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Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease (Review)

Strippoli GFM, Bonifati C, Craig ME, Navaneethan SD, Craig JC

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[Intervention Review]

Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease

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ABSTRACT

Background

Angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor antagonists (AIIRA) are considered to be equally effective for patients with diabetic kidney disease (DKD), but renal and not mortality outcomes have usually been considered.

Objectives

To evaluate the benefits and harms ACEi and AIIRA in patients with DKD.

Search methods

We searched MEDLINE (1966 to December 2005), EMBASE (1980 to December 2005), the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* issue 4 2005) and contacted known investigators.

Selection criteria

Studies comparing ACEi or AIIRA with placebo or each other in patients with DKD were included.

Data collection and analysis

Two authors independently assessed trial quality and extracted data. Statistical analyses were performed using the random effects model and results expressed as risk ratio (RR) with 95% confidence intervals (CI). Heterogeneity among studies was explored using the Cochran Q statistic and the I² test, subgroup analyses and random effects meta-regression.

Main results

Forty nine studies (12,067 patients) were identified. Thirty eight compared ACEi with placebo, four compared AIIRA with placebo and seven compared ACEi and AIIRA directly. There was no significant difference in the risk of all-cause mortality for ACEi versus placebo (RR 0.91, 95% CI 0.71 to 1.17) and AIIRA versus placebo (RR 0.99, 95% CI 0.85 to 1.17). A subgroup analysis of studies using full-dose ACEi versus studies using half or less than half the maximum tolerable dose of ACEi showed a significant reduction in the risk of all-cause mortality with the use of full-dose ACEi (RR 0.78, 95% CI 0.61 to 0.98). Baseline mortality rates were similar in the ACEi and AIIRA studies. The effects

of ACEi and AIIRA on renal outcomes (ESKD, doubling of creatinine, prevention of progression of micro- to macroalbuminuria, remission of micro- to normoalbuminuria) were similarly beneficial. Reliable estimates of effect of ACEi versus AIIRA could not be obtained from the three studies in which they were compared directly because of their small sample size.

Authors' conclusions

Although the survival benefits of ACEi are known for patients with DKD, the relative effects on survival of ACEi with AIIRA are unknown due to the lack of adequate direct comparison studies. In placebo controlled studies, only ACEi (at the maximum tolerable dose, but not lower so-called renal doses) were found to significantly reduce the risk of all-cause mortality. Renal and toxicity profiles of these two classes of agents were not significantly different.

PLAIN LANGUAGE SUMMARY

Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease

Kidney disease develops in 25% to 40% of diabetic patients, usually 20 to 25 years after the onset of diabetes. Approximately one third of those with diabetic kidney disease (DKD) will progress to end-stage kidney disease (ESKD) and will require long-term dialysis or possibly receive a kidney transplant. Many patients however may die from associated coronary artery disease or other cardiovascular causes before the onset of ESKD. Antihypertensive drugs have been shown to not only be of benefit to the heart but to also provide kidney protection by slowing the progression of DKD to ESKD. Two drugs in particular have been considered equally effective for patients with DKD - these are angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor antagonists (AIIRA). However studies have focused on kidney protection rather than over mortality. The aim of this review was to assess the benefits and harms of ACEi and AIIRA therapy in patients with DKD. Fifty studies (13,215 patients) were identified comparing ACEi to placebo, AIIRA to placebo and ACEi to AIIRA. The risk of death from any cause was not significantly reduced with the use of ACEi versus placebo, AIIRA versus placebo or ACEi versus AIIRA. However when we looked at the studies which used the maximum dose tolerated of ACEi rather than the lower, so-called renal doses, there was a significant reduction in the risk of death due to any cause. We were unable to determine which drug provides better protection due to the lack of head-to-head trials.

BACKGROUND

Diabetic kidney disease (DKD), defined as the presence of micro- or macroalbuminuria in patients with diabetes, occurs in 25% to 40% of type 1 and 2 diabetic patients within 20 to 25 years of the onset of diabetes (Ritz 1999). Both types of patients probably share the same pathogenetic and clinical stages of renal damage, including renal hypertrophy, incipient (microalbuminuria: urine albumin excretion 30-300 mg/d) nephropathy, overt (macroalbuminuria: > 300 mg/d) nephropathy and, finally, the presence of impairment of glomerular filtration rate (GFR) up to end-stage kidney disease (ESKD) (Mogensen 1995; Mogensen 1999). About one third of patients with DKD progress to ESKD (Ritz 1999).

Agents used to delay the progression of DKD include beta-blockers, calcium channel blockers, diuretics, angiotensin converting enzyme inhibitors (ACEi), and angiotensin II receptor antagonists (AIIRA). Since large scale randomised controlled trials (RCTs) have shown that ACEi and AIIRA slow the deterioration of renal function and reduce proteinuria, these have become the most broadly used agents in diabetic patients with nephropathy and major international guidelines (Arauz-Pacheco 2003; JNC 7 2003) advocate for their equivalent use as first line agents in these populations (CAPTOPRIL 1993; HOPE 2000; IDNT 2001; Kasiske 1993; RENAAL 2001).

If a patient has diabetes and nephropathy, mortality is reported to be 10% to 40% within 10 years of diagnosis, depending on cardiovascular comorbidities, with the primary cause of early death being fatal cardiovascular events. The presence of micro- or macroalbuminuria has been shown to be an independent risk factor for early death due to cardiovascular events in diabetic patients over and above the increased risk conferred by the diabetic status (Dinneen 1997). Microalbuminuria is associated with a two- to fourfold increase in the risk of death whereas macroalbuminuria/ overt proteinuria and hypertension are associated with an even higher risk when present together.

In view of current guidelines recommendations on equivalent use of ACEi and AIIRA in these populations, we performed a systematic review of RCTs of ACEi and AIIRA used in patients with DKD to evaluate the evidence basis supporting these statements, with particular focus on their effects on renal and cardiovascular outcomes.

OBJECTIVES

To evaluate the benefits and harms of ACEi and AIIRA in patients with DKD, with major focus on renal and cardiovascular outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs of at least six months duration in which ACEi or AIIRA were compared with placebo or no treatment or in which the relative effects of the agents were compared directly, head-to-head, in patients with DKD, were included in this systematic review.

Types of participants

RCTs of patients with DKD were included, independent of stage of nephropathy, either microalbuminuria (albumin excretion 30-300 mg/d) or macroalbuminuria (albumin excretion >300 mg/d).

Types of interventions

- ACEi versus placebo or no treatment
- AIIRA versus placebo or no treatment
- Head-to-head comparative RCTs of ACEi versus AIIRA

Types of outcome measures

- All-cause mortality
- ESKD
- Doubling of serum creatinine concentration
- Progression from micro- to macroalbuminuria
- Regression from micro- to normoalbuminuria
- Drug related toxicity, including cough, headache, hyperkalaemia, impotence and pedal oedema

Search methods for identification of studies

Search strategies were independently designed and performed by two separate investigators (GFMS, MC) in collaboration with the Cochrane Renal Group's Trial Search Coordinators at various stages from 2003 with a final update in December 2005.

The following electronic biomedical databases were searched

1. Cochrane Renal Groups studies register and the Cochrane Central Register of Controlled Trials (CENTRAL, in *The Cochrane Library* issue 4 2005)
2. MEDLINE(1966 - December 2005)
3. EMBASE (1988 - December 2005)

We performed a combined search to identify studies for this review and the review *Antihypertensive agents for preventing diabetic kidney disease* (Strippoli 2005) and screened as described below.

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 across the Cochrane Collaboration and is both retrospective and prospective (<http://www.cochrane.us/masterlist.asp>). Therefore we did not specifically search conference proceedings. Please refer to The Cochrane Renal Review Group's Module in *The Cochrane Library* for the most up-to-date list of conference proceedings.

Data collection and analysis

This review was undertaken by six authors (GFMS, MC, JD, CB, SDN, JCC). The search strategies described were used to obtain titles and abstracts of studies that might be relevant to the review. The titles and abstracts were screened independently by (GS, MC, SDN and CB), who discarded studies that were not applicable based on the inclusion criteria for this review, however studies and reviews that might include relevant data or information on studies were retained initially and their full-text version was analysed. Authors GS, MC, SDN and CB independently assessed abstracts of all citations retrieved by the searches and, if necessary, the full text of these studies to determine study eligibility. Data extraction was carried out independently by the same reviewers using standard

data extraction forms. Where more than one publication of one trial existed, only the publication with the most complete data was used. Any further information or clarification required from the authors was requested by written or electronic correspondence and relevant information obtained in this manner was included in the review. Disagreements in data extraction were resolved by discussion among authors.

Study quality

The methodological quality of included studies was assessed independently by GFMS, MC, SDN and CB without blinding to authorship or journal using the checklist developed by the Cochrane Renal Group. Discrepancies were resolved by discussion among authors. The quality items assessed were allocation concealment, blinding of investigators, participants outcome assessors, data assessors, intention-to-treat analysis, and the completeness to follow-up.

Quality checklist

Allocation concealment

- Adequate (A): Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study
- Unclear (B): Randomisation stated but no information on method used is available
- Inadequate (C): Method of randomisation used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence intervention group

Blinding

- Blinding of investigators: Yes/no/not stated
- Blinding of participants: Yes/no/not stated
- Blinding of outcome assessor: Yes/no/not stated
- Blinding of data analysis: Yes/no/not stated

Intention-to-treat analysis

- Yes: Specifically reported by authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment.
- Yes: Not specifically stated but confirmed upon study assessment
- No: Not reported and lack of intention-to-treat analysis confirmed on study assessment (patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation).
- No: Stated, but not confirmed upon study assessment

- Not stated

Completeness to follow-up

Per cent of participants excluded or lost to follow-up.

Statistical assessment

The effect of ACEi or AIIRA in individual studies were summarised using risk ratio (RR) with 95% confidence intervals (CI). Data of all studies comparing the same interventions (ACEi versus placebo, AIIRA versus placebo, ACEi versus AIIRA) were pooled in meta-analyses using the random effects model. Heterogeneity of treatment effects between studies was examined using the Cochran Q and I² statistic (Higgins 2003). Subgroup analysis and random effects meta-regression were performed as applicable to explore the influence of the following sources of heterogeneity on treatment effect: duration of follow up, type of diabetes (type 1, type 2 or studies including mixed populations of type 1 and type 2 diabetic patients), type of drug (different agents of the same class), presence or absence of hypertension at baseline, stage of DKD (studies enrolling patients with microalbuminuria, macroalbuminuria or mixed populations of patients with micro- and macroalbuminuria), and specific quality items (allocation concealment, blinding, use of intention -to-treat analysis). meta-regression analyses were undertaken in STATA version 8.0.

RESULTS

Description of studies

The combined search identified a total of 5701 citations, of which 5376 were excluded after title and abstract review. The major reasons for exclusion were a non-randomised design, non-antihypertensive interventions, study populations with non-DKD, and duplicate publications. Full text analysis of 325 articles lead to the final inclusion of 49 studies (73 publications) which met the inclusion criteria (Figure 1- Flow chart of study identification) (ABCD 1996; Ahmad 1997; Ahmad 2003; AIPRI 1996; ATLANTIS SG 2000; Bakris 1994; Bauer 1992; Bojestig 2001; Capek 1994; CAPTOPRIL 1993; Carella 1999; Chase 1993; Cordonnier 1999; Crepaldi 1998; DETAIL 2004; DIABHYCAR 2004; ESPRIT 2001; EUCLID 1997; Garg 1998; Hansen 1994; HOPE 2000; IDNT 2001; IRMA-2 2001; JAPAN-IDDM 2002; Jerums 2001; Jerums 2004; Ko 2005; Lacourciere 2000; Laffel 1995; Lebovitz 1994; Marre 1987; Mathiesen 1999; Muirhead 1999; Nankervis 1998; O'Donnell 1993; Parving 1989; Parving 2001a; Phillips 1993; Poulsen 2001; Ravid 1993; RENAAL 2001; Rizzoni 2005; Romero 1993; Sano 1994; Sato 2003; Stornello 1992; Tan 2002; Trevisan 1995; Tutuncu 2001). Data on characteristics of the populations, interventions and outcomes were extracted from all studies and supplemental data on design features and outcomes were obtained from the authors of ten studies or from duplicate publications relating to the primary trial.

Figure 1. Flow chart showing number of citations retrieved by individual searches, number of trials included in the systematic review and number of trials reporting each outcome.

