Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for adults with early (stage 1 to 3) non-diabetic chronic kidney disease (Review)

Sharma P, Blackburn RC, Parke CL, McCullough K, Marks A, Black C

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for adults with early (stage 1 to 3) non-diabetic chronic kidney disease.

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Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for adults with early (stage 1 to 3) non-diabetic chronic kidney disease

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ABSTRACT

Background

Chronic kidney disease (CKD) is a long term condition that occurs as a result of damage to the kidneys. Early recognition of CKD is becoming increasingly common due to widespread laboratory estimated glomerular filtration rate (eGFR) reporting, raised clinical awareness, and international adoption of Kidney Disease Outcomes Quality Initiative (K/DOQI) classification. Early recognition and management of CKD affords the opportunity not only to prepare for progressive kidney impairment and impending renal replacement therapy, but also for intervening to reduce the risk of progression and cardiovascular disease. Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are two classes of antihypertensive drugs that act on the renin-angiotensin-aldosterone system. Beneficial effects of ACEi and ARB on renal outcomes and survival in people with a wide range of severity of renal impairment have been reported; however, their effectiveness in the subgroup of people with early CKD (stage 1 to 3) is less certain.

Objectives

This review aimed to evaluate the benefits and harms of ACEi and ARB or both in the management of people with early (stage 1 to 3) CKD who do not have diabetes mellitus.

Search methods

In March 2010 we searched The Cochrane Library, including The Cochrane Renal Group’s specialised register and The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE. Reference lists of review articles and relevant studies were also checked. The search was conducted using the optimally sensitive strategy developed by the Cochrane Collaboration for the identification of randomised controlled trials (RCTs) with input from an expert in trial search strategy.

Selection criteria

All RCTs reporting the effect of ACEi or ARB in people with early (stage 1 to 3) CKD who did not have diabetes mellitus were selected for inclusion. Only studies of at least four weeks duration were selected. Authors, working in teams of two, independently assessed the retrieved titles and abstracts, and whenever necessary the full text of these studies were screened to determine which studies satisfied the inclusion criteria.
Data collection and analysis

Data extraction was carried out by two authors, independently, using a standard data extraction form and cross checked by two other authors. Methodological quality of included studies was assessed using the Cochrane risk of bias tool. Data entry was carried out by one author and cross checked by another author. When more than one study reported similar outcomes, data were pooled using the random-effects model, but a fixed-effect model was also analysed to ensure the robustness of the model chosen and to check susceptibility to outliers. Heterogeneity was analysed using a Chi² test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I² test. Where data permitted, subgroup analysis was used to explore possible sources of heterogeneity. The quality of the evidence was analysed.

Main results

Four RCTs enrolling 2177 participants met our inclusion criteria. Of these, three compared ACEi with placebo and one compared ACEi with ARB. Two studies had an overall low risk of bias, and the other two were considered to be at moderate to high risk of bias. Low to moderate quality of evidence (from two studies representing 1906 patients) suggested that ACEi had no impact on all-cause mortality (RR 1.80, 95% CI 0.17 to 19.27, P = 0.63) or cardiovascular events (RR 0.87, 95% CI 0.66 to 1.14, P = 0.31) in people with stage 3 CKD. For all-cause mortality, there was substantial heterogeneity in the results. One study (quality assessment: low risk of bias) reported no difference in the risk of end-stage kidney disease in those with an eGFR > 45 mL/min/1.74 m² treated with ACEi versus placebo (RR 1.00, 95% CI 0.09 to 1.11, P = 0.99). The (high risk of bias) study that compared ACEi with ARB reported little difference in effect between the treatments when urinary protein, blood pressure or creatinine clearance were compared. No published studies comparing ARB with placebo or ACEi and ARB with placebo were identified.

Authors’ conclusions

Our review demonstrated that there is currently insufficient evidence to determine the effectiveness of ACEi or ARB in patients with stage 1 to 3 CKD who do not have diabetes mellitus. We have identified an area of significant uncertainty for a group of patients who account for most of those labelled as having CKD.

Plain Language Summary

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for adults with early chronic kidney disease who do not have diabetes

Chronic kidney disease (CKD) is a long-term condition that occurs as a result of the kidneys being damaged. Progressive deterioration of kidney function can lead to end-stage kidney disease (ESKD). People with ESKD cannot maintain healthy kidney function and need kidney dialysis or transplant. In the early stages of CKD, patients may not have any outward symptoms or signs of illness, and may only be detected following investigations such as urine or blood testing. Two types of drugs - angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) - have been widely recommended in clinical guidelines for doctors to use in the management of CKD. This review identified four studies (enrolling 2177 people). Three studies compared ACEi to placebo or no treatment and one study compared ACEi to ARB. There is not enough evidence in the published literature at present to determine how effective drugs in the ACEi or ARB families are for treating patients with early (stage 1 to 3) CKD who do not have diabetes.
### SUMMARY OF FINDINGS FOR THE MAIN COMPARISON

**ACEi compared to placebo for early (stage 1 to 3) non-diabetic chronic kidney disease**

**Patient or population:** patients with early (stage 1 to 3) non-diabetic chronic kidney disease  
**Settings:** hospital  
**Intervention:** ACEi  
**Comparison:** placebo

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **Mortality - CKD stage 3**  
Follow-up: 36 to 42 months | **Study population**  
103 per 1000 (18 to 1000)  
76 per 1000 (13 to 1000) | RR 1.8 (0.17 to 19.27)  
RR 0.87 (0.66 to 1.14) | 1906 (2 studies)  
1906 (2 studies) | ⊕⊕ ⊕⃝ ⼿⃝  
⊕⊕⊕ ⼿⃝ | low  
moderate |

**Cardiovascular events - CKD stage 3**  
Follow-up: 36 to 42 months | **Study population**  
104 per 1000 (69 to 119)  
82 per 1000 (54 to 93) | RR 0.87 (0.66 to 1.14)  
RR 0.87 (0.66 to 1.14) | 1906 (2 studies)  
1906 (2 studies) | ⊕⊕⊕ ⼿⃝  
⊕⊕⊕ ⼿⃝ | moderate  
moderate |
The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

---

1. There was a significant heterogeneity of 81%. One study favours control while another favours ACEI.

2. The quality of evidence is imprecise because the total number of events is less than 300 (a threshold rule-of-thumb value)(based on: Mueller et al. Ann Intern Med. 2007;146:878-881 <http://www.annals.org/cgi/content/abstract/146/12/878>)

3. Less than 10 studies, so creating a funnel plot was not applicable.
BACKGROUND

Description of the condition

Chronic kidney disease (CKD) is a long-term condition that occurs as a result of damage to the kidneys. In 2002, the US Kidney Disease Outcomes Quality Initiative (K/DOQI) proposed a classification for CKD that has been widely adopted internationally (Levey 2003).

K/DOQI Stages for CKD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal GFR: GFR &gt; 90 mL/min/1.73 m² with other evidence of chronic kidney damage*</td>
</tr>
<tr>
<td>2</td>
<td>Mild impairment: GFR 60 to 89 mL/min/1.73 m² with other evidence of chronic kidney damage*</td>
</tr>
<tr>
<td>3</td>
<td>Moderate impairment: GFR 30 to 59 mL/min/1.73 m²</td>
</tr>
<tr>
<td>4</td>
<td>Severe impairment: GFR 15 to 29 mL/min/1.73 m²</td>
</tr>
<tr>
<td>5</td>
<td>End stage kidney disease (ESKD): GFR &lt; 15 mL/min/1.73 m²</td>
</tr>
</tbody>
</table>

* Other evidence of CKD may be one of the following: persistent proteinuria; persistent haematuria (after exclusion of other causes, such as urological disease); structural abnormalities of the kidneys demonstrated on ultrasound scanning or other radiological tests (e.g. polycystic kidney disease, reflux nephropathy); or biopsy-proven chronic glomerulonephritis (most of these patients will have microalbuminuria or proteinuria, and/or haematuria).

Classification is based on two markers: evidence of kidney damage (such as the presence of microalbuminuria, proteinuria or structural abnormality); and the sustained impairment of glomerular filtration rate (GFR) for at least three months. Normal GFR in young adults is around 100 to 120 mL/min/1.73 m².

Early CKD has been described as stages 1 to 3 of the K/DOQI classification. At these stages, a patient may have no outward symptoms or signs of illness and only testing such as dipstick urine measurement for proteinuria/haematuria or blood test may detect the presence of a renal abnormality.

Prevalence

Prevalence estimates for CKD vary substantially. Several large, high quality, population-based screening studies have reported the prevalence of CKD stage 3 to 5 disease to be around 3.8% to 4.7%; more than 95% of people with an estimated GFR of less than 60 mL/min/1.73 m² have stage 3 disease (Coresh 2005; Drey 2003; Hallan 2006). In most epidemiological studies, the GFR is estimated (eGFR) from serum creatinine (SCr) measurements using an equation; several equations exist and this contributes to the variation in prevalence reported in these studies. The prevalence of stage 1 and 2 disease (based on microalbuminuria (albumin/creatinine ratio (ACR) of 17 to 250 mg/g for men or 25 to 355 mg/g for women) or macroalbuminuria (ACR > 250 mg/g for men or > 355 mg/g for women) has been reported to be as high as 11% of the population (CDC 2007). The prevalence of CKD increases with age (Coresh 2005; Hallan 2006; Imai 2007; John 2004). An ageing population, escalating prevalence of diabetes mellitus (one of the major risk factors for CKD), and increasing recognition are contributing to a reported increase in the prevalence of early CKD and its growing recognition as a major public health problem.

