:** The authors stated that large high-quality RCTs were needed to determine the effects of ACE inhibitors and ARBs in people undergoing peritoneal dialysis.

**Funding**
None stated.

**Bibliographic details**

PubMedID
19776050

Original Paper URL
http://www.pdiconnect.com/cgi/content/abstract/29/5/554

Indexing Status
Subject indexing assigned by NLM

MeSH
Angiotensin Receptor Antagonists; Angiotensin-Converting Enzyme Inhibitors /therapeutic use; Cardiovascular Diseases /prevention & control; Humans; Kidney Failure, Chronic /mortality; Peritoneal Dialysis; Randomized Controlled Trials as Topic

AccessionNumber
12010000626

Date bibliographic record published
16/06/2010

Date abstract record published
25/08/2010

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.