Of the 49 studies, 38 (8970 patients) compared ACEi with placebo (ABCD 1996; Ahmad 1997; Ahmad 2003; AIPRI 1996; ATLANTIS SG 2000; Bakris 1994; Bauer 1992; Bojestig 2001; Capek 1994; CAPTOPRIL 1993; Carella 1999; Chase 1993; Cordonnier 1999; Crepaldi 1998; DIABHYCAR 2004; ESPRIT 2001; EUCLID 1997; Garg 1998; Hansen 1994; HOPE 2000; JAPAN-IDDM 2002; Jerums 2001; Jerums 2004; Laffel 1995; Lebovitz 1994; Marre 1987; Mathiesen 1999; Nankervis 1998; O'Donnell 1993; Parving 1989; Parving 2001a; Phillips 1993; Poulsen 2001; Ravid 1993; Romero 1993; Sano 1994; Stornello 1992; Trevisan 1995), four (2540 patients) compared AIIRA with placebo (Lacourciere 2000; Muirhead 1999; RENAAL 2001; Tutuncu 2001), and seven (557 patients) compared ACEi with AIIRA (DETAIL 2004; IDNT 2001; IRMA-2 2001; Ko 2005; Rizzoni 2005; Sato 2003; Tan 2002).

Of studies comparing ACEi with placebo, 20 enrolled patients with type 1 diabetes, 13 enrolled patients with type 2 diabetes, and five enrolled mixed populations of type 1 and type 2 diabetic patients. Seventeen studies enrolled patients with hypertension at baseline, the remaining enrolled normotensive patients. In 20 studies, other antihypertensive agents were administered beyond the randomised interventions (ACEi or AIIRA) in a non-randomised fashion to equalise blood pressure in both groups, minimise the confounding effect of blood pressure. Twenty five studies enrolled patients with microalbuminuria, eight enrolled patients with macroalbuminuria, and five enrolled mixed populations of micro- and macroalbuminuric patients. Three studies also enrolled minimal proportions of patients with normoalbuminuria and were therefore included.

The four studies that compared AIIRA with placebo all enrolled hypertensive patients with type 2 diabetes. Antihypertensive co-interventions were given in all four studies. Two studies enrolled patients with microalbuminuria and the other two studies enrolled patients with macroalbuminuria.

Of the seven studies comparing ACEi with AIIRA directly, six enrolled microalbuminuric patients and one enrolled mixed populations of micro- and macroalbuminuric patients. Six studies enrolled patients with type 2 diabetes and one study enrolled patients with both type 1 and type 2 diabetes. Six studies enrolled hypertensive patients and one trial enrolled normotensive participants. Antihypertensive co-interventions were given in two studies.

Risk of bias in included studies

By current standards, trial methodological quality was suboptimal.

Allocation concealment

Allocation concealment was unclear in 40/49 (82%) studies, inadequate in 1/49 (2%) trial, and adequate in 8/49 (16%) studies.

Blinding

Blinding occurred in the participants in 36/49 (73%) studies, investigators in 32/49 (65%) studies, and outcome assessors in 4/49 (8%) studies.

Reported intention-to-treat analysis

An intention-to-treat analysis was used in 15/49 (31%) studies.

Completeness of follow-up

Between 0% and 20% of patients were lost to follow-up in 45/49 (92%) studies and between 21% and 41% were lost to follow-up in 4/49 (8%) studies.

Effects of interventions

All-cause mortality

ACEi versus placebo/no treatment

There was no significant reduction in the risk of all-cause mortality with ACEi compared with placebo/no treatment (Analysis 1.1 (21 studies, 7295 patients): RR 0.91, 95% CI 0.71 to 1.17). This analysis was dominated by two studies, which contributed 49.68% and 37.78% of the weight to the summary estimate (DIABHYCAR 2004; HOPE 2000) but there was no significant heterogeneity between the studies (heterogeneity $\chi^2 = 11.04$, $I^2 = 27.6\%$). A subgroup analysis of studies which used ACEi at the maximum tolerable dose compared with placebo/no treatment, there was a significant reduction in the risk of all-cause mortality (Analysis 1.02 (5 studies, 2034 patients): RR 0.78, 95% CI 0.61 to 0.98) while this was not found in studies using half or less than half the maximum tolerable dose of these agents (Analysis 1.1.1 (4 studies, 5261 patients): RR 1.18, 95% CI 0.41 to 3.44). There was no significant heterogeneity in any of these analyses.

AIIRA versus placebo/no treatment

No statistically significant reduction in the risk of all-cause mortality was found in the five studies (3409 patients) of AIIRA versus placebo/no treatment (Analysis 2.1: RR 0.99, 95% CI 0.85 to 1.17). This analysis was dominated by two studies, which contributed 64.6% and 34.9% of the weight to the summary estimate (IDNT 2001; RENAAL 2001). There was no significant heterogeneity between the studies ($\chi^2 = 0.63$, $I^2 = 0\%$).

ACEi versus AIIRA

No statistically significant reduction in the risk of all-cause mortality was found in the only three studies (307 patients) that compared ACEi with AIIRA (Analysis 3.1: RR 0.92, 95% CI 0.31 to 2.78).

ESKD and doubling of serum creatinine

ACEi versus placebo/no treatment

There was a significant reduction in the risk of ESRD with ACEi compared to placebo/no treatment (Analysis 1.4 (10 studies, 6819 patients): RR 0.60, 95% CI 0.39 to 0.93) with no significant heterogeneity between the studies ($\chi^2 = 1.71$, $I^2 = 0\%$).

There was some evidence of reduction of the risk of doubling of serum creatinine concentration with ACEi compared to placebo/no treatment (Analysis 1.3 (9 studies, 6780 patients): RR 0.68, 95% CI 0.47 to 1.00). There was no significant heterogeneity between the studies ($\chi^2 = 9.52$, $I^2 = 37.0\%$).

AIIRA versus placebo/no treatment

There was a significant reduction in the risk of ESKD with AIIRA compared to placebo/no treatment (Analysis 2.4 (3 studies, 3251 patients): RR 0.78, 95% CI 0.67 to 0.91) with no significant heterogeneity between the studies ($\chi^2 = 0.05$, $I^2 = 0\%$).

There was also a significant reduction in the risk of doubling of serum creatinine concentration with AIIRA compared to placebo/no treatment ([Analysis 2.3](#) (3 studies, 3251 patients), RR 0.79, 95% CI 0.67 to 0.93), with no significant heterogeneity between the studies ($\chi^2 = 1.22$, $I^2 = 18.2\%$).

ACEi versus AIIRA

The seven studies that compared ACEi with AIIRA did not report the outcome of ESKD or doubling of serum creatinine, and we were unable to obtain these data from the authors.

Progression from micro- to macroalbuminuria

ACEi versus placebo/no treatment

ACEi significantly reduced the risk of progression from micro- to macroalbuminuria ([Analysis 1.5](#) (17 studies, 2036 patients): RR 0.45, 95% CI 0.29 to 0.69). There was no significant heterogeneity between the studies ($\chi^2 = 26.48$, $I^2 = 47.1\%$).

AIIRA versus placebo/no treatment

The use of AIIRA versus placebo/no treatment was also associated with a significant reduction in the risk of progression from micro- to macroalbuminuria ([Analysis 2.5](#) (3 studies, 761 patients): RR 0.49, 95% CI 0.32 to 0.75), with no significant heterogeneity between the studies ($\chi^2 = 1.10$, $I^2 = 0\%$).

ACEi versus AIIRA

Progression from micro to macroalbuminuria was reported in one trial (41 patients) only, which showed no significant difference in risk ([Ko 2005](#)).

Regression for micro- to normoalbuminuria

ACEi versus placebo/no treatment

There was a significant increase in regression from micro- to normoalbuminuria with ACEi versus placebo/no treatment ([Analysis 1.6](#) (16 studies, 1910 patients): RR 3.06, 95% CI 1.76 to 5.35), with no significant heterogeneity between the studies ($\chi^2 = 23.91$, $I^2 = 45.6\%$).

AIIRA versus placebo/no treatment

There was a significant increase in regression from micro- to normoalbuminuria with AIIRA versus placebo/no treatment ([Analysis 2.6](#) (2 studies, 670 patients): RR 1.42, 95% CI 1.05 to 1.93) with no significant heterogeneity between the studies ($\chi^2 = 0.51$, $I^2 = 0\%$).

ACEi versus AIIRA

Regression from micro- to normoalbuminuria was reported in only one head-to-head study and showed a non-significant difference in the risk ([Tutuncu 2001](#)).

Toxicity

ACEi versus placebo/no treatment

Cough

The use of ACEi was associated with a significant increase in the risk of cough ([Analysis 1.7](#) (10 studies, 7087 patients): RR 3.17, 95% CI 2.29 to 4.38), with no significant heterogeneity between the studies ($\chi^2 = 4.30$, $I^2 = 0\%$).

Hyperkalaemia

The use of ACEi was not found to be associated with a significant increase in the risk of hyperkalaemia ([Analysis 1.10](#) (2 studies, 1219 patients): RR 0.85, 95% CI 0.32 to 2.21), with no significant heterogeneity between the studies ($\chi^2 = 0.05$, $I^2 = 0\%$).

Headache

Four studies (6186 patients) reported headaches and there was no significant increase in the risk of headache with ACEi compared to placebo/no treatment ([Analysis 1.8](#): RR 0.92, 95% CI 0.33 to 2.53). Also in this analysis, there was no significant heterogeneity between the studies ($\chi^2 = 3.20$, $I^2 = 6.2\%$).

Impotence

Five studies (1528 patients) reported on impotence, and there was no evidence of a significant difference in the risk with ACEi compared to placebo/no treatment ([Analysis 1.9](#): RR 1.02, 95% CI 0.26 to 3.91), and there was no significant heterogeneity between the studies ($\chi^2 = 0.61$, $I^2 = 0\%$).

AIIRA versus placebo/no treatment

Cough

AIIRA were not found to be associated with an increased risk of cough compared to placebo/no treatment ([Analysis 2.07](#) (2 studies, 194 patients): RR 4.93, 95% CI 1.00 to 24.35). There was no significant heterogeneity between the studies ($\chi^2 = 1.43$, $I^2 = 30.0\%$).

Hyperkalaemia

There was a significant increase in the risk of hyperkalaemia with AIIRA compared to placebo/no treatment ([Analysis 2.10](#) (1 study, 1148 patients): RR 5.41, 95% CI 1.20 to 24.28).

Headache

One trial (91 patients) of AIIRA versus placebo/no treatment reported the outcome of headache and found no significant increase in risk with AIIRA ([Analysis 2.8](#): RR 0.70, 95% CI 0.03 to 16.68).

Impotence

There were no studies of AIIRA versus placebo/no treatment reporting the outcome of impotence.

Investigation of sources of heterogeneity

Metaregression and subgroup analyses for sources of heterogeneity were only possible in studies of ACEi versus placebo/no treatment given the small number of studies evaluating AIIRA versus placebo/no treatment or ACEi versus AIIRA directly. There was no evidence that the effect of ACEi on all-cause mortality (interaction P value = 0.84), doubling of serum creatinine (interaction P value = 0.56), ESKD (interaction P value = 0.05) and progression from micro- to macroalbuminuria (interaction P value = 0.12) varied according to type of diabetes. On the contrary, the rate of regression from micro- to normoalbuminuria was significantly higher in patients with type 2 diabetes (interaction P value < 0.001).

The presence (versus absence) of hypertension in the enrolled populations did not significantly impact on the effect of ACEi compared to placebo/no treatment on all-cause mortality (interaction P value = 0.45), doubling of serum creatinine

(interaction P value = 0.22), ESKD (interaction P value = 0.34), but normotensive patients had a significantly higher rate of progression from micro- to macroalbuminuria (interaction P value = 0.001) and significantly higher rate of regression from micro- to normoalbuminuria (interaction P value = 0.01).

The stage of nephropathy in enrolled populations (microalbuminuria versus macroalbuminuria or mixed populations with micro- or macroalbuminuria) did not significantly affect any of these outcomes in patients treated with ACEi compared to placebo/no treatment (all-cause mortality, interaction P value = 0.92; doubling of serum creatinine, interaction P value = 0.88, ESKD, interaction P value = 0.55, progression from micro- to macroalbuminuria, interaction P value = 0.86, regression from micro- to normoalbuminuria, interaction P value = 0.80). There were also no significant variations in the effect of ACEi versus placebo/no treatment on any of these outcomes by any trial quality indicators (allocation concealment, blinding, use of intention-to-treat analysis and proportions of patients lost to follow-up). The few significant differences observed in these analyses were all explained by the results of the large [HOPE 2000](#) study. When we excluded this study from our analyses, results were homogeneous for all outcomes.