Consequences of early CKD

Early CKD, whilst often asymptomatic, is an important health issue and has implications for individuals and health services. Pro-
Progressive deterioration of kidney function can result in end-stage kidney disease (ESKD) and the need for renal replacement therapy (RRT) in the forms of dialysis or transplantation. The rate of progression of CKD may be influenced by secondary factors such as age, race, intraglomerular haemodynamic factors, hypertension and proteinuria. ESKD has risen globally over the last two decades at high cost to individuals, their carers and families, and health services. However, the proportion of people with early CKD who progress to ESKD is low (Daly 2007; Hallan 2006). A greater risk for people with early CKD is cardiovascular disease (CVD). One study that followed patients over a period of five years, reported that 3.1% of people with CKD progressed to requiring RRT, whereas 24.9% died before reaching dialysis, probably as a result of CVD (Daly 2007).

Early recognition and management of CKD affords the opportunity not only to prepare for progressive kidney impairment and impending RRT (CHOICE Study 2001; Dogan 2005; Khan 2007; Kinchen 2002), but also for intervening to reduce the risk of progression and CVD.

**Description of the intervention**

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are two classes of antihypertensive drugs that act on the renin-angiotensin-aldosterone system (RAAS). Both drug classes have been widely recommended in guidelines for the management of CKD, particularly in patients with evidence of proteinuria, and have been reported to provide both cardioprotective and renoprotective effects. Beneficial effects of ACEi and ARB on renal outcomes and survival in people with diabetic kidney disease (DKD) have been reported (Strippoli 2006). For non-diabetic patients with moderate to severe CKD, there was evidence of benefit in terms of renal outcomes whether or not proteinuria was present (Jafar 2003a). The evidence for cardioprotective effects, particularly in non-diabetic patients with CKD, is less consistent (ASCOT-BPLA Study 2005; HOPE Study 2000; Strippoli 2006).

To date, reviews have combined evidence from study participants with a wide range of severity of renal impairment but the subgroup of those with early CKD (stage 1 to 3) have not been presented separately.

**How the intervention might work**

As kidneys become damaged and begin to lose nephrons, patients experience systemic hypertension, proteinuria and a progressive decline in GFR (Metcalf 2007). Common pathological changes are observed regardless of the underlying causes and include early renal inflammation; tubulointerstitial injury, and glomerulosclerosis (Ruster 2006). The pathophysiology of progressive kidney function loss involves complex haemodynamic, endocrine, and inflammatory factors (Metcalf 2007; Ruster 2006).

ACEi and ARB both act to inhibit the RAAS endocrine system. ACEi mode of action includes blocking the conversion of inactive angiotensin I to active angiotensin II at the level of the enzyme needed for its conversion. ARB works at a later stage in the RAAS system and selectively blocks the type I subtype which is a receptor for angiotensin II (Kumar 2002). Once thought of as a systemic endocrine system important in mediating vascular tone, RAAS is now understood to be complex, operating both systemically and locally within the kidney. Products of the RAAS are understood to impact on a wide range of renal, as well as haemodynamic, factors that contribute to the progression of CKD (Kshirsagar 2000a; Kumar 2002; Ruster 2006).

The action of ACEi and ARB extends beyond simple blood pressure (BP) control and may reflect effects on the complex RAAS pathways. The ability of both of these drugs to inhibit the RAAS at different points means that they have the potential to moderate the functional and structural changes that occur in progressive renal insufficiency (Giatras 1997a; Jafar 2003a; Kshirsagar 2000a).

**Why it is important to do this review**

Early recognition of CKD is becoming increasingly common due to widespread laboratory reporting of eGFR, raised clinical awareness, and international adoption of K/DOQI classification. The high prevalence of early CKD means that many individuals and clinicians are faced with choices about management. Another Cochrane review (Strippoli 2006) has reviewed the evidence of effectiveness in people with diabetic CKD and demonstrated that ACEi and ARB play a core role in the management and prevention of DKD where proteinuria is a key feature. For people without diabetes, particularly those with normal or mild to moderate kidney function impairment where proteinuria may or may not be present, the role of ACEi and ARB is less certain. This review seeks to summarise the evidence in relation to benefits and harms of ACEi and ARB for non-diabetic patients with early (stage 1 to 3) CKD.

**OBJECTIVES**

This review aimed to evaluate the benefits and harms of ACEi and ARB or both in the management of people with early (stage 1 to 3) non-diabetic CKD.

**METHODS**

Criteria for considering studies for this review

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for adults with early (stage 1 to 3) non-diabetic chronic kidney disease (Review)

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Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (studies in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at the effect of ACEi or ARB were included. The first period of randomised cross-over studies were considered for inclusion. Only studies of at least four weeks duration were included.

Types of participants

Inclusion criteria

All non-diabetic adults (18 years or over) with early CKD, with no restriction to gender or race, were considered. Early CKD was defined as K/DOQI stage 1 to 3. We included studies that measured eGFR by any method (excretion of iohexol, inulin or similar marker; estimated from 24 hour urine collection; or estimated from SCr using a recognised equation).

Studies defining CKD based on SCr or other thresholds of GFR were included in the review where the results had been presented separately for those with and without diabetes. If the results were not presented separately, and less than 30% of the study population had diabetes mellitus, then the study was included and the effect on the outcomes assessed in the sensitivity analysis. The same process was adopted for study populations that included people with specific renal pathologies (e.g. immunoglobulin A (IgA) nephropathy, lupus nephritis, polycystic kidney disease).

Exclusion criteria

Any studies of patients with a diagnosis of diabetes mellitus (type I or II) were excluded. Because the prognosis for people with specific renal diagnoses cannot be generalised to the wider population with CKD, studies restricted to patients with a single specific renal diagnosis (e.g. IgA nephropathy, lupus nephropathy, polycystic kidney disease) were excluded.

Types of interventions

All ACEi and ARB or combinations were included as outlined below:

1. Treatment with ACEi versus placebo
2. Treatment with ARB versus placebo
3. Treatment with ACEi and ARB versus placebo
4. Treatment with ACEi versus ARB.

The ACEi class includes:
- Captopril
- Enalapril maleate
- Lisinopril
- Telmisartan
- Ramipril
- Valsartan
- Zofenopril.

Any dose and dosing regimen was included in the review. Combination preparations with medicines other than ACEi and ARB were not included. Only oral preparations were included.

As they are licensed, new drugs will be added to the review in subsequent updates.

Types of outcome measures

Primary outcomes

1. All-cause mortality
2. CVD morbidity and mortality (including myocardial infarction, cerebrovascular accident, congestive heart failure)
3. ESKD (including RRT)

Secondary outcomes

1. Quality of life (QoL) measured by the visual analogue scale, such as SF-36 and KDQoL
2. Adverse events including but not limited to: allergic reactions, cough, headache, hyperkalaemia, hypotension, angioedema and acute kidney injury (AKI)
3. Kidney failure progression defined by: GFR rate of decline, doubling of creatinine or progression of CKD stage
4. Proteinuria and albuminuria including: progression of microalbuminuria to macroalbuminuria, regression of macroalbuminuria to microalbuminuria, progression of normoalbuminuria to microalbuminuria, regression of microalbuminuria to normoalbuminuria measured by protein/
creatine ratio (mg/mmol); urinary total protein excretion (g/24 hours); urinary ACR (mg/mmol); urinary albumin excretion (µg/min)
5. BP: systolic and diastolic BP (mm Hg) reported as mean change from baseline or percentage reaching study specific target
6. Costs: total health care costs
7. Hospital admission rates.

Search methods for identification of studies
We searched the following resources:

Electronic searches
1. The Cochrane Renal Group's specialised register (searched 8 March 2010) and the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, Issue 1, 2010. CENTRAL and the Renal Group's specialised register contain the handsearched results of conference proceedings from general and speciality meetings. This is an ongoing activity of the Cochrane Collaboration and is both retrospective and prospective (Master List 2009). We did not therefore specifically search conference proceedings. The Cochrane Renal Group's Module in The Cochrane Library provides an up-to-date list of conference proceedings (Renal Group 2011).
2. MEDLINE (OvidSP 1950 - 8 March 2010) search was conducted using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs (Lefebvre 2008) with a search strategy developed with input from the Cochrane Renal Group's Trial Search Co-ordinator.
3. EMBASE (OvidSP 1980 - 8 March 2010) search was conducted using a search strategy adapted from that developed for the Cochrane Collaboration for the identification of RCTs (Lefebvre 2008) with a search strategy developed with input from the Cochrane Renal Group's Trial Search Co-ordinator. See Appendix 1 for search terms used.

Searching other resources
1. Reference lists of review articles and relevant studies.
2. We planned to write letters seeking information about unpublished or incomplete studies to investigators where only abstracts were identified, but none of the included studies presented this requirement.

Data collection and analysis

Selection of studies
The review was undertaken by six authors (CB, PS, RB, CP, KMCC, AM). The search strategy described was used to obtain titles and abstracts of studies potentially relevant to the review. The titles and abstracts were shared for screening by two teams of two authors who worked independently (CB, RB, CP and PS). The authors discarded the studies that were not applicable; however, studies and reviews that might include relevant data or information on trials were retained initially. Authors, working in teams of two as before, independently assessed the retrieved abstracts, and whenever necessary the full text of these studies were screened to determine which studies satisfied the inclusion criteria.

Data extraction and management
Data extraction was carried out by at least two authors, independently, using a standard data extraction form. Studies reported in non-English language journals were to be translated before assessment, but none of the included studies required translation. Where more than one publication of one study existed, reports were grouped together and only the publication with the most complete data was included. Where relevant outcomes were only published in earlier versions, these data were used. Any discrepancy between published versions was highlighted. It was planned that any further information required from the original investigator was to be requested by written correspondence and any relevant information obtained in this manner was to be included in the review. Disagreements were resolved in consultation with KMCC.

Assessment of risk of bias in included studies
The following items were independently assessed by two authors (CP, RB) using the risk of bias assessment tool (Higgins 2008) (see Appendix 2). Discrepancies were resolved by discussion with CB.

• Was there adequate sequence generation?
• Was allocation adequately concealed?
• Was knowledge of the allocated interventions adequately prevented during the study?
• Were incomplete outcome data adequately addressed?
• Are reports of the study free of suggestion of selective outcome reporting?
• Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect
Data entry was carried out by CB and cross checked by PS. For dichotomous outcomes (such as death, cardiovascular morbidity, adverse events) results were expressed as risk ratios (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (such as SCR), the mean difference (MD) was used. According to the protocol, the standardised mean difference (SMD) was to be used where different scales had been applied. In instances where change from
baseline data (change scores) were reported, the difference in mean change scores was to be used. It was planned that if standard deviations for change scores were not available, missing data were not to be imputed. Data were presented in tabular form and, where appropriate, final score data and change from baseline were incorporated into meta-analyses. If adjustment had been undertaken to account for baseline values, these data were to be reported. Time to event data (such as survival, time to ESKD) were to be analysed as a dichotomous variable where data were presented for all participants up to a specified time period. Alternatively, hazard ratios (and 95% CI) were to be used, with application of the proportional hazard assumption, for the purpose of comparison and meta-analysis (Higgins 2008).

Unit of analysis issues
We did not anticipate that there would be any non-standard designs, such as crossover studies and cluster-RCTs, but multiple arm studies could be identified. Here, all intervention groups relevant to the review were included. It was planned that if there were several relevant comparisons, all independent comparisons were to be included. It was also planned that if a comparator group overlapped (such as a single placebo arm), either comparison groups would be combined (if appropriate), or only the most important comparison would be selected for meta-analysis.

Dealing with missing data
Intention-to-treat was the primary analysis sought from studies. Missing outcomes data, and the implications were discussed but imputation of missing data was not undertaken.

Assessment of heterogeneity
Heterogeneity was analysed using a Chi² test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I² test (Higgins 2003). I² values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases
It was planned that funnel plots were to be assessed for evidence of publication bias, and to plot effect estimates against study size where data permit.

Data synthesis
Data were pooled using the random-effects model but the fixed-effects model was also analysed to ensure the robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity
Where data were available subgroup analysis was undertaken to explore possible sources of heterogeneity related to the following characteristics:
- CKD stage
- Presence of microalbuminuria/proteinuria
- Age and gender
- Comorbidities (CVD, hypertension)
- Distribution of underlying renal pathologies
- Interventions (heterogeneity in treatments could be related to prior agent(s) used and the agent, dose and duration of therapy)
- Study quality.

Adverse effects were tabulated and assessed with descriptive techniques because they were likely to be different for the various agents used. Where possible, the risk difference (RD) with 95% CI was to be calculated for each adverse effect, compared with either no treatment or another agent.

It was planned that QoL measures would be tabulated and reported descriptively, or if data permitted, meta-analysis would be undertaken as described.

Sensitivity analysis
It was planned to undertake sensitivity analysis to explore the robustness of findings to key decisions in the review process. These were to be determined as the review process took place (Higgins 2008).

The authors aimed to determine the applicability of the results to the individual with early CKD (stage 1 to 3).

R E S U L T S

Description of studies
See Characteristics of included studies tables.

Results of the search
Electronic searching retrieved a total of 2118 titles and abstracts, from which 126 potentially eligible studies were considered further. Analysis of the full text left us with four studies that met the inclusion criteria (AIPRI Study 1996; Matsuda 2003; PEACE Study 2006; REIN Stratum 1 1999). There was no disagreement among the authors about the inclusion of studies. Further information is presented in the study flow diagram (Figure 1).
Included studies

Types of study

All four included studies were RCTs and were published in full.

Types of participants

Of the four studies, three recruited patients with CKD using a range of definitions:

1. Matsuda 2003: stage 1 to 3 CKD (SCr < 265 µmol/L or “creatinine clearance > 30 mL/min/1.73 m²” plus proteinuria > 0.3 g/24 hours).
2. AIPRI Study 1996: stage 3 CKD only (SCr 133 to 354 µmol/L and 24 hour creatinine clearance (CrCl) 30 to 60 mL/min).
3. REIN Stratum 1 1999: included those with eGFR 20 to 70 mL/min/1.73 m² plus proteinuria ≥ 1 to 2.9 g/24 hours at baseline but reported a relevant CKD group - eGFR > 45 mL/min/1.73 m² separately (stage 1 to 3a).
4. PEACE Study 2006: included patients with stable coronary artery disease and those with reduced left ventricular function at baseline. The study reported relevant CKD group with eGFR 45 to 59.9 mL/min/1.73 m² (stage 3a) and eGFR < 45 mL/min/1.73 m² (minimum 27 mL/min/1.73 m²) (stage 3b).

Therefore, in two studies the included participants were a subgroup of the originally randomised patients (PEACE Study 2006; REIN Stratum 1 1999).

The proportion of participants in CKD stage 3a and 3b varied; 39% (AIPRI Study 1996) to 88% (PEACE Study 2006) were in stage 3a CKD, and 12% (PEACE Study 2006) to 61% (AIPRI Study 1996) were in stage 3b CKD. Different definitions and measures of GFR were reported in each study.

One study had fewer than 100 participants (Matsuda 2003); two had between 100 and 1000 (AIPRI Study 1996; REIN Stratum 1 1999); and one had more than 1000 participants (PEACE Study 2006).

All studies included both male and female adult participants, although a higher proportion of males was common among all studies. Two studies had an age range of 18 to 70 years (AIPRI Study 1996; REIN Stratum 1 1999); one study included participants aged over 50 years (PEACE Study 2006), and another indicated that at baseline, all participants were adults without specifying an age range (Matsuda 2003).

There were two studies that included patients with diabetes mellitus (AIPRI Study 1996; PEACE Study 2006), but these patients represented less than 30% of the total participants at baseline. One study included only people with stable coronary artery disease or left ventricular failure (PEACE Study 2006).

Hypertension was common among study participants: one study included only patients with hypertension (Matsuda 2003); and in the other three studies, more than 50% of participants were hyper-
Each study included multiple underlying kidney diseases: glomerular diseases accounted for 33% (AIPRI Study 1996) to 98% (Matsuda 2003) of study participants; interstitial nephritis or polycystic disease was present in 7% (REIN Stratum 1 1999) to 29% (AIPRI Study 1996); nephrosclerosis occurred 2% (Matsuda 2003) to 16% (AIPRI Study 1996); and 18% (AIPRI Study 1996) to 47% (REIN Stratum 1 1999) of patients had unknown or other renal diagnosis. The results were not presented separately for different disease subgroups.

Two studies defined CKD based on CrCl level from 24 hour urine collection at baseline (AIPRI Study 1996; Matsuda 2003); one estimated GFR using iohexol clearance (REIN Stratum 1 1999); and another used eGFR (four-variable Modification of Diet in Renal Disease [MDRD] formula) to define relevant CKD groups (PEACE Study 2006). One study used SCr (133 to 354 µmol/L) in addition to CrCl level, thus excluding patients with the most mild stage 3 CKD (AIPRI Study 1996).

Two studies included patients with proteinuria at baseline (REIN Stratum 1 1999: ≥ 1 to 2.9 g/24 hours; Matsuda 2003: > 0.3 g/24 hours); the remaining two studies did not report presence or absence of proteinuria among participants at baseline (AIPRI Study 1996; PEACE Study 2006).

Types of interventions
Three of the four included studies compared three different ACEi drugs with placebo:
- Ramipril (REIN Stratum 1 1999)
- Benazepril (AIPRI Study 1996)
- Trandolapril (PEACE Study 2006).

None of the included studies compared ARB with placebo or ACEi and ARB with placebo.

Only one study compared ACEi (perindopril or trandolapril) with ARB (losartan or candesartan) (Matsuda 2003).

Type of outcomes
Three studies presented data on our listed primary outcomes:
- All-cause mortality (AIPRI Study 1996; PEACE Study 2006)
- Cardiovascular morbidity/mortality (AIPRI Study 1996; PEACE Study 2006)
- ESKD (REIN Stratum 1 1999).

Of our listed secondary outcomes, no study reported findings for QoL, hospital admission rates or costs. Two studies reported their findings for stage 3a and 3b CKD separately (AIPRI Study 1996; PEACE Study 2006) and one study reported by low and high proteinuria level (Matsuda 2003).

Excluded studies
A total of 93 studies were excluded. The main reason for exclusion was that studies did not present outcomes separately for stage 1 to 3 CKD. See Characteristics of excluded studies for further information.

The COOPERATE Study 2003 was excluded after a letter of retraction was published by the editors of The Lancet in October 2009.

The REIN study was split into two stratum based on baseline proteinuria. The low proteinuria study has been reported here. The high proteinuria study (> 3 g/24 hours) did not report findings separately by eGFR or CKD stage and was excluded (REIN Stratum 2 1997).

Risk of bias in included studies
Details of the risk of bias are given in the Risk of Bias Table. Two studies had an overall low risk of bias (PEACE Study 2006; REIN Stratum 1 1999). One small study was characterised by particularly high risk of bias: there was little information reported about the randomisation method and no indication of blinding (Matsuda 2003). Two studies reported longer term follow-up beyond the end of the treatment phase and were subject to substantial switching between treatment groups (AIPRI Study 1996; PEACE Study 2006). See Figure 2 and Figure 3 for the summary results for risk of bias.
Figure 2. Methodological quality summary: review authors’ judgements about each methodological quality item for each included study.