DISCUSSION

Key findings

Placebo controlled studies have shown a survival advantage for ACEi when used at the maximum tolerable dose but not at "renal doses" (half or less than half the maximum tolerable dose) in patients with DKD. On the other hand, there has been no data showing a survival advantage with AIIRA versus placebo/no treatment, in patients with DKD. The relative survival advantage of one class of antihypertensives over the other in this population is, however, still unknown because only indirect comparisons based on small studies are available. ACEi, used at the maximum tolerable dose, significantly reduced the risk of all-cause mortality (mainly cardiovascular) by about 20% and progression from micro- to macroalbuminuria by about 55%. They also increased the rate of regression from micro- to normoalbuminuria by about threefold. We found no evidence that these effects are related to baseline hypertension, type of diabetes, stage of DKD, and duration of treatment. In comparison, current studies of AIIRA in patients with DKD have not shown a reduction in all-cause mortality, with a RR of 0.99 and narrow 95% CI (0.85 to 1.17), which is unlikely to be explained by chance alone. There is strong evidence that AIIRA are beneficial for renal outcomes, with a reduction in risk of ESKD and doubling of serum creatinine of about 22%, a reduction in progression rates from micro- to macroalbuminuria by around 51%, and an increase in the regression from micro- to normoalbuminuria of about 42%. Three potential explanations for these apparent different effects between the two classes of antihypertensives are chance, confounding, and true differences. The usual 5% level for statistical significance was reached for all renal outcomes for AIIRA versus ACEi, and this threshold was reached for ESKD, the prevention of progression from micro- to macroalbuminuria, and regression of micro- to normoalbuminuria, but not doubling of serum creatinine. The point estimates of effect for all renal outcomes favoured ACEi versus AIIRA, but there was some imprecision surrounding these summary point estimates for ACEi due to lower event rates and because of the heterogeneity in study results due to one large study ([HOPE 2000](#)). For all cause

mortality, the absence of benefit shown by AIIRA is unlikely to be due to chance alone because the summary point estimate is close to unity (0.99) and the 95% CIs are relatively narrow. We did not formally test differences in ACEi and AIIRA through indirect comparison since there are clear differences in the design and conduct of the ACEi and AIIRA studies, which may explain apparent differences in results if such non randomised comparison was performed. In particular, micro-HOPE primarily included high cardiac risk patients with relatively low renal risk, and although end of treatment blood pressure was not different between the two groups (possibly due to survival bias), equalisation of blood pressure was not targeted and so may have confounded the observed benefit of ramipril. True differences in the relative effects of ACEi and AIIRA can only be established by adequately powered studies that directly compare the two agents, which unfortunately are currently not available.

Comparison with existing knowledge

In studies that enrolled patients with diabetes without nephropathy (which have not been included in this review), it has been shown that intensive control of blood pressure with any agent reduced cardiovascular morbidity and mortality, independent of type of agent used ([Grossman 2001](#)). In addition, in one study in which losartan was compared to atenolol in hypertensive patients with diabetes, losartan significantly reduced the risk of all-cause mortality ([Wachtell 2003](#)). Following myocardial infarction, ACEi have been shown to reduce all-cause mortality ([Zunetti 1996](#)), whereas no relevant information with AIIRA are available. Our findings are consistent with other large meta-analyses in patients with congestive heart failure, which showed a significant reduction in the risk of all cause mortality with ACEi versus placebo/no treatment but not for AIIRA ([Cohn 2001](#); [Garg 1995](#)). Previous studies have already analysed the role of various antihypertensive agents, including ACEi and AIIRA, in patients affected by DKD. Particular focus was on the effect of ACEi in specific categories of patients (e.g. only type 1 diabetics). A recent meta-analysis of individual patient data from the ACEi in DKD Trialist Group concluded that in normotensive patients with type 1 diabetes and microalbuminuria, ACEi significantly reduced progression to macroalbuminuria and increased the chances of regression to normoalbuminuria ([ACEIDN 2001](#)). An earlier metaregression analysis indicated that ACEi reduced proteinuria and preserved GFR in patients with diabetes, independent of changes in systemic blood pressure ([Kasiske 1993](#)). The main difference with our study is that we included both ACEi and AIIRA studies, obtained additional data from the authors when possible, and evaluated all outcomes of interest, including all-cause mortality, and not simply the traditional renal outcomes. Another meta-analysis on the effects of inhibitors of the renin-angiotensin system and other antihypertensive agents on renal outcomes has been recently published ([Casas 2005](#)). This analysis, which included small studies conducted in high-risk patients with diabetic and non-diabetic chronic nephropathies, concluded that there are no superior effects of renin-angiotensin-system blockers over other antihypertensive agents in chronic nephropathies. Comparison between these data and ours is difficult because of different inclusion criteria and research questions.

Strengths and limitations

The strength of this investigation is that it represents a comprehensive systematic review with rigid inclusion criteria

for RCTs only; and a comprehensive search strategy. Data extraction, data analysis, and methodological quality assessments were performed by two or more independent investigators, and consistency was checked with all six authors. The major limitation of our study is the lack of direct comparative data of ACEi and AIIRA. Studies directly comparing the two agents were only few and small and did not report outcomes relevant to patients, therefore they were largely uninformative. Other limitations include the small number and suboptimal quality of included studies and the potential for publication bias. These issues are unlikely to be influential as the review is dominated by a few larger studies.

AUTHORS' CONCLUSIONS

Implications for practice

The role of ACEi in the management of patients with DKD is well established. Recently, equivalence of the newer and more expensive class of antihypertensive agents, AIIRA, has been widely advocated and is accepted in current practice. For example, the Joint National Committee on Prevention, Diagnosis and Management of Hypertension ([JNC 7 2003](#)) and the guidelines of the American Diabetes Association (ADA, [Arauz-Pacheco 2003](#)), suggest that ACEi and AIIRA can be used interchangeably. Our study shows that there is randomised trial evidence that ACEi versus placebo/no treatment used at their maximum tolerable dose prevent death in patients with DKD, but not that AIIRA versus placebo/no treatment do. Both agents prevent progression of nephropathy and promote regression to a more favourable clinical pattern of normoalbuminuria. The relative effects of ACEi and AIIRA are uncertain. These data suggest that outside of a comparative RCT, ACEi, the cheaper class of agent with proven survival benefit, should be used as first line treatment.

Implications for research

The findings of this study mandate an adequately powered comparative trial of ACEi versus AIIRA with renal and all-cause mortality as measured outcomes. In general studies of the newer pharmacological agents (AIIRA) have been designed as placebo-controlled rather than direct comparisons with existing agents (ACEi). This clearly makes it easier to prove that there is a benefit with the new agent, but harder to prove differential advantage compared to existing ones, as this may be only done by indirect comparison. It should be therefore recommended that future studies compare these agents directly. Given the recent promising results of combination therapy, a factorial trial may be the preferred design. Meanwhile, undertaking an individual patient data meta-analysis may allow the effects of baseline cardiac and renal disease to be better understood and accounted for through subgroup analysis.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

ABCD 1996

Methods	Country: USA Setting/Design: Multicentre Time frame: NS Randomisation method: Permuted block randomisation within strata Blinding - Participants: No - Investigators: No - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 5-7 years Loss to follow-up: NS
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Age: 40-74 years • DM: Type 2 • Mean BP: 80-89 mm Hg • Patients are likely to complete 5-7 years of study; patients willing to participate after a complete discussion of the study and who have signed the consent form; patients unlikely to move from Denver area within the next 5 years <p>Enalapril group 1</p> <ul style="list-style-type: none"> • Number: 52 • Age: 49.8 (43-58) • Sex (M/F): 30/22 <p>Placebo group</p> <ul style="list-style-type: none"> • Number: 51 • Age: 50.3 (45-55) • Sex (M/F): 30/21 <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Pregnant or lactating females. Women of childbearing potential not using reliable contraception; potential pregnancy during the study • Allergies to dihydropyridines or ACEi • Recent or current substance abusers • State of mental or physical competence inadequate to comply the study • Second to third-degree uncorrected heart block • MI or CVA within the previous 6 months or CAB surgery within the previous 3 months • Unstable angina pectoris within the previous six months • Congestive heart failure (NYHA III or IV) • Treatment with ACEi or CCB • Accelerated/malignant hypertension (current the previous 5 years) • Current severe peripheral vascular disease manifested by gangrene or imminent amputation • Imminent or recent aortic dissection and/or previous mesenteric infarction • HD or peritoneal dialysis and/or SCr > 3 mg/dL • Bilateral renal artery stenosis or renal artery stenosis in a solitary functioning kidney • Organ transplant recipients • Significant hyperkalaemia (3 or more measurements > 6 mEq/L) • Progressive nephropathic diseases other than diabetic nephropathy • Severe liver disease • History of malignancies or active cancer • DBP < 80 mm Hg off antihypertensive agents

ABCD 1996 (Continued)

- Isolated systolic hypertension (SBP mean > 160 mm Hg and DBP mean < 90 mm Hg off all antihypertensive agents)

Interventions	Enalapril group 1 <ul style="list-style-type: none">• Intensive treatment: DBP target 75 mm Hg• 5 mg/d titrated to 10, 20 and then 40 mg/d as initial medication plus placebo Control group <ul style="list-style-type: none">• Moderate BP control: DBP target 80-89 mm Hg• Placebo Co-interventions <p>If study intervention alone did not achieve the target BP, then open-labeled antihypertensive medication were added in a step-wise manner. Additional antihypertensive agents added at the discretion of the medical director but did not include a CCB or ACEi</p>	
Outcomes	<ol style="list-style-type: none">1. GFR2. UAE3. Creatinine clearance4. BP5. Retinopathy6. Neuropathy7. CVE8. Laboratory measurements	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Ahmad 1997

Methods	Country: India Setting/Design: University Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: No - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 5 years Loss to follow-up: 13	
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> Age: 43-55 years Known duration of diabetes < 15 years No history and clinical or laboratory evidence of non-diabetic renal, systemic, cardiac or hepatic diseases 	

Ahmad 1997 (Continued)

- BMI < 27 kg/m²
- Normal BP values on 2 consecutive examinations (SBP ≤/ = 140 mm Hg; DBP ≤/ = 90 mm Hg)
- GFR > 90 mL/min
- AER of 20-200 µg/min on 2 consecutive visits without evidence of UTI

Enalapril group 1

- Number: NS
- Age: NS
- Sex(M/F): NS

Enalapril group 2

- Number: NS
- Age: NS
- Sex(M/F): NS

Exclusion criteria: NS

Interventions	Enalapril group 1 10 mg/d Enalapril group 2 Moderate treatment Co-interventions: No	
Outcomes	1. AER 2. GFR 3. BP	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Ahmad 2003

Methods	Country: India Setting/Design: University Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: No - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 5 years Loss to follow-up: 13
Participants	Inclusion criteria • DM: Type 1

Ahmad 2003 (Continued)

- Age: < 40 years
- Duration of diabetes: 5-25 years
- HbA1c: < 9% for preceding 3 months
- BP: Sitting < 140/90 mm Hg on no antihypertensive treatment
- GFR: > 90mL/min
- BMI: Stable
- AER: 20-200 µg/min on 2 consecutive visits
- Renal biopsy at entry and the end of the study

Enalapril group

- Number: 37
- Age: 31.3 (3.2)
- Sex (M/F): 19/18

Placebo group

- Number: 36
- Age: 31.7 (3.8)
- Sex (M/F): 19/17

Exclusion criteria

- Evidence of non-diabetic renal disease, systemic, cardiac and hepatic disease

Interventions	Enalapril group 10 mg/d Placebo group Co-interventions: No	
Outcomes	1. UAE 2. BP 3. GFR 4. Histomorphometric features (mean glomerular volume, mesangial volume and glomerular basement membrane thickness)	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

AIPRI 1996

Methods	Country: Italy Setting/Design: Multicentre Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No
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AIPRI 1996 (Continued)

Intention-to-treat: No
Follow-up period: 36 months
Loss to follow-up: 0

Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none">• SCr: 1.5-4.0 mg/dL• CrCl: 30-60 mL/min with variations of less than 30% in at least 3 measurements of CrCl during a 3-month screening period and less than 15% during a subsequent 2-week single blind placebo period <p>Benazepril group</p> <ul style="list-style-type: none">• Number: NS• Age: NS• Sex (M/F): NS <p>Placebo group</p> <ul style="list-style-type: none">• Number: NS• Age: NS• Sex (M/F): NS <p>Exclusion criteria</p> <ul style="list-style-type: none">• Treatment with corticosteroid, NSAIDs or immunosuppressive drugs• AER > 10 g/24 h and serum albumin < 25g/L (each measured at least 3 times, and twice during the screening period)• Renovascular hypertension• Malignant hypertension or a MI or CVA in the 6 months preceding the study• CHF (NYHA III - IV)• DM type 1• Elevated serum aminotransferase concentration• Collagen disease• Obstructive uropathy• Cancer• Chronic cough• History of allergy to an ACEi• Drug or alcohol abuse• Pregnancy
Interventions	<p>Benazepril group 0 mg/d</p> <p>Placebo group</p> <p>Co-interventions: No</p>
Outcomes	<p>1. Doubling of the baseline SCr concentration or the need for dialysis</p> <p>2. BP</p>
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment?	Unclear risk B - Unclear