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding (performance bias and detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIPRI Study 1996</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Matsuda 2003</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>PEACE Study 2006</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>REIN Stratum 1 1999</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
Two studies reported data for relevant subgroups but the full study population is not included here (PEACE Study 2006; REIN Stratum 1 1999).

Using funnel plots to detect publication bias was not feasible because of the small number of studies included in this review.

**Allocation**

The method of sequence generation and allocation concealment was adequately reported in two studies (PEACE Study 2006; REIN Stratum 1 1999), unclear in one (AIPRI Study 1996), and the method of randomisation was not described in the fourth study (Matsuda 2003).

**Blinding**

Two studies were double blinded (AIPRI Study 1996; REIN Stratum 1 1999) and one study was blinded to treatment only (PEACE Study 2006). The study that compared two active treatment groups did not report on blinding (Matsuda 2003). The PEACE Study 2006, which started randomisation in 1996, blinded study treatment until 2002, when the study's steering committee recommended open label treatment with ACEi of those patients with diabetes, hypertension and microalbuminuria, or proteinuria. The REIN Stratum 1 1999 continued its treatment as open label after 27 months of blinding.

**Incomplete outcome data**

Two studies reported no missing data (AIPRI Study 1996; Matsuda 2003) and the other two addressed missing data (PEACE Study 2006; REIN Stratum 1 1999). Analysis was performed based on intention-to-treat analysis in all but one study (Matsuda 2003).

**Selective reporting**

There was no evidence of the selective reporting of outcomes in the included studies.

**Other potential sources of bias**

Studies presenting long term outcomes were based on open label follow-up (AIPRI Study 1996; PEACE Study 2006). The proteinuria subgroup of the REIN Stratum 1 1999 was stopped ahead of schedule by the advisory panel because of significant benefits to the treatment group. Matsuda 2003 provided insufficient information to determine if there were any other potential sources of bias.

**Effects of interventions**

See: Summary of findings for the main comparison ACEi compared to placebo for early (stage 1 to 3) non-diabetic chronic kidney disease; Summary of findings 2 ACEi compared to placebo (single study outcomes)

See Summary of findings for the main comparison; Summary of findings 2.

**ACEi versus placebo**

Three studies compared ACEi with placebo. Duration of treatment ranged from 36 (AIPRI Study 1996) to 63 months (REIN Stratum 1 1999). Follow-up extended to 6.6 years (AIPRI Study 1996). None of the studies reported information for subgroups based on age, gender, proteinuria or comorbidities. Where subgroup data were available by disease stage and underlying kidney...
 PRIMARY OUTCOMES

ALL-CAUSE MORTALITY

Two studies reported all-cause mortality for stage 3 CKD only. A total of 170 deaths occurred in 1906 patients (77/1001 in the treated group versus 93/905 in the placebo group). In the AIPRI Study 1996, a total of nine deaths occurred (8/300 in the treatment group versus 1/283 in the placebo group) during a treatment period of three years. In the PEACE Study 2006, 161 deaths were reported (69/701 in the treatment group versus 92/622 in the placebo group) during a median follow-up period of 4.8 years. There was no statistically significant difference in the risk of death among those treated with ACEi compared with placebo. (Analysis 1.1.1 (2 studies, 1906 participants): RR 1.80, 95% CI 0.17 to 19.27). There was statistically significant heterogeneity (I² = 81%, P = 0.02); PEACE Study 2006 reported a statistically significant reduction in deaths in the treated group (RR 0.67, 95% CI 0.50 to 0.89); AIPRI Study 1996 observed fewer deaths in the placebo group.

LONG-TERM FOLLOW-UP

AIPRI Study 1996 reported an extended period of follow-up at the end of the treatment phase of the study to give a total median duration of 6.6 years. During the extended follow-up, 64% of those patients randomised to benazepril continued on an ACEi, and 61% in the placebo arm started treatment with an ACEi. At the end of this time no statistically significant differences were observed in the number of deaths between the groups (based on their original treatment allocation); 25/300 patients who were originally treated with benazepril and 23/283 who received placebo had died (RR 1.55; 95% CI 0.95 to 2.59).

CARDIOVASCULAR MORTALITY AND MORBIDITY

Two studies reported cardiovascular events (AIPRI Study 1996; PEACE Study 2006) for stage 3 CKD only. A total of 186 cardiovascular events occurred in 1906 patients (92/1001 in the treatment group and 94/905 in the placebo group).

ESKD

Only REIN Stratum 1 1999 reported kidney survival in a subgroup of patients whose baseline GFR was > 45 mL/min/1.73 m² (maximum GFR 70 mL/min/1.73 m²). At 63 months, only 3% of patients in this subgroup progressed to RRT. No statistically significant difference in RR was reported between ACEi and placebo (RR 1.00, 95% CI 0.09 to 1.11, P = 0.99).

KIDNEY IMPAIRMENT AND PROGRESSION

DOUBLING OF CREATININE

AIPRI Study 1996 reported 88/583 participants experienced doubling of creatinine or the need for dialysis during a follow-up of 3 years. (Of the 583 patients only two needed dialysis, one each in the treatment group and the placebo group). There was a statistically significant reduction in the doubling of creatinine among the ACEi group versus placebo (Analysis 1.3.1: RR 0.51, 95% CI 0.34 to 0.77).

CHANGE IN GFR

REIN Stratum 1 1999 reported the mean rate of change in GFR/month for patients whose baseline GFR was > 45 mL/min/1.73 m² as 0.19 mL/min/1.73 m² (standard error (SE) 0.07) in the ACEi group compared with 0.34 mL/min/1.73 m² (SE 0.09) in the placebo group (P = 0.25).

ADVERSE EVENTS AND WITHDRAWALS

Only AIPRI Study 1996 reported adverse events or withdrawals for relevant patient groups (See Table 1). A total of 71 adverse events were reported in 583 patients (38/300 in the ACEi group and 33/283 in the placebo group) (Analysis 1.5: RR 1.09, 95% CI 0.70 to 1.68). Fewer than 1% of patients reported dry cough in both the ACEi and the placebo groups. Few patients experienced dry cough.
hyperkalaemia (2% ACEi versus 1% placebo). Hypertensive crisis was not reported by any patient in the treatment group compared with 1.4% of patients in the placebo group. Adverse events caused withdrawal from the study by 12% of patients in the ACEi group and 9% in the placebo group. Withdrawals due to other events, such as loss to follow-up, protocol violation or lack of cooperation, was 6% in the ACEi group and 8% in the placebo group. Further details on withdrawals and adverse events are presented in Table 1.

Two studies (PEACE Study 2006; REIN Stratum 1 1999) reported adverse events and withdrawals for those who were randomised at study level, but not for the relevant subgroups that were of interest for this review.

**Secondary outcomes**

**Proteinuria**  
AIPRI Study 1996 reported on proteinuria observing a decrease in urinary protein of 29% in the ACEi group and an increase by 9% in the placebo group at 36 months (statistical significance not reported).

**Blood pressure**  
AIPRI Study 1996 reported change in mean BP from baseline values at 36 months. Mean systolic BP decreased by 4.5 to 8.0 mm Hg in the ACEi group versus an increase of 1.0 to 3.7 mm Hg in the placebo group at 6, 12, 24 and 36 months. Mean diastolic BP decreased by 3.5 to 5.0 mm Hg in the ACEi group versus increases of 0.2 to 1.5 mm Hg in the placebo group at 6, 12, 24 and 36 months. The study also reported that uncontrolled hypertension decreased from 28% to 18% in the ACEi group and there was an increase from 27% to 32% in the placebo group.

**Subgroup analyses**  
There was insufficient data to pool estimates for subgroup analysis for any of the outcomes. The analysis is based on single study data.

**CKD stage**  
PEACE Study 2006, which reported results for all-cause mortality and CVD events, stratified by stage 3a and 3b, found no statistical significant effect of ACEi over placebo in either mortality (Analysis 1.1.2, stage 3a: RR 0.73, 95% CI 0.52 to 1.01; Analysis 1.1.3, stage 3b: RR 0.64, 95% CI 0.34 to 1.20) or CVD events (Analysis 1.2.2, stage 3a: RR 0.92, 95% CI 0.67 to 1.26; Analysis 1.2.3, stage 3b: RR 0.83, 95% CI 0.46 to 1.50).  
AIPRI Study 1996 reported results for doubling of creatinine by CKD stage. The effect of ACEi to reduce the number with doubling of creatinine varied according to stage of CKD. A 70% reduction in the risk of doubling creatinine was observed in the ACEi group versus placebo for CKD stage 3a (Analysis 1.3.2: RR 0.30, 95% CI 0.11 to 0.79) and 39% reduction for stage 3b (Analysis 1.3.3: RR 0.61, 95% CI 0.39 to 0.94).

**Presence of proteinuria**  
REIN Stratum 1 1999 included only participants with proteinuria. AIPRI Study 1996 reported reduction in risk of the doubling of creatinine level (or ESKD) in people with stage 3 CKD stratified by baseline 24 hour urinary protein. For those with ≤ 1 g/L and > 1 g/L to < 3 g/L there was no statistically significant difference compared with placebo (≤ 1 g: 31%, 95% CI -67 to 71; > 1 g to < 3 g: 53%, 95% CI -14 to 81) but a statistically significant reduction was observed for those with ≥ 3 g/L (66%, 95% CI 34 to 82). A similar pattern was observed when adjusted for change in diastolic BP and change in urinary protein excretion. PEACE Study 2006 did not report on proteinuria.

**Age and comorbidities**  
PEACE Study 2006, which included older patients who had established CVD at baseline, reported a significant beneficial effect of ACEi on all-cause mortality, but not on cardiovascular or renal outcomes. Most of the included study participants were hypertensive (PEACE Study 2006: 54%; AIPRI Study 1996: 81% (ACEi group), 83% (placebo group); REIN Stratum 1 1999: 79% (ACEi group), 85% (placebo group)). AIPRI Study 1996 reported the effect of ACEi on doubling of creatinine stratified by baseline diastolic BP. For those with a treated diastolic BP > 90 mm Hg there was a statistically significant reduction in doubling of creatinine in those treated with ACEi compared with placebo (51%, 95% CI 13 to 73). After adjusting for changes in diastolic BP and proteinuria, the difference was lost. For those with normal, untreated BP or a treated diastolic BP > 90 mm Hg at baseline, there was no statistically significant difference (58%, 95% CI -72 to 89; 50%, 95% CI -8 to 76 respectively).

**Distribution of underlying renal pathologies**  
AIPRI Study 1996 reported data for doubling of creatinine or ESKD at 36 months by underlying renal pathology (Analysis 1.4). The effect of ACEi in reducing doubling of creatinine varied according to the underlying renal pathologies. Among those with underlying glomerular diseases, a statistically significant reduction in the doubling of creatinine was observed in the ACEi group compared with placebo (Analysis 1.4.1: RR 0.42, 95% CI 0.22 to 0.81). In the patients with other renal diagnoses (diabetic kidney disease, polycystic kidney disease, nephroclerosis, interstitial nephritis and unknown renal disorders), there was no statistically significant difference observed.
None of the included studies reported ESKD events and change in GFR by subgroup.

**ARB versus placebo**
There were no published studies identified that compared ARB with placebo.

**ACEi plus ARB versus placebo**
There were no published studies identified that compared ACEi plus ARB with placebo.

**ACEi versus ARB**

Matsuda 2003 compared ACEi with ARB. The study reported BP, CrCl and proteinuria stratified by baseline proteinuria level; those with mild (< 1 g/day), and moderate (> 1 g/day) proteinuria levels. The authors reported that no significant difference was observed between ACEi and ARB in terms of change of BP from baseline and at 48 weeks (no values reported). Twenty seven patients were treated with ACEi (perindopril or trandolapril) and 25 patients were treated with ARB (losartan or candesartan).

**Subgroup analysis**

**Presence of proteinuria**

No significant change in urinary protein excretion was observed for patients with mild proteinuria who received either ACEi or ARB (data were reported graphically only). A statistically significant benefit was observed among patients with moderate proteinuria at 48 weeks: ACEi significantly reduced urinary protein excretion by 54% (standard error of mean (SEM) 7%) (from 2.7 (SEM 0.5) g/day to 1.2 (0.2) g/day, P < 0.05). Similarly, a statistically significant reduction of 41% (SEM 6%) (from 2.7 (0.4) g/day to 1.6 (0.3) g/day, P < 0.05) was observed in the ARB group. For ARB versus ACEi, there was a statistically significant reduction in the ARB group at 48 weeks (P < 0.05) but not at 12 weeks (P > 0.2).

Among patients with mild proteinuria, a statistically significant reduction in systolic/diastolic BP was reported from baseline to 48 weeks for both ACEi and ARB.

- ACEi: difference of mean* 17/12 mm Hg; from 148/86 (SEM 3/5) mm Hg to 131/74 (SEM 4/4) mm Hg, (P < 0.05)
- ARB: difference of mean* 17/15 mm Hg; from 154/86 (SEM 4/3) mm Hg to 137/71 (SEM 3/2) mmHg, P < 0.05).

For those with moderate proteinuria, marked reductions in BP (systolic/diastolic) were observed at 48 weeks in the ACEi group (difference of mean* 28/12 mm Hg; from 152/90 (SEM 4/3) mm Hg to 124 (SEM 4/3)(diastolic BP only reported in graph) mm Hg, P < 0.01) while only a modest reduction was observed in the ARB group (difference of mean* 13/10; from 150/89 (SEM 3/3) mm Hg to 137/79 (SEM 4/3) mm Hg, P < 0.05).

(*difference of mean baseline values and the values at 48 weeks).

CrCl was stable (data were reported graphically only) in both ACEi and ARB treatment groups and for both mild and moderate proteinuria.
### ADDITIONAL SUMMARY OF FINDINGS

**Explanation**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI) for study population</th>
<th>Relative effect (95% CI)</th>
<th>No. of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality - CKD stage 3a</td>
<td>Study population</td>
<td>RR 0.73 (0.52 to 1.01)</td>
<td>1203</td>
</tr>
<tr>
<td>Follow-up: median 4.8 years</td>
<td>124 per 1000 (64 to 125)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality - CKD stage 3b</td>
<td>Study population</td>
<td>RR 0.64 (0.34 to 1.2)</td>
<td>157</td>
</tr>
<tr>
<td>Follow-up: median 4.8 years</td>
<td>256 per 1000 (87 to 307)</td>
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</tr>
<tr>
<td>Cardiovascular events - CKD Stage 3a</td>
<td>Study population</td>
<td>RR 0.92 (0.67 to 1.26)</td>
<td>1203</td>
</tr>
<tr>
<td>Follow-up: median 4.8 years</td>
<td>117 per 1000 (78 to 147)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular events - CKD Stage 3b</td>
<td>Study population</td>
<td>RR 0.83 (0.46 to 1.5)</td>
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<tr>
<td>Follow-up: median 4.8 years</td>
<td>244 per 1000 (112 to 366)</td>
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</tr>
<tr>
<td>Doubling of creatinine - CKD stage 3</td>
<td>Study population</td>
<td>RR 0.51 (0.34 to 0.77)</td>
<td>583</td>
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<tr>
<td>Follow-up: 36 months</td>
<td>201 per 1000 (88 to 155)</td>
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<tr>
<td>Doubling of creatinine - CKD Stage 3b</td>
<td>Study population</td>
<td>RR 0.61 (0.39 to 0.94)</td>
<td>356</td>
</tr>
<tr>
<td>Follow-up: 36 months</td>
<td>239 per 1000 (93 to 225)</td>
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<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>Study population</td>
<td>RR 1.09 (0.7 to 1.68)</td>
<td>583</td>
</tr>
<tr>
<td>Follow-up: 36 months</td>
<td>117 per 1000 (82 to 197)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio
DISCUSSION

Summary of main results

Despite growing international emphasis on the early detection and management of CKD, and that stage 1 to 3 CKD accounts for most people with evidence of kidney impairment, we found very few studies that reported the effectiveness of ACEi or ARB in this population. Only three studies that compared ACEi with placebo in people with stage 1 to 3 CKD were identified (AIPRI Study 1996; PEACE Study 2006; REIN Stratum 1 1999), and one study that compared ACEi with ARB was found (Matsuda 2003). Two studies were considered to be at moderate to high risk of bias (Matsuda 2003; REIN Stratum 1 1999). The patient groups included in the studies varied considerably, particularly in terms of comorbidities and severity of proteinuria. This made it difficult to draw any overall conclusions. Each of the four included studies differed in their definitions of CKD in terms of GFR cutoff levels and measures of GFR. These differences are particularly important when identifying a cohort of people with stage 3 CKD. Invariably, participants in each study differed in regard to their reported degrees of kidney impairment.

The low to moderate quality evidence from two studies (AIPRI Study 1996; PEACE Study 2006) suggested that ACEi had no impact on all-cause mortality or cardiovascular events in people with stage 1 to 3 CKD. There was substantial heterogeneity in the results relating to all-cause mortality: one study reported a modest benefit and the other reported potential harm. The study that showed a small potential benefit included older patients (aged > 50 years) with coronary artery disease (PEACE Study 2006). Approximately 20% of patients who participated in this study had diagnoses of diabetes at baseline. The study that reported potentially harmful outcomes (AIPRI Study 1996) included comparatively younger patients with no underlying CVD, but including small numbers of participants with hypertension and with diabetes mellitus (4%). There was insufficient evidence to assess whether these are true subgroups of the study population who had different responses to ACEi treatment, or if these outcomes reflect chance or other variations in the studies, including the specific ACEi study drug (Trandolapril was used in the PEACE Study 2006 and benazepril in the AIPRI Study 1996).

In terms of renal outcomes, one study assessed as having a low risk of bias reported no difference in the risk of ESKD among those with an eGFR > 45 mL/min/1.73 m² treated with ACEi versus placebo (REIN Stratum 1 1999). One study that featured a moderate risk of bias reported a 50% reduction in the risk of creatinine doubling in those with stage 3 CKD who were treated with ACEi (AIPRI Study 1996). This study also reported a reduction in proteinuria among people in the ACEi group. The greatest benefit was observed in those people with stage 3a CKD. Only one study reported adverse events for the relevant study participants, and no statistically significant difference between patients in the ACEi and placebo groups (AIPRI Study 1996). Very few people reported cough or hyperkalaemia. The one study with a high risk of bias that compared ACEi with ARB (Matsuda 2003), reported little difference in effect between treatments when urinary protein, BP or CrCl were measured. This study did not report all-cause mortality, cardiovascular events, ESKD or adverse events.

Overall completeness and applicability of evidence

This review highlights the striking lack of studies in people with stage 1 to 3 CKD, which is the population group that accounts for most people identified as having CKD. Identification of CKD stages 1 and 2 requires evidence of kidney damage such as confirmation of proteinuria, haematuria or structural abnormality. This requirement may make identifying people to participate in studies more challenging, and even more so for investigators looking into single, specific renal diagnoses.

The two major issues around applicability of the evidence to clinical practice and patients were:

- definition of CKD and
- the underlying pathologies that caused the kidney damage.