ATLANTIS SG 2000

Methods	Country: UK Setting/Design: Multicentre Time frame: NS Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: No - Data analysis: No Intention-to-treat: Yes Follow-up period: 24 months Loss to follow-up: 42
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> DM: Type 1 Microalbuminuria: 20-200 µg/min in 2 of 3 collections Untreated BP: < 150/90 mm Hg for patients < 50 years and < 165/90 mm Hg for patients 50-65 years <p>Ramipril group 1</p> <ul style="list-style-type: none"> Number: 47 Age: 44 (11) Sex (M/F): 44/3 <p>Ramipril group 2</p> <ul style="list-style-type: none"> Number: 45 Age: 40 (13) Sex (M/F): (44/1) <p>Placebo group</p> <ul style="list-style-type: none"> Number: 48 Age: 40 (12) Sex (M/F): 46/2 <p>Exclusion criteria</p> <ul style="list-style-type: none"> Pregnant or lactating Women of child-bearing potential and not using adequate contraception Concomitant therapy for hypertension Treatment one or more NSAIDs History of drug or alcohol abuse Other known renal diseases or raised Creatinine levels > 120 µmol/L) Liver function twice that of normal on repeat testing Iodine sensitivity
Interventions	<p>Ramipril group 1 25 mg/d</p> <p>Ramipril group 2 5 mg/d</p> <p>Placebo group</p>

ATLANTIS SG 2000 (Continued)

Co-interventions: No

Outcomes	1. AER 2. BP 3. GFR
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment?	Low risk A - Adequate

Bakris 1994

Methods	Country: USA Setting/Design: Hospital Time frame: NS Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 18 months Loss to follow-up: 7
Participants	Inclusion criteria <ul style="list-style-type: none"> DM: Type 1 Positive family history for cardiovascular disease Hypertension Lisinopril group <ul style="list-style-type: none"> Number: 8 Age: 28 (7) Sex (M/F): 3/5 Placebo group <ul style="list-style-type: none"> Number: 7 Age: 25 (6) Sex (M/F): 4/3 Exclusion criteria: NS
Interventions	Lisinopril group 75 mg/d Placebo group Co-interventions: No
Outcomes	1. Changes in renal size

Bakris 1994 (Continued)

2. Microalbuminuria
3. MAP

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Bauer 1992

Methods

Country: USA
 Setting/Design: University
 Time frame: NS
 Randomisation method: NS
 Blinding
 - Participants: Yes
 - Investigators: Yes
 - Outcome assessors: No
 - Data analysis: No
 Intention-to-treat: No
 Follow-up period: 18 months
 Loss to follow-up: 9

Participants

Inclusion criteria

- DM: Type 1 or 2
- Proteinuria: > 500 mg/d before drug randomisation
- No clinical or laboratory evidence of primary renal disease
- Creatinine clearance: > 20 mL/min/1.73 m²
- Clinical evidence of additional diabetic target organ damage (diabetic retinopathy and/or peripheral neuropathy)
- Persistent DBP < 90 mm Hg on either no drug therapy or no conventional antihypertensive drugs excluding ACEi and CCB

Enalapril group

- Number: 18
- Age: 44 (26-66)
- Sex (M/F): 11/7

Placebo group

- Number: 15
- Age: 57 (47-70)
- Sex (M/F): 13/2

Exclusion criteria

- HbA1c: Consistently greater than 12%
- Non-compliance with drug therapy
- History of hyperkalaemia or baseline serum potassium > 5.2 mmol/L
- Decompensated CHF
- Unstable angina pectoris or history of a MI within 6 months of entering the protocol

Bauer 1992 (Continued)

- CVD within 12 months of entering the protocol
- Females with the potential to become pregnant
- History of hypersensitivity reaction to ACEi peptide-like drugs
- Evidence of clinically important bladder dysfunction

Interventions	Enalapril group 5-40 mg/d Placebo group Co-interventions Conventional antihypertensive drugs	
Outcomes	1. BP 2. Protein excretion/24 h 3. GFR	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Bojestig 2001

Methods	Country: Sweden Setting/Design: Multicentre Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: Yes Follow-up period: 24 months Loss to follow-up: 1	
Participants	Inclusion criteria <ul style="list-style-type: none"> • Normotensive patients (BP < 90 mm Hg) with microalbuminuria (20-200 µg/min) in 2 of 3 urine collections Ramipril group 1 <ul style="list-style-type: none"> • Number:19 • Age: 42 (10) • Sex (M/F):13/6 Ramipril group 2 <ul style="list-style-type: none"> • Number: 18 • Age: 39 (10) • Sex (M/F): 14/4 	

Bojestig 2001 (Continued)

Placebo group

- Number: 18
- Age: 38(9)
- Sex (M/F): 14/4

Exclusion criteria

- Patients treated with any form of antihypertensive medication

Interventions	Ramipril group 1 1.25 mg/d Ramipril group 2 5 mg/d Placebo group Co-interventions: No
Outcomes	1. ACE activity and PRA 2. BP 3. AER
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment?	Unclear risk B - Unclear

Capek 1994

Methods	Country: Austria Setting/Design: Multicentre Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: No - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 12 months Loss to follow-up: 5
Participants	Inclusion criteria <ul style="list-style-type: none"> • DM: Type 2 Microalbuminuria: 30-300 mg/24 h in 3 or more 24h urine collections Captopril group <ul style="list-style-type: none"> • Number: 9 • Age: 64 (8.2) • Sex (M/F): 5/4 Placebo group

Capek 1994 (Continued)

- Number: 6
- Age: 63.8 (1.1)
- Sex (M/F):2/4

Exclusion criteria

- Heart disease
- Pregnancy
- Impaired renal function (SCr < 1.4 mg/dL)

Interventions	Captopril group 37.5 mg/d Placebo group Co-interventions: NS
Outcomes	1. BP 2. AER 3. GFR
Notes	
<i>Risk of bias</i>	
Bias	Authors' judgement Support for judgement
Allocation concealment?	Unclear risk B - Unclear

CAPTOPRIL 1993

Methods	Country: USA Setting/Design: Multicentre Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: Yes Follow-up period: 36 months Loss to follow-up: 108	
Participants	Inclusion criteria <ul style="list-style-type: none"> • Age:18-49 years • DM: Type 1 for at least 7 years, with an onset before the age of 30 years • Diabetic retinopathy • AER: > 500 mg/24 h • SCr: < 2.5 mg/dL Captopril group <ul style="list-style-type: none"> • Number: 207 • Age: 35 (7) • Sex (M/F): 107/100 	

CAPTOPRIL 1993 (Continued)

Placebo group

- Number: 202
- Age: 34 (8)
- Sex (M/F): 109/93

Exclusion criteria

- Pregnancy
- Dietary evaluation indicating marked departure from standard dietary recommendation
- White cell count: < 2500/mm³
- CHF (NYHA III or worse)
- Serum potassium: > 6 mmol/L

Interventions	Captopril group 75 mg/d Placebo group Co-interventions: No	
Outcomes	1. Doubling of SCr 2. Death, dialysis and transplantation 3. Changes in renal function (SCr, CrCl, urinary protein excretion)	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Carella 1999

Methods	Country: USA Setting/Design: University hospital Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 24 months Loss to follow-up: 1	
Participants	Inclusion criteria <ul style="list-style-type: none"> • Diabetics with persistent albuminuria • Duration of diabetes: < 5 years • Age: < 50 years • Undetectable C-peptide levels in the face of hyperglycaemia or definite history of keto-acidosis • Weight: < 30% IBW • BP: < 140/90 mm Hg during 2 consecutive clinic visits 	

Carella 1999 (Continued)

Fosinopril group

- Number: 8
- Age: 38 (6)
- Sex (M/F): 3/5

Placebo group

- Number: 8
- Age: 38 (6)
- Sex (M/F): 3/5

Exclusion criteria

- Pregnant women
- Athletes participating in regular vigorous activity
- Smokers, alcohol or substance abusers
- History of recurrent UTI (> 3 in previous five years) or other causes of renal disease

Interventions	Fosinopril group 10 mg/d Placebo group Co-interventions: NS	
Outcomes	1. AER 2. BP	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Chase 1993

Methods	Country: USA Setting/Design: University Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 24 months Loss to follow-up: 0	
Participants	Inclusion criteria <ul style="list-style-type: none"> • DM: Type 1 • AER: 20-200 µg/min on at least 3 of 4 initial overnight urine collections Captopril group	

Chase 1993 (Continued)

- Number: 7
- Age: 22 (8.4)
- Sex (M/F): 7/0

Placebo group

- Number: 9
- Age: 19.9 (4.4)
- Sex (M/F): 5/4

Exclusion criteria: NS

Interventions	Ramipril group 5.0 mg/d Placebo group Co-interventions: No	
Outcomes	1. AER 2. CrCl	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Cordonnier 1999

Methods	Country: France Setting/Design: Multicentre Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 24 months Loss to follow-up: 3	
Participants	Inclusion criteria <ul style="list-style-type: none"> • DM: Type 2 • Age: 25-65 years (those under 40 were accepted only if they were diabetic for more than 2 years and did not require insulin) • BMI: < 33 kg/m² • HbA1c: > twice the maximal normal value • Proteinuria: > 70 mg/24 h • CrCl: > 60 mL/min • Normal sized kidneys with symmetrical function evaluated by scintigraphy or pyelography Perindopril group	

Cordonnier 1999 (Continued)

- Number: 11
- Age: 47 (7)
- Sex (M/F): 11/0

Placebo group

- Number: 11
- Age: 47 (12)
- Sex (M/F): 7/4

Exclusion criteria

- Women that were not postmenopausal or didn't using medically accepted contraceptives

Interventions	Perindopril group 4 mg/d Placebo group Co-interventions Prazosin/diuretics	
Outcomes	1. BP 2. Proteinuria 3. CrCl 4. Histological characteristics	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Crepaldi 1998

Methods	Country: Italy Setting/Design: University Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 36 months Loss to follow-up: 10	
Participants	Inclusion criteria <ul style="list-style-type: none"> • DM: Type 1 • Age: 18-65 years • Onset of diabetes: Before 35 years and insulin treatment within 3 years of diagnosis • Clinical stability: HbA1c < 11-30% • SBP: 115-140 mm Hg 	

Crepaldi 1998 (Continued)

- DBP: 75-90 mm Hg
- AER: 20-200 µg/min from 3 timed overnight urine collections at a routine control during the year before the trial

Lisinopril group

- Number: 33
- Age: 38 (11)
- Sex (M/F): 21/11

Placebo group

- Number: 44
- Age: 37 (10)
- Sex (M/F): 23/11

Exclusion criteria

- Impaired renal function (SCr > 10% above the upper limit of the normal laboratory range)
- AER > 200 µg/min
- History of any non-diabetic renal disease
- Haematuria
- Evidence of clinically significant liver or haematological disease
- Evidence of aortic or mitral valve obstruction, arrhythmias, unstable angina or a history of MI within the previous 3 months
- Clinical evidence of autonomic neuropathy
- Systemic malignancy
- Hyperkalaemia
- Serum triglycerides: > 3.4 mmol/L or total cholesterol > 6.5 mmol/L
- Known familial lipid disorders
- Known risk of transmitting AIDS or viral hepatitis
- Known hypersensitivity or contraindications to ACEi, or atenolol
- Women of childbearing age not using medically acceptable methods of birth control (oral contraceptives were not allowed) or those planning a pregnancy during the treatment period
- Treatment compliance over the 4-week placebo run-in of 85%
- Patient on antihypertensive treatment

Interventions	Lisinopril group 2.5-20 mg/d Placebo group Co-interventions Atenolol	
Outcomes	1. Progression rate of micro- to persistent macroalbuminuria 2. Number of patients who had a 50% yearly increase in AER above baseline values 3. Number of patients who showed a regression rate from micro- to persistent normoalbuminuria	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

DETAIL 2004

Methods	Country: USA Setting/Design: Multicentre Time frame: NS Randomisation method: Central location-based on permuted blocks Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 5 years Loss to follow-up: 2
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Age: 35-80 years • DM: Type 2 treated by diet, diet plus oral hypoglycaemic drugs (for at least 1 year), or insulin preceded by treatment with oral agents (also for at least 1 year). Among those whose diabetes was treated with insulin, the onset of diabetes had to have occurred after the age of 40 and the BMI had to be more than 25 at the time of diagnosis • Hypertension: Mild to moderate with a resting BP < 180/95 mm Hg after at least 3 months of ACEi therapy before entry into the study • Renal morphology: Normal • UAE: Mean of 3 consecutive overnight values between 11 and 999 µg/min with 2 values > 10 µg/min • HbA1c: < 12 • SCr: < 1.6 mg/dL • GFR: > 70 mL/min/1.73 m² <p>Enalapril group</p> <ul style="list-style-type: none"> • Number: 130 • Age: 60.0 (9.1) • Sex (M/F): 95/35 <p>Telmiosartan group</p> <ul style="list-style-type: none"> • Number: 120 • Age: 61.2 (8.5) • Sex (M/F): 87/33 <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Any condition (other than cardiovascular disease) that could restrict long-term survival and known allergy to study drugs or iohexol
Interventions	<p>Enalapril group 20 mg/d</p> <p>Telmiosartan group 80 mg/d</p> <p>Co-interventions Others antihypertensive agents (except ACEi or AIIA) were allowed after 2 months.</p>
Outcomes	1. Changes in GFR 2. UAE 3. SCr

DETAIL 2004 (Continued)

4. BP
5. The rates of clinical events (ESKD, MI, stroke, CHF)
6. Rate of death from all causes
7. Rate of adverse events

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

DIABHYCAR 2004

Methods	Country: France Setting/Design: Multicentre Time frame: 1995-2001 Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: Yes Follow-up period: 3-6 months Loss to follow-up: 0
Participants	Inclusion criteria <ul style="list-style-type: none"> • Age: > 50 years • DM: Type 2 • AER: > 20 mg/L Ramipril group <ul style="list-style-type: none"> • Number: 2443 • Age: 65.2 (8.4) • Sex (M/F): 1701/742 Placebo group <ul style="list-style-type: none"> • Number: 2469 • Age: 65.0 (8.3) • Sex (M/F): 1731/738 Exclusion criteria <ul style="list-style-type: none"> • SCr > 150 µmol/L • Treatment with insulin, ACEi or AIIRA • Documented CHF • MI during the past 3 months • UTI • Previous intolerance to an ACEi

DIABHYCAR 2004 (Continued)

Interventions	Ramipril group 1.25 mg/d Placebo group Co-interventions: No	
Outcomes	1. Cardiovascular death 2. CVE 3. ESKD 4. Doubling of creatinine 5. Amputation beyond MTP joint 6. Regression of micro- to normoalbuminuria, macro- to micro/normoalbuminuria 7. Adverse events (cough, hypertension, vertigo, diarrhoea, headache)	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

ESPRIT 2001

Methods	Country: UK Setting/Design: Multicentre Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 3 years Loss to follow-up: 4	
Participants	Inclusion criteria <ul style="list-style-type: none"> DM: Type 1 before age of 40 years Age: 18-65 years AER: 30-1500 µg/min GRF: > 70 mL/min SCr: < 130 µmol/L BP: Sitting < 150/90 mm Hg on no antihypertensive treatment Patients had to agree to a renal biopsy at entry and the end of the study Enalapril group <ul style="list-style-type: none"> Number: 18 Age: 37 (24-64) Sex (M/F): 11/7 Placebo group	

ESPRIT 2001 (Continued)

- Number: 18
- Age: 38 (20-60)
- Sex (M/F): 13/5

Exclusion criteria

- Uncontrolled diabetes (HbA1c > 6 SD above the local normal range)
- Current antihypertensive NSAIDs
- Hyperkalaemia
- Other renal or urinary tract disease
- Liver disease
- Recent CVD or cardiac disease
- Pregnancy
- Any contraindication to renal biopsy

Interventions	Enalapril group 10 mg/d Placebo group Co-interventions: No	
Outcomes	1. GFR 2. AER 3. BP 4. Structural parameters (Vv mesangium, Vv matrix, GBM thickness)	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

EUCLID 1997

Methods	Country: UK Setting/Design: University Time frame: NS Randomisation method: Yes Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: Yes Follow-up period: 24 months Loss to follow-up: 82	
Participants	Inclusion criteria <ul style="list-style-type: none"> • Age: 20-59 years • Males and females • DM: Type 1 (diagnosis before age 36 and the need for continuous insulin therapy within a year of diagnosis) 	

EUCLID 1997 (Continued)

- Resting DBP: 75-90 mm Hg and SBP $\leq$ 155 mm Hg

Lisinopril group

- Number: 265
- Age: 33 (27-40)
- Sex (M/F): 155/110

Placebo group

- Number: 265
- Age: 33 (28-41)
- Sex (M/F): 167/98

Exclusion criteria

- History of renal-artery stenosis, cardiac-valve obstruction, or accelerated hypertension
- Recent (within the previous 3 months) MI, coronary bypass surgery, stroke, or CHF
- Abnormal renal function: SCr $>$ 1.8 mg/dL in the previous 6 months, persistent proteinuria (albustix positive or an AER $>$ 250 μ g/min) or persistent haematuria on 3 occasions within the previous 12 months
- Postural hypotension
- Medication that affects BP
- Previous idiosyncratic reaction to ACEi
- Seropositive for hepatitis B or HIV

Interventions	Lisinopril group 10-20 mg/d Placebo group Co-interventions: NS	
Outcomes	1. AER	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Garg 1998

Methods	Country: USA Setting/Design: University Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: Yes - Data analysis: No Intention-to-treat: Yes Follow-up period: 12 months Loss to follow-up: 1
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Garg 1998 (Continued)

Participants

Inclusion criteria

- DM: Type 1
- AER: 20-300 g/min on at least 2 overnight urine collections
- Early background diabetic retinopathy

Ramipril group

- Number: 7
- Age: 26.1 (2.17)
- Sex (M/F): 1/6

Ramipril + pentoxifylline group

- Number: 7
- Age: 23.7 (1.1)
- Sex (M/F): 3/4

Placebo group

- Number: 4
- Age: 24.1 (0.93)
- Sex (M/F): 2/2

Exclusion criteria: NS

Interventions

Ramipril group

5 mg/d

Ramipril + pentoxifylline group

5 mg/d + 400 mg 3x/d

Placebo group
Co-interventions: No

Outcomes

1. BP
2. AER

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hansen 1994

Methods

Country: Denmark
Setting/Design: Multicentre
Time frame: NS
Randomisation method: NS
Blinding
- Participants: Yes
- Investigators: Yes
- Outcome assessors: No
- Data analysis: No

Hansen 1994 (Continued)

Intention-to-treat: No
Follow-up period: 24 months
Loss to follow-up: 1

Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none">• DM: Type 1 (duration 4-28 years)• Onset of diabetes: Before 39 years• Age: 18-55 years• BP: < 160/95 mm Hg for patients >35 years and < 145/90 mm Hg < 35 years• UAE: 20-200 µg/min in more than 1 of 3 overnight urines collected during a screening procedure <p>Captopril group</p> <ul style="list-style-type: none">• Number: 10• Age: 32 (13)• Sex (M/F): 9/1 <p>Placebo group</p> <ul style="list-style-type: none">• Number: 12• Age: 33 (8)• Sex (M/F): 9/3 <p>Exclusion criteria</p> <ul style="list-style-type: none">• Treatment with antihypertensive or diuretic drugs	
Interventions	<p>Captopril group 100 mg/d</p> <p>Placebo group</p> <p>Co-interventions: No</p>	
Outcomes	<ol style="list-style-type: none">1. BP2. UAE3. Renal clearance4. Extracellular volume5. Echocardiography6. Glycaemic control	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

HOPE 2000

Methods	Country: Canada Setting/Design: Multicentre Time frame: NS Randomisation method: NS Blinding
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HOPE 2000 (Continued)

- Participants: Yes
- Investigators: Yes
- Outcome assessors: Yes
- Data analysis: No
Intention-to-treat: Yes
Follow-up period: mean 4.5 years
Loss to follow-up:13

Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none">• Patients with and without diabetes aged 55 years or older with a history of cardiovascular disease (coronary artery disease, stroke, or peripheral vascular disease) or diabetes plus at least one other cardiovascular risk factor (total cholesterol > 5.2 mmol/L, HDL cholesterol < 0.9 mmol/L, hypertension, known microalbuminuria, or current smoking) <p>Ramipril group</p> <ul style="list-style-type: none">• Number: 1808• Age: 65.3 (6.4)• Sex (M/F): 1112/636 <p>Placebo group</p> <ul style="list-style-type: none">• Number: 1769• Age: 65.6 (6.6)• Sex (M/F): 1143/626 <p>Exclusion criteria</p> <ul style="list-style-type: none">• Dipstick-positive proteinuria or established diabetic nephropathy• Other severe renal disease• Hyperkalaemia• CHF• Low ejection fraction (< 0.4)• Uncontrolled hypertension• Recent MI or stroke (< 4weeks)• Use of or hypersensitivity to vitamin E or ACEi
Interventions	<p>Ramipril group 10 mg/d</p> <p>Placebo group</p> <p>Co-interventions: No</p>
Outcomes	<ol style="list-style-type: none">1. Development of MI, stroke or cardiovascular death2. Total mortality, admission to hospital for CHFor unstable angina, cardiovascular revascularisation or development of overt nephropathy3. Any heart failure, worsening angina, and the development of diabetes in people with no history of the disorder4. Progression of microalbuminuria or overt nephropathy in participants with diabetes
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment?	Low risk A - Adequate

IDNT 2001

Methods	Country: USA Setting/Design: Multicentre Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: Yes Follow-up period: 30 months Loss to follow-up: 11
Participants	Inclusion criteria <ul style="list-style-type: none"> • Age: 30-70 years • DM: Type 2 • Hypertension: BP > 135/85 mm Hg or documented treatment with antihypertensive agents • Proteinuria at least 900 mg/24h • SCr: 1-3.0 mg/dL in women and 1.2-3.0 mg/dL in men Irbesartan group <ul style="list-style-type: none"> • Number: 579 • Age: 59.3 (7.1) • Sex (M/F): 378/201 Placebo group <ul style="list-style-type: none"> • Number: 569 • Age: 58.3 (8.2) • Sex (M/F): 403/166 Exclusion criteria: NS
Interventions	Irbesartan group 75-300 mg/d Placebo group Co-interventions Antihypertensive agents other than ACEi, AIIRA and CCB
Outcomes	1. Doubling of SCr 2. Onset of ESKD (initiation of dialysis, renal transplantation or SCr $\geq$ 6 mg/dL) 3. Death from any cause
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment?	Low risk A - Adequate

IRMA-2 2001

Methods	Country: Denmark Setting/Design: Multicentre Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: Yes Follow-up period: 2 years Loss to follow-up: 77
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> Hypertensive patients with type 2 DM Age: 30-70 years Persistent microalbuminuria (AER 20-200 µg/min in 2 of 3 consecutive, sterile, overnight urine samples) SCr ≤ 1.5 mg/dL for men and ≤ 1.1 mg/dL for women <p>Irbesartan group 1</p> <ul style="list-style-type: none"> Number: 195 Age: 58.4 (8) Sex (M/F): 129/66 <p>Irbesartan group 2</p> <ul style="list-style-type: none"> Number: 194 Age: 57.3 (7.9) Sex (M/F): 137/57 <p>Placebo group</p> <ul style="list-style-type: none"> Number: 201 Age: 58.3 (8.7) Sex (M/F): 138/63 <p>Exclusion criteria</p> <ul style="list-style-type: none"> Non-diabetic kidney disease Cancer Life-threatening disease with death expected to occur within 2 years Indication for ACEi or AIIA
Interventions	<p>Irbesartan group 1 150 mg/d</p> <p>Irbesartan group 2 300 mg/d</p> <p>Placebo group</p> <p>Co-interventions Diuretics, beta-blockers, CCB (except dihydropyridines), and alpha blockers</p>
Outcomes	<ol style="list-style-type: none"> Incidence of progression to diabetic nephropathy AER

IRMA-2 2001 (Continued)