Two of the four included studies that reported data for all-cause mortality and cardiovascular morbidity and mortality defined their CKD groups based on single eGFR assays (AIPRI Study 1996; PEACE Study 2006), and therefore were prone to classification bias because of the chance of including people with AKI. Only one study based the definition of CKD on an eGFR using standard equations (PEACE Study 2006), which is the method most widely adopted in clinical practice, but likely to underestimate GFR in those with true GFR level of around 60 mL/min/1.73 m². The included patient population comprised mainly hypertensive patients with varying renal pathologies, and 4% (AIPRI Study 1996) to 19% (PEACE Study 2006) had diabetes mellitus at baseline. The high proportion of people with diabetes, and the inclusion of only people with existing CVD in the PEACE Study 2006, make it difficult to draw conclusions for the wider population with early CKD. The PEACE Study 2006 reported a reduction in all-cause mortality consistent with other studies of ACEi in populations with CVD; however the investigators did not report the statistically significant benefits in kidney outcomes that were observed in other studies conducted among diabetic study participants only. The proportions of patients with CVD and specifically reported renal diagnoses varied from study to study.

We identified a number of significant gaps in the evidence. No studies were identified that compared ARB with placebo or ACEi combined with ARB. Only some of the many preparations of ACEi and ARB drugs available were investigated in the studies and none compared one preparation with another. Intervention features such as compliance, timing, dosing or intensity could not

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be elicited because of poor reporting in studies. Although most of the included studies reported on some measure of kidney function over time, mortality and ESKD, none reported on quality of life, admissions to hospital or costs.

Quality of the evidence

Figure 2 and Figure 3 summarise the quality of the included studies. Although it was found that two studies were of low risk of bias, the small number of studies, their relatively small size, and low event rates for some of the primary outcomes meant that the evidence was of low to moderate quality or based on a single study. Findings should therefore be viewed with caution.

Potential biases in the review process

Strengths and limitations

This review was conducted as per the protocol following pre-specified inclusion criteria and included comprehensive literature searches to find all relevant studies. Two authors screened all titles, abstracts and full papers to avoid selection bias. There was no arbitration required during the selection process, data extraction or quality assessment that needed a third author. We found very few studies reporting outcomes for the group of patients of interest in this review (stage 1 to 3 CKD). We excluded studies of single specific renal diagnoses, and it is acknowledged that some of these may include patients with evidence of isolated proteinuria (stage 1 CKD). A large number of studies conducted in people with CKD were excluded because the authors did not report their findings in subgroups that were relevant to this study. In addition, studies of the use of ACEi and ARB drugs in hypertensive patients may also include people with stage 1 to 3 CKD. Before asking authors to consider re-analysing data into specified subgroups, we considered it appropriate to establish what data were available in the published literature.

Agreements and disagreements with other studies or reviews

We did not find any other published reviews that matched our inclusion criteria. Two systematic reviews reported that ACEi was found to have little benefit over placebo or other antihypertensive drugs in reducing all-cause mortality among patients with CKD or hypertension (P = 0.12) (Jafar 2001) or those with diabetes mellitus (Strippoli 2006). In the meta-analysis (21 studies, 7295 patients) of patients with diabetes and CKD, no survival benefit was observed compared with placebo (RR 0.91, 95% CI 0.71 to 1.17) except when treated with maximum tolerable doses (RR 0.78, 95% CI 0.61 to 0.98) (Strippoli 2006). Jafar 2001 reported ACEi to be effective in reducing mean BP (mean decrease - systolic: 4.5 mm Hg; 95% CI 3.0 to 6.1 mm Hg and diastolic: 2.3 mm Hg; 95% CI 1.4 to 3.2 mm Hg); protein excretion (mean decrease: 0.46 g/d; 95% CI 0.33 to 0.59 g/d); and in reducing the risk of renal progression (doubling of SCr or onset of ESKD: RR 0.70 95% CI 0.55 to 0.88) compared with placebo or other antihypertensive drugs. The 11 included studies used different measures of CKD. Baseline mean creatinine was >155 µmol/L in all but two studies (where it was 124 µmol/L and 88 µmol/L). In general, these studies included participants with greater kidney impairment than we have included here. The findings reported by Jafar 2001 were not stratified by CKD stage, and therefore, they could not be compared directly. The authors did note that the benefit of ACEi on reducing progression to ESKD was modified by the presence of proteinuria at baseline (RR 0.09, 95% CI 0.07 to 0.11) and was lower for those with proteinuria levels of 2.0 g/24 hours compared with 1.0 g/24 hours). Baseline creatinine was not found to modify the effect of ACEi on ESKD. Similarly, in people with diabetes and CKD, ACEi produced a 31% risk reduction of ESKD compared with placebo (RR 0.60, 95% CI 0.39 to 0.93). These outcomes were found to be similar for ARB (RR 0.78, 95% CI 0.67 to 0.91) (Strippoli 2006). However, the findings were not reported separately by stage.

Authors’ conclusions

Implications for practice

With increased recognition of the importance and impact of CKD, the diagnosis and labelling of people with early (stage 1 to 3) CKD is now common. Drugs in the ACEi and ARB families are the cornerstone for management of CKD. This review highlights that there have been very few studies that report on the effectiveness of ACEi and ARB drugs for patients with early CKD, without those studies investigating single, specific renal diagnoses. Despite that people with early CKD are at greater risk of all-cause mortality and cardiovascular events than progression to ESKD (Daly 2007; Hallan 2006; Sharma 2010), we found very few studies that considered the early management of CKD to reduce cardiovascular risk, all-cause mortality or kidney disease progression.

Our review demonstrated that there is currently insufficient evidence to determine the effectiveness of ACEi or ARB treatment for patients with stage 1 to 3 CKD who do not have diabetes mellitus. Studies have been conducted among patients with single, specific renal diagnoses but we have not included these here. Based on evidence from studies of specific renal conditions, current clinical guidelines (Levey 2003; NICE Guideline 2008; SIGN Guideline 2008) and practice support the use of ACEi and ARB drugs for...
patients with proteinuric kidney disease. We have not found sufficient evidence to support any change in current practice.

**Implications for research**

We have identified an area of significant uncertainty for a group of patients who account for most of those labelled as having CKD. We identified more than 50 studies where relevant data may exist, but the subgroups of patients that are necessary to derive supported evidence were not presented in the original publications (see Characteristics of excluded studies). These studies may provide relevant subgroup or individual patient data for analysis of patients with stage 1 to 3 CKD. In addition, studies of ACEi (such as HOPE Study 2000; PART 2 (MacMahon 2000); PROGRESS Collaborative Group 2001; SCAT Study 2000) and ARB (such as LIFE (Lindholm 2002); SCOPE (Lithell 2003)) conducted in people with hypertension or CVD may also include people who meet the criteria of CKD stage 1 to 3 that would potentially enable subgroup or individual patient data analysis.

There is potential need for further RCTs to be conducted that focus on patients with stage 1 to 3 CKD. These studies should feature designs that are adequate in size and duration, include quality of life outcomes and establish recruitment criteria to ensure that the study population can be generalised to the wider community.

**Acknowledgements**

We wish to thank the referees for their comments and feedback during the preparation of this review.

**References**

**References to studies included in this review**

**AIPRI Study 1996** (*published data only*)


**Matsuda 2003** (*published data only*)


**PEACE Study 2006** (*published data only*)


**REIN stratum 1 1999** (*published data only*)


References to studies excluded from this review

AASK Pilot Study 1996 [published data only]

Acone 2003 [published data only]

Appel 2008 [published data only]

Aranda 2005 [published data only]

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Nakao N, Seno H, Kasuga H, Toriyama T, Kawahara H, Fukagawa M. Effects of combination treatment with losartan and trandolapril on office and ambulatory blood pressures in non-diabetic renal disease: a COOPERATE-
Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for adults with early (stage 1 to 3) non-diabetic chronic kidney disease (Review)

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Nakao N, Takada M, Nakagawa T, Sanaka T, Kayano T. Combination therapy of ace inhibitor and A-II receptor antagonist more powerfully retard progression of non-diabetic renal failure than monotherapy of each drug - a multicenter, three year, double-blind, randomized trial in Japan (COOPERATE) [abstract]. Nephrology Dialysis Transplantation 2001;16(6):A99.


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Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for adults with early (stage 1 to 3) non-diabetic chronic kidney disease (Review)

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Mann 1997 [published data only]

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Pedersen EB. [Reduced progression, increased mortality in chronic renal failure after treatment with the angiotensin-converting enzyme inhibitor benazepril] [Danish]. Ugeskrift for Læger 1996;158(41):5798–9. [MEDLINE: 8928272]

Phillips 2007 [published data only]

Plum 1998 [published data only]

Praga 2002 [published data only]

PROGRESS Study 2007 [published data only]

REIN Stratum 2 1997 [published data only]


Renke 2004 [published data only]

ROAD Study 2007 [published data only]

Ruliope 2000 [published data only]

Rump 1999 [published data only]

Sanchez 1991 [published data only]

Santoni 1989 [published data only]

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Scaglione 2005 [published data only]

Schmieder 2004 [published data only]

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Menne J, Farsang C, Deak L, Klebs S, Meier M, Handrock R, et al. Valsartan in combination with lisinopril versus the...