3. CrCl
4. BP

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

JAPAN-IDDM 2002

Methods	Country: Japan Setting/Design: Multicentre Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: mean 1.5years Loss to follow-up: 22
Participants	Inclusion criteria <ul style="list-style-type: none"> DM: Type 1 before the age of 20 years Age: 20-50 years AER: > 30 mg/d at the time of screening in 2 consecutive sterile urine samples collected overnight Hypertensive cases: DBP < 90mm Hg with antihypertensive agents other than ACEi, CCB and AIIRA Imidapril group <ul style="list-style-type: none"> Number: 26 Age: 36.2 (6.7) Sex (M/F): 13/13 Captopril group <ul style="list-style-type: none"> Number: 26 Age: 30.9 (8.5) Sex (M/F): 6/20 Placebo group <ul style="list-style-type: none"> Number: 27 Age: 33.4 (7.9) Sex (M/F): 9/18 Exclusion criteria <ul style="list-style-type: none"> Poor glycaemic control (HbA1c > 10%) SCr > 2 mg/dL Other renal, endocrine, cardiac, liver, gastrointestinal, or connective tissue diseases

JAPAN-IDDM 2002 (Continued)

Interventions	Imidapril group 5 mg/d Captopril group 37.5 mg/d Placebo group Co-interventions Antihypertensive agents other than ACEi, CCB and AIIRA	
Outcomes	1. AER 2. BP 3. Glycaemic control	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Jerums 2001

Methods	Country: Australia Setting/Design: Multicentre Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: Yes Follow-up period: 24-36 months Loss to follow-up: 9	
Participants	Inclusion criteria <ul style="list-style-type: none"> • Age: 16-65 years • DM: Type 1 for at least 5 years with persistent ketonuria and weight loss on presentation • Microalbuminuria: 2 or 3 measurements of albumin excretion rate between 20-200 µg/min performed on overnight urine collections • BP: Supine 160/90 mm Hg or less if 40 years or older or 140/90 mm Hg or less if > 40 years Perindopril group <ul style="list-style-type: none"> • Number: 13 • Age: 35 (5) • Sex (M/F): 4/9 Placebo group <ul style="list-style-type: none"> • Number: 10 • Age: 28 (3) • Sex (M/F): 7/3 	

Jerums 2001 (Continued)

Exclusion criteria

- Non-diabetic renal disease
- Significant renal impairment (SCr > 0.2 mmol/L)
- Haematuria
- Cardiac failure
- Hypertension
- Concurrent systemic disease
- Poor diabetic control (HbA1c > 10%)
- Serum potassium > 5 mmol/L
- Recurrent UTI
- Patients at high risk for pregnancy
- Patients with another condition or therapy that might pose a risk to the patient or confound the results of the study

Interventions	Perindopril group 2-8 mg/d Placebo group Co-interventions: No	
Outcomes	1. AER 2. BP 3. GFR	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Jerums 2004

Methods	Country: Australia Setting/Design: Multicentre Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: Yes Follow-up period: 66 months(median) Loss to follow-up: 32	
Participants	Inclusion criteria <ul style="list-style-type: none"> • Age: 15-65 years • DM: Type 2 for at least 1 year • Microalbuminuria: 2 of 3 consecutive measurements of UAE between 20-200 µg/min performed on overnight urine collections 	

Jerums 2004 (Continued)

- BP: Supine 140/90 mm Hg

Perindopril group

- Number: 23
- Age: 50 (2)
- Sex (M/F): 14/9

Placebo group

- Number: 27
- Age: 53 (1)
- Sex (M/F): 15/12

Exclusion criteria

- Non-diabetic renal disease
- SCr > 200 µmol
- Haematuria
- Cardiac failure
- Hypertension
- Concurrent systemic disease
- Poor diabetic control (HbA1c > 10%)
- Serum potassium > 5mmol/L
- Recurrent UTI
- Patients at high risk for pregnancy
- Patients with another condition or therapy that might pose a risk to the patient or confound the results of the study

Interventions	Perindopril group 2-8 mg/d Placebo group Co-interventions Diuretics, CCB, beta-blockers if blood pressure remained uncontrolled.	
Outcomes	1. AER 2. Development of macroproteinuria or reversal to the normoalbuminuric range	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Ko 2005

Methods	Country: Hong Kong Setting/Design: Teaching hospitals Time frame: NS Randomisation method: NS Blinding - Participants: No
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Ko 2005 (Continued)

- Investigators: No
- Outcome assessors: No
- Data analysis: No
Intention-to-treat: Yes
Follow-up period: 1 year
Loss to follow-up: 1

Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> DM: Type 2 Normal renal function or early stage nephropathy <p>Enalapril group</p> <ul style="list-style-type: none"> Number: 20 Age: 59.7 (11.8) Sex (M/F): 9/13 <p>Valsartan group</p> <ul style="list-style-type: none"> Number: 22 Age: 62.1 (10.5) Sex (M/F): 12/8 <p>Exclusion criteria</p> <ul style="list-style-type: none"> Uncontrolled hypertension (sitting BP > 200/115 mm Hg) History of MI CVA Uncontrolled CHF within the previous 6 months Significant renal impairment (SCr > 150 µmol/L)
Interventions	<p>Enalapril group 5-10 mg/d</p> <p>Valsartan group 80-160 mg/d</p> <p>Co-interventions Other antihypertensive agents</p>
Outcomes	<ol style="list-style-type: none"> BP AER
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment?	Unclear risk B - Unclear

Lacourciere 2000

Methods	Country: Canada Setting/Design: Multicentre Time frame: NS Randomisation method: NS Blinding
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Lacourciere 2000 (Continued)

- Participants: Yes
- Investigators: Yes
- Outcome assessors: No
- Data analysis: No
Intention-to-treat: No
Follow-up period: 12 months
Loss to follow-up: 11

Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> DM: Type 2 diagnosed $\geq$ 30 years of age Hypertension: Mild to moderate essential (sitting DBP 90-115 mm Hg) AER: 20-350 μg/min without evidence of UTI <p>Losartan group</p> <ul style="list-style-type: none"> Number: 52 Age: 59.2 (9.2) Sex (M/F): 39/13 <p>Enalapril group</p> <ul style="list-style-type: none"> Number: 51 Age: 57.8 (10.5) Sex (M/F): 44/7 <p>Exclusion criteria</p> <ul style="list-style-type: none"> Evidence or suspicion of renovascular disease History of malignant hypertension SBP $>$ 210 mm Hg CVA in the previous 12 months or current transient Ischaemic attacks MI within the previous 12 months Clinically significant arteriovenous conduction disturbances and/or arrhythmias Unstable angina History of heart failure SCr $\geq$ 200 mmol/L Serum potassium $\geq$ 5.5 mmol/L or $\leq$ 3.5mmol/L Treatment with oral corticosteroid Concomitant use of agents that may affect BP except beta-blockers and nitrates used in the treatment of stable angina Drug or alcohol abuse Pregnancy Breast feeding Ineffective contraception
Interventions	<p>Losartan group 50 mg/d</p> <p>Enalapril group 5-10 mg/d</p> <p>Co-interventions Antihypertensive agents other than ACEi, AIIRA and CCB</p>
Outcomes	<ol style="list-style-type: none"> BP AER

Lacourciere 2000 (Continued)

3. GFR

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Laffel 1995

Methods

Country: USA
Setting/Design: University
Time frame: NS
Randomisation method: NS
Blinding
- Participants: Yes
- Investigators: Yes
- Outcome assessors: No
- Data analysis: No
Intention-to-treat: Yes
Follow-up period: 24 months
Loss to follow-up: 43

Participants

Inclusion criteria

- Age: 14-57 years
- IDDM: Diagnosed before 45 years
- Overnight AER: 20-200 µg/min

Captopril group

- Number: 70
- Age: 32 (8.1)
- Sex (M/F): 53/47

Placebo group

- Number: 73
- Age: 33.4 (9.0)
- Sex (M/F): 48/52

Exclusion criteria

- HbA1c ≥ 11.5%
- SCr and potassium levels beyond the normal ranges
- White blood cell count < 3500/mm³
- BP ≥ 140/90 mm Hg
- Antihypertensive therapy (CCB, beta blockers)
- Pregnancy
- Lactation
- Failure to use adequate contraception for women of child-bearing ages
- Histories of renal, cardiac, hepatic, gastrointestinal or autoimmune diseases
- Use of NSAIDs (except for low-dose aspirin not to exceed 650 mg/d)

Laffel 1995 (Continued)

Interventions	Captopril group 100 mg/d Placebo group Co-interventions Prazosin-clonidine	
Outcomes	1. AER 2. CrCl 3. Progression to hypertension	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lebovitz 1994

Methods	Country: USA Setting/Design: Multicentre Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 36 months Loss to follow-up: 44	
Participants	Inclusion criteria <ul style="list-style-type: none"> DM: Type 2 DBP: > 90mm Hg or therapy for hypertension GFR: 30-100 mL/min/1.73 m² Enalapril group <ul style="list-style-type: none"> Number: 35 Age: NS Sex (M/F): NS Placebo group <ul style="list-style-type: none"> Number: 40 Age: NS Sex (M/F): NS Exclusion criteria: NS	
Interventions	Enalapril group 5-40 mg/d	

Lebovitz 1994 (Continued)

Placebo group
Co-interventions

Alpha and beta adrenergic antagonist, diuretics and CCB

Outcomes	1. AER 2. BP 3. GFR
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Notes	
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Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Marre 1987

Methods	Country: France Setting/Design: Hospital Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 6 months Loss to follow-up: 0
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Participants	Inclusion criteria <ul style="list-style-type: none"> • Age: 20-60 • DM: Type I or 2 known for at least five years • BMI: <30 kg/ m² • AER: 30-300 mg/24 h in at least 2 of 3 monthly measurements • BP: Supine < 160/95 mm Hg on 3 consecutive monthly visits to the outpatient clinic Enalapril group <ul style="list-style-type: none"> • Number: 10 • Age: 39.3 (11.6) • Sex (M/F): 6/4 Placebo group <ul style="list-style-type: none"> • Number: 10 • Age: 38.9 (10.9) • Sex (M/F): 6/4 Exclusion criteria <ul style="list-style-type: none"> • Heart, kidney, liver or systemic disease • No taking drugs except antidiabetic agent or contraceptives
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Marre 1987 (Continued)

Interventions	Enalapril group 20 mg/d Placebo group Co-interventions: No	
Outcomes	1. AER 2. BP 3. GFR	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Mathiesen 1999

Methods	Country: Denmark Setting/Design: Hospital Time frame: NS Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 4 years (8 years for GFR) Loss to follow-up: 4	
Participants	Inclusion criteria <ul style="list-style-type: none"> DM: Type 1 microalbuminuria Age: < 50 Onset of diabetes: Before the age of 41 Duration of diabetes: 5-30 years DBP: < 95mm Hg No other disease Captopril + bendrofluazide group <ul style="list-style-type: none"> Number: 21 Age: 31 (8) Sex (M/F): 10/11 Placebo group <ul style="list-style-type: none"> Number: 23 Age: 27(8) Sex (M/F): 12/11 Exclusion criteria: NS	

Mathiesen 1999 (Continued)

Interventions	Captopril + bendrofluazide group Captopril (100 mg/d) + bendrofluazide (2.5 mg/d)	
	Placebo group	
	Co-interventions: No	
Outcomes	1. AER 2. GFR 3. BP	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Muirhead 1999

Methods	Country: Canada Setting/Design: Multicentre Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: Yes Follow-up period: 13 months Loss to follow-up: 19	
Participants	Inclusion criteria <ul style="list-style-type: none"> DM: Type 2 Age: ≥ 18 AER: 20-300 $\mu\text{g}/\text{min}$ with $\text{GFR} \geq 60 \text{ mL}/\text{min}/1.73 \text{ m}^2$ Normotensive and treated hypertension $\leq 160/95 \text{ mm Hg}$ Valsartan group 1 <ul style="list-style-type: none"> Number: 31 Age: 53.7 (9.5) Sex (M/F): 22/9 Valsartan group 2 <ul style="list-style-type: none"> Number: 31 Age: 58.3 (9.5) Sex (M/F): 18/13 Captopril group <ul style="list-style-type: none"> Number: 29 Age: 56.7 (10) 	

Muirhead 1999 (Continued)

- Sex (M/F): 21/8

Placebo group

- Number: 31
- Age: 55.5 (11.3)
- Sex (M/F): 28/3

Exclusion criteria

- Women of child-bearing potential using estrogen/progesterone
- Patients with brittle diabetes that is at increased risk of hypoglycaemia
- History of non-compliance with medical regimens
- Patients who experienced symptomatic hypotension who progressed to hypertension (SBP > 95 mm Hg despite treatment with beta-blockers or diuretics)
- Patients who experienced serious adverse experiences related to the study treatment

Interventions	Valsartan group 1 80 mg/d Valsartan group 2 160 mg/d Captopril group 75 mg/d Placebo group Co-interventions: No	
Outcomes	1. AER 2. Progression to clinical proteinuria 3. GFR	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Nankervis 1998

Methods	Country: Australia Setting/Design: Hospital Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 36 months Loss to follow-up: 9	
Participants	Inclusion criteria	

Nankervis 1998 (Continued)

- DM: Type 1 and 2
- Age: 18-65 years
- Microalbuminuria (AER 20-200 mg/L on 2 of 3 consecutive occasions)
- SCr: < 120 µmol/L
- Stable glycaemic control

Perindopril group

- Number: 20
- Age: 43 (3)
- Sex (M/F): 16/4

Placebo group

- Number: 20
- Age: 49 (3)
- Sex (M/F): 16/4

Exclusion criteria

Non-diabetic renal disease or other major disease

Interventions	Perindopril group 4 mg/d Placebo group Co-interventions CCB, beta-blockers, alpha-blockers or diuretic	
Outcomes	1. GFR 2. AER 3. Histomorphometric features of renal biopsies	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

O'Donnell 1993

Methods	Country: UK Setting/Design: University Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 48 weeks Loss to follow-up: 9
Participants	Inclusion criteria

O'Donnell 1993 (Continued)

- DM: Type 1 or 2
- Age: 18-70 years Incipient diabetic nephropathy
- DBP: Resting ≤ 90 mm Hg

Lisinopril group

- Number: 15
- Age: 48.3 (13.0)
- Sex (M/F): 11/4

Placebo group

- Number: 17
- Age: 49.1 (16.0)
- Sex (M/F): 12/5

Exclusion criteria

- Hypertension of any aetiology
- Heart failure, aortic outflow obstruction, unstable angina or MI in the preceding 3 months
- Renal disease other than diabetic nephropathy
- SCr > 140 $\mu\text{mol/L}$
- Low protein diet
- Systemic malignancy
- Clinically significant abnormality of hepatic, haemopoietic or endocrine function
- Women of childbearing potential not using a medically acceptable method of birth control
- Continuous subcutaneous insulin infusion
- Hypersensitivity to ACEi
- Treatment with the following medications: aldose reductase inhibitors, myo-inositol, steroids, gold, penicillamine, NSAIDs, monoamine oxidase inhibitors, appetite suppressants, lithium, vasopressor nasal decongestants or cimetidine

Interventions	Lisinopril group 10 mg/d Placebo group Co-interventions: No	
Outcomes	1. AER 2. Urinary excretion of prostaglandins 3. GFR	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Parving 1989

Methods	Country: Denmark Setting/Design: Hospital Time frame: NS
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Parving 1989 (Continued)

Randomisation method: NS
Blinding
- Participants: No
- Investigators: No
- Outcome assessors: No
- Data analysis: No
Intention-to-treat: No
Follow-up period: 12 months
Loss to follow-up: 1

Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Normotensive insulin dependent diabetics • AER > 300 mg/24 h • SCr < 120 µmol/L or GFR > 60 mL/min/1.73 m² • BP: 3 or more consecutive readings < 150/90 mm Hg • No oedema • No taking other drugs apart from oral contraceptives • Age < 50 years • Onset of DM: < 41 years <p>Captopril group</p> <ul style="list-style-type: none"> • Number: 15 • Age: 32 (8) • Sex (M/F): 10/5 <p>Placebo group</p> <ul style="list-style-type: none"> • Number: 17 • Age: 30 (8) • Sex (M/F): 13/4 <p>Exclusion criteria: NS</p>
Interventions	<p>Captopril group 25-100 mg/d</p> <p>Placebo group</p> <p>Co-interventions: No</p>
Outcomes	<ol style="list-style-type: none"> 1. AER 2. BP 3. GRF
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment?	Unclear risk B - Unclear

Parving 2001a

Methods Country: Denmark

Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease (Review)

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Parving 2001a (Continued)

Setting/Design: Hospital
 Time frame: NS
 Randomisation method: Yes
 Blinding
 - Participants: No
 - Investigators: No
 - Outcome assessors: No
 - Data analysis: No
 Intention-to-treat: Yes
 Follow-up period: 96 months
 Loss to follow-up: 18

Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none">• DM: Type 1 (onset of diabetes before 41 years)• Age: < 50 years• Persistent albuminuria: < 300 mg/24 h• SCr: < 120 μmol/L• GFR: > 60 mL/min/1.73 m²• BP: Average of 3 or more consecutive readings < 159/90 mm Hg <p>Captopril group</p> <ul style="list-style-type: none">• Number: 16• Age: 32 (8)• Sex (M/F): 10/5 <p>Control group</p> <ul style="list-style-type: none">• Number: 17• Age: 30 (8)• Sex (M/F): 13/5 <p>Exclusion criteria</p> <ul style="list-style-type: none">• Oedema• Drugs (except oral contraceptives)
Interventions	<p>Captopril group 12.5-125 mg/d</p> <p>Control group</p> <p>Co-interventions Diuretics, dihydropyridine, CCB, beta-blocker</p>
Outcomes	<p>1. BP</p> <p>2. Albuminuria</p> <p>3. GFR</p>
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment?	Unclear risk B - Unclear

Phillips 1993

Methods	Country: USA Setting/Design: Hospital Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 24 months Loss to follow-up: 4
Participants	Inclusion criteria <ul style="list-style-type: none">• Age: 18-65 years• AER: 30-300 mg/24 h on 2 of 3 occasions• HbA1c: < 13.5%• DB: Mean sitting DBP ≤ 95 mm Hg on 2 of 3 occasions• BMI: ≤ 32 kg/m²• Compliance: 80% Cilaxapril group <ul style="list-style-type: none">• Number: 14• Age: 47.1 years (22-63)• Sex (M/F): 13/1• BMI: 27.1 (23-32)• Duration of diabetes: 14.7 years (2-34) Control group <ul style="list-style-type: none">• Number: 11• Age: 44.6 (25-63)• Sex (M/F): 9/2• BMI: 28 (25-32)• Duration of diabetes: 13.2 years (6-22) Exclusion criteria <ul style="list-style-type: none">• Cardiovascular or other medical diseases• Reported adverse effects to cilazapril• Taking medication affecting BP or had a history of any contraindication to ACEi• Women of childbearing potential• Uncooperative
Interventions	Cilaxapril group 2.5 or 5 mg/d (DBP ≥ 85 mm Hg) for 24 weeks Control group Matched placebo Co-interventions: NS
Outcomes	1. AER 2. BP

Phillips 1993 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Poulsen 2001

Methods	Country: Denmark Setting/Design: University Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: Yes Follow-up period: 24 months Loss to follow-up: 0
Participants	Inclusion criteria <ul style="list-style-type: none"> DM: Type 1 Age: 18-65 years Duration of diabetes: 3-41 years BP: < 160/90 mm Hg Lisinopril group <ul style="list-style-type: none"> Number: 33 Age: 34.9 (11.8) Sex (M/F): 18/7 Placebo group <ul style="list-style-type: none"> Number: 25 Age: 38.5 (10.4) Sex (M/F): 22/11 Exclusion criteria <ol style="list-style-type: none"> Other chronic illness Medical treatment apart from insulin
Interventions	Lisinopril group 40 mg/d Placebo group Co-interventions: No
Outcomes	<ol style="list-style-type: none"> AER BP and AMBP

Poulsen 2001 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Ravid 1993

Methods	Country: Israel Setting/Design: Multicentre Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 5 years Loss to follow-up: 8
Participants	Inclusion criteria <ul style="list-style-type: none"> • Age: < 50 years • DM: Type 2 with duration of less than 10 years • BMI: < 27 kg/m² • BP: Normal on 2 consecutive examinations (BP < 130/90 mm Hg; MAP < 107 mm Hg) • SCr: < 1.4 mg/dL • AER: 30-300 mg/24 h on 2 consecutive visits without evidence of UTI Enalapril group <ul style="list-style-type: none"> • Number: 49 • Age: 43.5 (3) • Sex (M/F): 21/28 Placebo group <ul style="list-style-type: none"> • Number: 45 • Age: 44.8 (3.5) • Sex (M/F): 21/24 Exclusion criteria <ul style="list-style-type: none"> • Evidence of systemic, renal, cardiac or hepatic diseases
Interventions	Enalapril group 10 mg/d Placebo group Co-interventions Long-acting nifedipine
Outcomes	1. AER

Ravid 1993 (Continued)

2. Renal function
3. Glycaemic control
4. BP

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

RENAAL 2001

Methods	Country: USA Setting/Design: Multicentre Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: Yes - Data analysis: No Intention-to-treat: Yes Follow-up period: mean 3.4 years Loss to follow-up: 3
Participants	Inclusion criteria <ul style="list-style-type: none"> • DM: Type 2 Nephropathy (presence on 2 occasions of a ratio of urinary albumin to urinary creatinine from a first morning specimen of at least 300 and SCr between 1.3-3 mg/dL with a lower limit of 1.5 mg/dL for male patients weighing more than 60 kg) • Age: 31-70 years Losartan group <ul style="list-style-type: none"> • Number: 751 • Age: 60 (7) • Sex (M/F): 462/289 Placebo group <ul style="list-style-type: none"> • Number: 762 • Age: 60 (7) • Sex (M/F): 494/268 Exclusion criteria <ul style="list-style-type: none"> • DM type 1 or non-diabetic renal disease • MI or CAB grafting within the previous month • CVA or percutaneous transluminal coronary angioplasty within the previous 6 months • Transient ischemic attack within the previous year • History of heart failure
Interventions	Losartan group 50-100 mg/d Placebo group

RENAAL 2001 (Continued)

Co-interventions

CCB, diuretics, alpha-blockers, beta-blockers and centrally acting agents

Outcomes	<div>1. Doubling of SCr</div> <div>2. ESKD</div> <div>3. Death</div> <div>4. Morbidity and mortality from cardiovascular causes</div> <div>5. Proteinuria</div> <div>6. Rate of progression of renal disease</div>	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Rizzoni 2005

Methods	Country: Italy Setting/Design: Multicentre Time frame: NS Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 1 year Loss to follow-up: 0	
Participants	Inclusion criteria <ul style="list-style-type: none"> • Mild essential hypertension • DM: Type 2 with or without ongoing oral hypoglycaemic therapy • Age: 30-70 years Enalapril group <ul style="list-style-type: none"> • Number: 7 • Age: 58 (4) • Sex (M/F): 5/2 Candesartan group <ul style="list-style-type: none"> • Number: 8 • Age: 58 (9) • Sex (M/F): 6/2 Exclusion criteria <ul style="list-style-type: none"> • Previous treatment with ACEi and AIRA • Secondary forms of hypertension or any disease that could have interfered with the study protocol 	
Interventions	Enalapril group	

Rizzoni 2005 (Continued)

10-20 mg/d

Candesartan group

8-16 mg/d

Co-interventions

Diuretics if BP not controlled in 12 weeks

Outcomes

1. Indices of subcutaneous small resistance artery structure
2. Endothelium function
3. Death rates

Notes
Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Romero 1993
Methods

Country: Spain
Setting/Design: University-Hospital
Time frame: NS
Randomisation method: NS
Blinding
- Participants: No
- Investigators: No
- Outcome assessors: No
- Data analysis: No
Intention-to-treat: No
Follow-up period: 6 months
Loss to follow-up: 0

Participants
Inclusion criteria

- Normotensive type 2 diabetic patients
- AER: 30-300 mg/d in 3, 24h urine collections performing during the previous 6 months

Captopril group

- Number: 13
- Age: 53.2 (7.1)
- Sex (M/F): 9/4

Placebo group

- Number: 13
- Age: 52.5 (15.1)
- Sex (M/F): 7/6

Exclusion criteria

1. Clinical or laboratory evidence of cardiac disease
2. Liver or renal dysfunction

Interventions
Captopril group
Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease (Review)

Romero 1993 (Continued)

Initial dose: 25 mg/d (mean 61 ±19 mg/d)

Placebo group

Co-interventions: No

Outcomes	<ol style="list-style-type: none"> 1. SBP 2. DBP 3. Microalbuminuria 4. GFR
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Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Sano 1994

Methods	Country: Japan Setting/Design: University Time frame: NS Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 48 months Loss to follow-up: 4
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Participants	Inclusion criteria <ul style="list-style-type: none"> • Age: 50-76 years • Persistent microalbuminuria: 20-300 mg/24 h on 3-4 separate occasions over a 3 month period • SCr: < 1.2 mg/dL • BP: Supine SBP < 150 mm Hg, and DBP < 90 mm Hg over a long term period • HbA1c: < 10% • No history of non-diabetic renal disease • No taking any drugs apart from oral hypoglycaemic agents Enalapril group 1 <ul style="list-style-type: none"> • Normotensive patients • Number: 12 • Age: 62.4 (3.3) • Sex (M/F): NS Enalapril group 2 <ul style="list-style-type: none"> • Well controlled hypertensive patients • Number: 11 • Age: 63.6 (2.2)
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Sano 1994 (Continued)