**van Hout 1997** *published data only*


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### Additional references

**ASCOT-BPLA Study 2005**


**CDC 2007**


**CHOICE Study 2001**


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**Daly 2007**


**Dogan 2005**


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**Higgins 2003**


**Higgins 2008**


**HOPE Study 2000**


**Imai 2007**


**Jafar 2003a**


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Sharma 2010

SIGN Guideline 2008
Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for adults with early (stage 1 to 3) non-diabetic chronic kidney disease (Review)

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Strippoli 2006

* Indicates the major publication for the study
### Characteristics of included studies  
(order by study ID)

**AIPRI Study 1996**

| Methods | Study design: randomised, double-blind, placebo-controlled RCT  
Study period: January 1989 to December 1990  
Duration of follow-up: median 3.6 year additional extended follow-up |
|---|---|
| Participants | Inclusion criteria  
Setting: Hospitals (49 centres)  
Countries: Germany, Italy, France  
Relevant health status  
Renal diagnosis (n): glomerular disease (192, 33%); interstitial nephritis (105, 18%); nephrosclerosis (97, 16%); polycystic kidney disease (64, 11%); DKD (21, 4%); chronic renal insufficiency of unknown cause (104, 18%)  
SCr: 1.5 to 4.0 mg/dL (133 to 354 μmol/L)  
24 hour estimated CrCl: 30 to 60 mL/min  
21 (4%) of participants with type 2 diabetes mellitus included and not presented separately  
Number: Treatment group (300); control group (283)  
Age (mean ± SD years): Treatment group (51 ± 13); control group (51 ± 12)  
Age range: 18 to 70 years  
Sex (M/F): Treatment group (220/80); control group (201/82)  
Hypertension: Treatment group (244, 81%); control group (234, 83%)  
Exclusion criteria  
Therapy-resistant oedema; treated with corticosteroids, NSAIDs, or immunosuppressive drugs; exhibited urinary protein excretion > 10 g/24 hours or serum albumin < 25 g/L; insulin-dependent diabetes mellitus, hypertension (renovascular, malignant); experienced myocardial infarction, cerebrovascular accident or congestive heart failure; elevated aminotransferase concentration; collagen disease; obstructive uropathy; cancer; chronic cough; allergy to ACEi, history of drug or alcohol abuse; pregnancy |
| Interventions | Treatment group (ACEi)  
Benazepril  
10 mg once daily  
Control group (placebo)  
Placebo  
1 tablet per day  
Co-interventions  
All patients were advised to reduce their salt intake to approximately 3 g/day and to consume 0.8 g protein/kg ideal body weight/day  
Antihypertensive therapy was adjusted as necessary to maintain the target value for the diastolic pressure |
| Outcomes | Reported outcomes (at 36 months)  
All-cause mortality  
Cardiovascular morbidity/mortality |
• Adverse events
• Kidney failure progression: time to sustained doubling of SCr or RRT
• Proteinuria: urinary protein excretion
• BP: systolic/diastolic

Open label follow-up at median of 6.6 years for all-cause mortality and kidney failure progression (ESKD reported only as part of composite renal progression endpoint)

Not studied
• QoL; costs; admissions to hospital

Definition of CKD

• 24 hour urine collection was used to calculate CrCl
• Relevant CKD group reported: all participants were required to have CrCl of 30 to 60 mL/min (Stage 3 CKD). Participants were also required to have SCr levels of 1.5 to 4.0 mg/dL (133 to 354 µmol/L), thus, some patients with the most mild stage 3 CKD may have been excluded.
• 39% (227) of participants had mild CKD (CrCl: 46 to 60 mL/min).
• 61% (356) of participants had moderate CKD (CrCl: 30 to 45 mL/min).

Notes
• Funded by grant from Ciba-Geigy and Novartis Pharma

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
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<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: “double blind, randomised study” “randomly assigned”. Comment: method not described</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: “randomisation balanced for disease severity at each centre” Comment: method not described</td>
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<tr>
<td>Blinding (performance bias and detection bias)</td>
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<td>Placebo given. “Each patient was examined by physician, who was unaware of the group assignment” Comment: probably done</td>
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<tr>
<td>All outcomes</td>
<td></td>
<td>No missing outcome data reported</td>
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<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Data for all stated outcomes reported</td>
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<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Long term outcomes based on open label follow-up (for 504 patients - various reasons for withdrawals given. “there was considerable usage of ACE i during the follow up period in both the randomised treatment groups: 64% of those randomised to be- nanzepril and 61% of those randomised to placebo.”</td>
</tr>
</tbody>
</table>
### AIPRI Study 1996 (Continued)

**Intention-to-treat analysis.**

### Matsuda 2003

| **Methods** | • Study design: RCT  
• Study period: 1998 to 1999  
• Study duration: 48 weeks |
|---|---|
| **Participants** | Inclusion criteria  
• Setting: Hospital (one centre)  
• Country: Japan  
• Relevant health status  
  ◦ Renal diagnosis: IgAN (8, 15%); membranous nephropathy (5, 10%); FSGS (1, 2%); proliferative glomerulonephritis (38, 73%).  
  ◦ SCr < 265 µmol/L or CrCl > 30 mL/min/1.73m² (reported to be measured by 24 hour CrCl - method not specified)  
  ◦ Hypertension: systolic > 140 mm Hg and/or diastolic 90 mm Hg  
  ◦ Proteinuria: > 0.3 g/24 hours  
  ◦ Diagnosis of CKD  
• Number: Treatment group 1 (27; mild proteinuria 13, moderate proteinuria 14); treatment group 2 (25; mild proteinuria 13, moderate proteinuria 12)  
• Age: Participants described only as “adult”  
• Sex (M/F): treatment group 1 (14/13); treatment group 2 (15/10)  
• Mean systolic/diastolic BP mm Hg (SEM)  
  ◦ Treatment group 1: mild proteinuria group (148/86 (3/5)); moderate proteinuria group (152/90 (4/3))  
  ◦ Treatment group 2: mild proteinuria group (154/86 (4/3)); moderate proteinuria group (150/89 (3/3))  
• Comorbidities: All patients were hypertensive  
Exclusion criteria  
• DKD; polycystic kidney disease and chronic pyelonephritis |
| **Interventions** | Treatment group 1 (ACEi)  
• Intervention: Perindopril or trandolapril  
• Perindopril 2 mg/day; trandolapril 1 mg/day orally  
• Doses titrated to achieve systemic BP to < 135/85 mm Hg  
Treatment group 2 (ARB)  
• Intervention: Losartan or candesartan  
• Losartan 25 mg; candesartan 4 mg orally  
• Doses adjusted according to the level of the blood pressure or renal haemodynamics  
Co-interventions  
• All patients underwent education on low protein and sodium diet |
| **Outcomes** | Reported outcomes (12, 24 and 48 weeks)  
• Kidney failure progression: CrCl (24 hour urine collection)  
• Proteinuria: urinary protein excretion  
• BP: systolic/diastolic  
Not studied |
Matsuda 2003  (Continued)

<table>
<thead>
<tr>
<th>Definition of CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 24 hour urine collection at baseline to calculate CrCl</td>
</tr>
<tr>
<td>• Relevant CKD group reported: all participants had proteinuria (&gt;0.3 g/24 hour) and CrCl &gt; 30 mL/min/1.73m² (stage 1 to 3)</td>
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</tbody>
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Notes
- Funding: NS

Risk of bias

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<th>Support for judgement</th>
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<td>High risk</td>
<td>Quote: &quot;patients were randomly assigned&quot; Comment: method not described. Study not described as randomised trial in title or methods. Probably not done</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>Quote: &quot;patients were randomly assigned&quot; Comment: method not described. Study not described as randomised trial in title or methods. Probably not done</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>High risk</td>
<td>Not described as &quot;blinded study&quot;. Comparison of two active treatment groups. No placebo mentioned</td>
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<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Not clear if all patients had complete follow up data. Probably complete</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Data for all stated outcomes reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>There is insufficient information to assess whether an important risk of bias exists</td>
</tr>
</tbody>
</table>

PEACE Study 2006

Methods
- Study design: Placebo controlled RCT. Design was changed to open label (ACEi) in 2002 for patients with diabetes or proteinuria or hypertension plus microalbuminuria - analysis as per randomisation allocation
- Study duration: November 1996 to June 2000
- Duration of follow-up: Planned for at least 3.5 years (median 4.8 years)

Participants
- Inclusion criteria
  - Setting: Hospitals (187 centres)
  - Countries: Canada, Italy, Puerto Rico, USA
  - Relevant health status: > 50 years with stable coronary artery disease and normal
or mildly reduced left ventricular function (left ventricular ejection fraction > 40%)

- Renal diagnosis: not reported
- Number: Treatment group (4153); control group (4127); CKD stage 3a (1198); CKD stage 3b (157)
  - Age (mean ± SD years): Treatment group (64 ± 8); control group (64 ± 8); CKD stage 3a (68.0 ± 7.7); CKD stage 3b (70.2 ± 7.9)
  - Sex (F, %): Treatment group (NS, 19); control group (NS, 17); CKD stage 3a (338, 28.2); CKD stage 3b (71, 45.2)
  - Systolic BP (mean ± SD mm Hg): Treatment group (134 ± 17); control group (133 ± 17); CKD stage 3a (135 ± 17.2); CKD stage 3b (138 ± 19.5)
  - Diastolic BP (mean ± SD mm Hg): Treatment group (78 ± 10); control group (78 ± 10); CKD stage 3a (76.9 ± 9.9); CKD stage 3b (75.9 ± 10.9)

### Comorbidities

- Hypertension (733, 54%); diabetes (262, 19%); myocardial infarction (711, 52%); angina pectoris (974, 72%); percutaneous transluminal coronary angioplasty (521, 38%); coronary artery bypass surgery (565, 42%); stroke (81, 6%)

### Exclusion criteria

- Hospitalised for unstable angina in preceding 2 months, coronary revascularisation within prior 3 months, had a planned elective coronary revascularisation or had SCr > 2.0 mg/dL (177 µmol/L), patients contraindicated to ACEi and ARB

### Interventions

#### Treatment group (ACEi)

- Intervention: Trandolapril
- Dose, duration, frequency, administration: oral (target 4 mg/d)
- 4158 randomised; 1 not treated; 3 did not attend after randomisation

#### Control group

- Intervention: Oral placebo oral
- 4132 randomised; 1 not treated; 8 did not attend after randomisation

Discrepancy not accounted for between publications

- Other treatments: none reported

### Outcomes

Outcomes at minimum 3.5 years after recruitment (median 4.8 years)

- All-cause mortality
- CVD morbidity/mortality

Not presented for relevant subgroups

- Adverse events; kidney failure progression; proteinuria; BP

Not studied

- costs; QoL; admissions to hospital

### Definition of CKD

- Single eGFR (4-variable Modification of Diet in Renal Disease) at baseline.
- Relevant CKD group reported:
  - eGFR 45 to 59.9 mL/min/1.73 m² (n=1198)
  - eGFR < 45 mL/min/1.73 m² (minimum eGFR 27 mL/min/1.73 m² so included as stage 3b) (n=157)
- eGFR estimated from the SCr concentration and the 4-variable Modification of Diet in Renal Disease equation
### PEACE Study 2006 (Continued)

#### Notes
- Baseline characteristics similar for two treatment groups
- Funding: National Heart, Lung and Blood Institute and Knoll Pharmaceuticals and Abbott Laboratories.

#### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “randomised by a call to the data coordination centre” Comment: probably adequate generation - not described further</td>
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<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: “randomised by a call to the data coordination centre”</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>Low risk</td>
<td>blinded to treatment until 2002 when study steering committee recommended open label treatment with ACEi of those with diabetes, hypertension and microalbuminuria, or proteinuria</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>10/8290 with missing baseline creatinine excluded. Intention to treat analysis. “The percentage of patients assigned to trandolapril or placebo who withdrew from therapy and were not taking an open label ACE inhibitor was 25.5% and 8.3% respectively”</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Data for all stated outcomes reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Long term outcomes based on open label follow up for some of the participants “The percentage of patients assigned to trandolapril or placebo who withdrew from therapy and were not taking an open label ACE inhibitor was 25.5% and 8.3% respectively” Intention to treat analysis.</td>
</tr>
</tbody>
</table>
## Methods
- **Study design:** Placebo controlled RCT
- **Study duration:** Treatment planned for minimum 27 months
- **Duration of follow-up:** 3 years additional extended follow-up (open label basis); median follow up: treatment group 32.2 months (IQR 29.4 to 54.5); placebo group 31.4 months (IQR 27.6 to 49.4)
- **Run-in period:** 1 month (single blind, placebo run-in phase)

## Participants
**Inclusion criteria**
- Setting: Hospital (14 centres)
- Country: Italy
- Relevant health status: glomerular disease (85, 46%), interstitial or polycystic disease (14, 7%), other or unknown (87, 47%); urinary protein excretion ≥ 1 g/24 hours over at least 3 months; eGFR of 20 to 70 mL/min/1.73 m² (measured by plasma clearance measurement of unlabelled iohexol); serum potassium 3.5 to 5.0 mmol/L and capsule compliance exceeding 80%; non-diabetic patients
- Number: Treatment group (99); control group (87)
- Age (mean ± SD years): ACEi (49.1 ± 1.3); placebo (50.3 ± 1.5); range (18 to 70)
- Sex(M/F): Treatment group (75/24); control group (64/23)

**Comorbidities**
- Hypertension: Treatment group (78, 79%); control group (74, 85%)
- Systolic/diastolic BP, mean (SE) mm Hg
  - Treatment group: 142.0 (1.9)/88.6 (1.2)
  - Control group: 144.9 (2.0)/89.8 (1.3)

**Exclusion criteria**
- ACEi therapy within 2 months prior to study start; treatment with corticosteroids, NSAIDs, or immunosuppressive drugs; acute myocardial infarction or cerebrovascular accident in the previous 6 months, severe uncontrolled hypertension (diastolic BP 115 and/or systolic BP 220 mm Hg); evidence or suspicion of renovascular disease; obstructive uropathy; insulin-dependent diabetes mellitus; collagen disease; cancer; higher serum aminotransferase concentrations; chronic cough; drug or alcohol abuse; pregnancy; breastfeeding; ineffective contraception

## Interventions
**Treatment (ACEi) group (ACEi)**
- Intervention: Ramipril
- Dose, duration, frequency, administration: 1.25 mg, 2.5 mg or 5.0 mg capsules

**Control group**
- Intervention: Placebo or conventional treatment
- Dose, duration, frequency, administration: NS

The dose (ACEi or placebo) was titrated every 2 weeks to achieve diastolic BP < 90 mm Hg.

**Other treatment**
- Other antihypertensive agents (excluding ACEi or ARB) introduced as required.
- Patients were recommended to limit sodium intake and to consume 0.6 to 0.8 g protein/kg body weight/day

## Outcomes
**Outcomes reported at 63 months**
- ESKD at 48 months and 63 months (survival analysis)
- Kidney failure progression (mean change in eGFR)
- Not presented for relevant subgroup: all-cause mortality; cardiovascular morbidity and mortality; adverse events
REIN Stratum 1 1999  (Continued)

| Definition of CKD | proteinuria; BP  
| Not studied  
| QoL; hospital admissions; costs |

- 24 hour urine collection to calculate CrCl
- All participants had proteinuria (1 to 2.9 g/24 hours) and eGFR 20 to 70 mL/min/1.73 m² (stage 1 to 3 plus some patients in high stage 4 CKD not presented separately)
- Relevant CKD subgroup reported: CrCl > 45 mL/min/1.73 m² (number of patients not reported)

| Notes | Funded by Hoechst Mario Roussel Clinical Research Institute, Frankfurt, Germany  
| Study divided into two subgroups at baseline:  
| Low proteinuria (1 to 2.9 g/24 hours) (REIN Stratum 1 1999)  
| High proteinuria (> 3 g/24 hours) (REIN Stratum 2 1997)  
| The "high proteinuria" subgroup was stopped early at second interim analysis (year 2) by independent adjudication panel because of evidence of significant benefit

<table>
<thead>
<tr>
<th>Bias</th>
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<th>Support for judgement</th>
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<td>Low risk</td>
<td>Quote: “Randomisation code prepared by Hoechst Clinical Research Institute”</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: “Randomisation code prepared by Hoechst Clinical Research Institute”. “A sequence of patient numbers were randomly assigned to each study centre, and the study medication randomly assigned to patient numbers in advance”</td>
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<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td>Double blind: placebo treatment given; doctors enrolling patients and responsible for follow up did not have access to the randomisation codes</td>
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<td>Incomplete outcome data (attrition bias)</td>
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<td>Low proteinuria subgroup: 175/186 had at least 3 eGFR estimates but all 186 included in main analysis</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Data for all stated outcomes reported</td>
</tr>
</tbody>
</table>
| Other bias | High risk | Trial in High proteinuria group stopped early due to apparent benefit  
Long term outcomes based on open label follow up |
### Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
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<tr>
<td>AASK Pilot Study 1996</td>
<td>Results not presented for stages 1 to 3</td>
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<tr>
<td>Acone 2003</td>
<td>Results not presented for stages 1 to 3</td>
</tr>
<tr>
<td>Appel 2008</td>
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<td>Bakris 2000</td>
<td>Results not presented for stages 1 to 3</td>
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<td>Bakris 2000a</td>
<td>Results not presented for stages 1 to 3</td>
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<tr>
<td>Balamuthusamy 2008</td>
<td>Results not presented for stages 1 to 3</td>
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<tr>
<td>Bianchi 1992</td>
<td>Presents results for a subgroup with CrCl &lt; 25 mL/min</td>
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<tr>
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<td>Campbell 2003</td>
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(Continued)

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<tr>
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DATA AND ANALYSES

Comparison 1. ACEi versus placebo

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<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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<td>1 Mortality</td>
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ADDITIONAL TABLES

Table 1. Withdrawals and adverse events for ACEi versus placebo

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<th>Study ID: AIPRI Study 1996</th>
<th>Treatment (N = 300)</th>
<th>Placebo (N = 283)</th>
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<tr>
<td>Total adverse events</td>
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<tr>
<td>Cancer</td>
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<tr>
<td>Dry cough</td>
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<tr>
<td>Hyperkalaemia</td>
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Table 1. Withdrawals and adverse events for ACEi versus placebo (Continued)

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<tr>
<td>Local or systemic allergic reaction</td>
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<tr>
<td>Other</td>
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Withdrawals due to other events

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<th>Total</th>
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<tr>
<td>Lack of cooperation</td>
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<td>15</td>
</tr>
<tr>
<td>Violation of protocol</td>
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CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: CB, RB, CP, PS, KMCC
2. Study selection: CB, RB, CP, PS
3. Extract data from studies: CB, RB, CP, PS
4. Enter data into RevMan: CB
5. Carry out the analysis: CB, PS, RB, CP, KMCC
6. Interpret the analysis: CB, PS, RB, CP, KMCC, AM
7. Draft the final review: CB, PS, RB, CP, KMCC, AM

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT
Internal sources

- University of Aberdeen, UK.
Funding of core staff salaries and support facilities

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Modifications were made to the background to clarify terminology around GFR and to provide context with what is known with regard to diabetic kidney disease.

INDEX TERMS

Medical Subject Headings (MeSH)

Angiotensin Receptor Antagonists [*therapeutic use]; Angiotensin-Converting Enzyme Inhibitors [*therapeutic use]; Chronic Disease; Glomerular Filtration Rate [physiology]; Kidney Diseases [*drug therapy]; Kidney Failure, Chronic [prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Female; Humans; Male