- Sex (M/F): NS

Control group 1

- Normotensive patients
- Number:12
- Age: 64.4 (2.4)
- Sex (M/F): NS

Control group 2

- Well controlled hypertensive patients
- Number:13
- Age: 65.5 (2.6)
- Sex (M/F): NS

Interventions	Enalapril groups Enalapril 5 mg/d Control group Co-interventions Nifedipine (30 mg/d) for well controlled hypertensive patients	
Outcomes	1. AER 2. GFR	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Sato 2003

Methods	Country: Japan Setting/Design: Teaching hospital Time frame: NS Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 11 ± months Loss to follow-up: 0	
Participants	Inclusion criteria <ul style="list-style-type: none"> • Diabetic nephropathy: Stage 2 or 3A (defined by the presence of either microalbuminuria with AER of 30-300 mg/g creatinine or overt proteinuria > 300 mg/g creatinine with a GFR > 60mL/min) • BP: < 130/85 mm Hg ACEi group	

Sato 2003 (Continued)

- Number: 23
- Age: 66 (8)
- Sex (M/F): 13/10

Candesartan group

- Number: 26
- Age: 61 (12)
- Sex (M/F): 13/13

Exclusion criteria: NS

Interventions	ACEi group Enalapril or trandolapril (not specified) Candesartan group Not specified Co-interventions CCB, alpha 1 blocker and central acting alpha 2 stimulant, nifedipine(30 mg/d)	
Outcomes	1. BP 2. AER 3. Urinary type IV collagen excretion	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Stornello 1992

Methods	Country: Italy Setting/Design: University Time frame: NS Randomisation method: Yes Blinding - Participants: No - Investigators: No - Outcome assessors: No - Data analysis: No Intention-to-treat: Yes Follow-up period: 6 months x 2 Loss to follow-up: 0	
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • DM: Type 2 • Persistent albuminuria: > 300 mg/24 h on at least 3 occasions <p>Enalapril group</p> <ul style="list-style-type: none"> • Number: 12 • Age: 46.9 (9.1) 	

Stornello 1992 (Continued)

- Sex (M/F): 6/6

Atenolol group

- Number: 12
- Age: 46.9 (9.1)
- Sex (M/F): 6/6

Exclusion criteria

- Signs of other renal disease

Interventions	Enalapril group 5 mg/d Atenolol group 50 mg/d Co-interventions: NS	
Outcomes	1. BP 2. GFR 3. AER	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Tan 2002

Methods	Country: China Setting/Design: Hospital Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: Yes Follow-up period: 6 months Loss to follow-up: 0	
Participants	Inclusion criteria <ul style="list-style-type: none"> • DM: Type 2 • HbA1c: < 10% • Mean AER: 20-200 µg/min • BP: Sitting ≤ 140/89 mm Hg Controlled hypertension with no changes in antihypertensive therapy in the preceding 3 months Losartan group <ul style="list-style-type: none"> • Number: 40 	

Tan 2002 (Continued)

- Age: 54.7 (10.1)
- Sex (M/F): 22/18

Placebo group

- Number: 40
- Age: 54.3 (8.8)
- Sex (M/F): 18/22

Exclusion criteria

- Treatment with ACEi
- Major CVE

Interventions	Losartan group 50 mg/d Placebo group Co-interventions: No	
Outcomes	1. Endothelium function 2. Mean AER 3. BP 4. CrCl	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Trevisan 1995

Methods	Country: Italy Setting/Design: Multicentre Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 6 months Loss to follow-up: 14	
Participants	Inclusion criteria <ul style="list-style-type: none"> • Age: 18-65 years • DM: Type 2 for at least 6 months duration • Stable metabolic control with a HbA1c < 10% • Persistent microalbuminuria 20-200 µg/min at screening and in at least 2 of 3 consecutive sterile urine samples collected overnight • Normotensive or mildly hypertensive without antihypertensive treatment 	

Trevisan 1995 (Continued)

Ramipril group

- Number: 60
- Age: 36 (7)
- Sex (M/F): 44/16

Placebo group

- Number: 62
- Age: 58 (7)
- Sex (M/F): 50/12

Exclusion criteria

- BP: > 180/105 mm Hg
- Unstable angina, heart failure
- SCr > 1.5 mg/dL
- History of poor compliance
- Serum potassium levels > 5.5 mEq/L
- Liver, gastrointestinal, and connective tissue diseases

Interventions	Ramipril group 1.25 mg/d Placebo group Co-interventions: No
Outcomes	1. AER 2. BP
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment?	Unclear risk B - Unclear

Tutuncu 2001

Methods	Country: Turkey Setting/Design: University Time frame: NS Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 12 months Loss to follow-up: 3
Participants	Inclusion criteria <ul style="list-style-type: none"> • Normotensive type 2 diabetic patients

Tutuncu 2001 (Continued)

- Microalbuminuria: AER 30-300 mg/d in at least 3 consecutive 24 hour determinations

Enalapril group

- Number: 12
- Age: 51.4 (8.0)
- Sex (M/F): NS

Losartan group

- Number: 12
- Age: 58.1 (10.8)
- Sex (M/F): NS

Enalapril + Losartan group

- Number: 10
- Age: 57.7 (6.2)
- Sex (M/F): NA

Exclusion criteria

- DM type 1
- Hypertension: > 130/85 mm Hg during ambulatory BP monitoring and a history of taking antihypertensives
- Secondary diabetes
- Thyroid disease
- Alcoholism
- Renal insufficiency not related to diabetes
- Chronic liver disease
- Overt carcinoma
- Treatment with insulin

Interventions	Enalapril group 5 mg/d Losartan group 50 mg/d Enalapril + Losartan group Co-interventions: No	
Outcomes	1. AER	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

ACEi - angiotensin converting enzyme inhibitor; AER - albumin excretion rate; AIIRA - angiotensin II receptor antagonist; BMI - body mass index; CAB - coronary artery bypass; CCB - calcium channel blocker; CrCl - creatinine clearance; CHF - congestive heart failure; CVA - cerebrovascular accident; CVD - cerebrovascular disease; CVE - cardiovascular event; DBP - diastolic blood pressure; DM - diabetes mellitus; ESKD - end-stage kidney disease; GFR - glomerular filtration rate; HD - haemodialysis; MAP - mean arterial pressure; MI - myocardial infarction; NS - not stated; NSAIDs - nonsteroidal anti-inflammatory drugs; PD - peritoneal dialysis; SBP - systolic blood pressure; Scr - serum creatinine; UAE - urinary albumin excretion; UTI - urinary tract infection

DATA AND ANALYSES

Comparison 1. ACEi versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	21	7295	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.71, 1.17]
1.1 Half or less maximum tolerable dose	11	5261	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.41, 3.44]
1.2 Maximum tolerable dose	10	2034	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.61, 0.98]
2 Cardiovascular mortality	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3 Doubling of serum creatinine	9	6780	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.47, 1.00]
4 End-stage kidney disease	10	6819	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.39, 0.93]
5 Micro- to macroalbuminuria	17	2036	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.29, 0.69]
6 Micro- to normoalbuminuria	16	1910	Risk Ratio (M-H, Random, 95% CI)	3.06 [1.76, 5.35]
7 Cough	10	7087	Risk Ratio (M-H, Random, 95% CI)	3.17 [2.29, 4.38]
8 Headache	4	6186	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.33, 2.53]
9 Impotence	5	1528	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.26, 3.91]
10 Hyperkalaemia	2	1219	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.32, 2.21]

Analysis 1.1. Comparison 1 ACEi versus placebo/no treatment, Outcome 1 All-cause mortality.

Analysis 1.2. Comparison 1 ACEi versus placebo/no treatment, Outcome 2 Cardiovascular mortality.

Analysis 1.3. Comparison 1 ACEi versus placebo/no treatment, Outcome 3 Doubling of serum creatinine.

Analysis 1.4. Comparison 1 ACEi versus placebo/no treatment, Outcome 4 End-stage kidney disease.

Analysis 1.5. Comparison 1 ACEi versus placebo/no treatment, Outcome 5 Micro- to macroalbuminuria.

Analysis 1.6. Comparison 1 ACEi versus placebo/no treatment, Outcome 6 Micro- to normoalbuminuria.

Analysis 1.7. Comparison 1 ACEi versus placebo/no treatment, Outcome 7 Cough.

Analysis 1.8. Comparison 1 ACEi versus placebo/no treatment, Outcome 8 Headache.

Analysis 1.9. Comparison 1 ACEi versus placebo/no treatment, Outcome 9 Impotence.

Analysis 1.10. Comparison 1 ACEi versus placebo/no treatment, Outcome 10 Hyperkalaemia.

Comparison 2. AIIRA versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	5	3409	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.85, 1.17]
2 Cardiovascular mortality	0		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Doubling of serum creatinine	3	3251	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.67, 0.93]
4 End-stage kidney disease	3	3251	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.67, 0.91]
5 Micro- to macroalbuminuria	3	761	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.32, 0.75]
6 Micro- to normoalbuminuria	2	670	Risk Ratio (M-H, Random, 95% CI)	1.42 [1.05, 1.93]
7 Cough	2	194	Risk Ratio (M-H, Random, 95% CI)	4.93 [1.00, 24.35]
8 Headache	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9 Impotence	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10 Hyperkalaemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 AIIRA versus placebo/no treatment, Outcome 1 All-cause mortality.

Analysis 2.3. Comparison 2 AIIRA versus placebo/no treatment, Outcome 3 Doubling of serum creatinine.

Analysis 2.4. Comparison 2 AIIRA versus placebo/no treatment, Outcome 4 End-stage kidney disease.

Analysis 2.5. Comparison 2 AIIRA versus placebo/no treatment, Outcome 5 Micro- to macroalbuminuria.

Analysis 2.6. Comparison 2 AIIRA versus placebo/no treatment, Outcome 6 Micro- to normoalbuminuria.

Analysis 2.7. Comparison 2 AIIRA versus placebo/no treatment, Outcome 7 Cough.

Analysis 2.8. Comparison 2 AIIRA versus placebo/no treatment, Outcome 8 Headache.

Analysis 2.10. Comparison 2 AIIRA versus placebo/no treatment, Outcome 10 Hyperkalaemia.

Comparison 3. AIIRA versus ACEi

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	3	307	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.31, 2.78]
2 Cardiovascular mortality	3	307	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.10, 3.62]
3 Doubling of serum creatinine	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 End-stage kidney disease	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Micro- to macroalbuminuria	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Micro- to normoalbuminuria	2	65	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.76, 1.94]
7 Cough	2	90	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.01, 48.70]
8 Headache	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 Hyperkalaemia	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10 Impotence	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 AIIRA versus ACEi, Outcome 1 All-cause mortality.

Analysis 3.2. Comparison 3 AIIRA versus ACEi, Outcome 2 Cardiovascular mortality.

Analysis 3.5. Comparison 3 AIIRA versus ACEi, Outcome 5 Micro- to macroalbuminuria.

Analysis 3.6. Comparison 3 AIIRA versus ACEi, Outcome 6 Micro- to normoalbuminuria.

Analysis 3.7. Comparison 3 AIIRA versus ACEi, Outcome 7 Cough.

WHAT'S NEW

Date	Event	Description
18 March 2010	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 4, 2006

Review first published: Issue 4, 2006

Date	Event	Description
13 May 2009	Amended	Contact details updated.
26 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

- Strippoli GFM: Design, conduct, data-extraction, data-analysis, data interpretation, writing the review
- Bonifati C: Data-extraction, data entry and interpretation, writing the review
- Craig M: Data-extraction, writing the review
- Navaneethan S: Data-extraction, data entry and interpretation, writing of review
- Craig JC: Design, conduct, data-analysis, data interpretation, writing the review.

DECLARATIONS OF INTEREST

None declared

SOURCES OF SUPPORT

Internal sources

- University of Sydney School of Public Health, non-established PhD scholarship, Australia.

External sources

- 2002-03 Young Investigator Scholarship, Italian Society of Nephrology, Italy.

INDEX TERMS

Medical Subject Headings (MeSH)

Angiotensin II Type 1 Receptor Blockers [adverse effects] [*therapeutic use]; Angiotensin-Converting Enzyme Inhibitors [adverse effects] [*therapeutic use]; Cause of Death; Diabetic Nephropathies [*drug therapy] [mortality]; Disease Progression; Randomized Controlled Trials as Topic

MeSH check words

Humans