ClinicalEvidence

Diabetic nephropathy: preventing progression

Search date November 2009

Michael Shlipak

ABSTRACT

INTRODUCTION: Up to one third of people with type 1 or 2 diabetes will develop microalbuminuria or macroalbuminuria after 20 years. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatments in people with type 1 diabetes and early nephropathy? What are the effects of treatments in people with type 1 diabetes and late nephropathy? What are the effects of treatments in people with type 2 diabetes and early nephropathy? What are the effects of treatments in people with type 2 diabetes and late nephropathy? We searched: Medline, Embase, The Cochrane Library, and other important databases up to November 2009 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 19 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, glycaemic control, protein restriction, and tight control of blood pressure.

QUESTIONS

INTERVENTIONS

TYPE 1 DIABETES AND EARLY NEPHROPATHY

Beneficial

Unknown effectiveness

TYPE 1 DIABETES AND LATE NEPHROPATHY

Beneficial

Unknown effectiveness

TYPE 2 DIABETES AND EARLY NEPHROPATHY

Beneficial

Unknown effectiveness

TYPE 2 DIABETES AND LATE NEPHROPATHY

Beneficial

Unknown effectiveness

Diabetic nephropathy: preventing progression

To be covered in future updates

Calcium channel blockers

Key points

- Up to one third of people with type 1 or 2 diabetes will develop microalbuminuria or macroalbuminuria after 20 years. Smoking, poor glycaemic control, male sex, older age, and ethnicity are also risk factors.

  Microalbuminuria can also be caused by hypertension, which often complicates type 2 diabetes and makes the diagnosis more difficult.

  Diabetic nephropathy increases the risk of end-stage renal disease and mortality, and is associated with increased cardiovascular risk.

- In people with type 1 diabetes, angiotensin-converting enzyme (ACE) inhibitors reduce progression of early nephropathy while, in people with late nephropathy, they reduce the risk of end-stage renal failure and death.

  Intensive glycaemic control reduces progression of nephropathy compared with conventional control in people with early renal disease, but we don't know whether glycaemic control is effective in people with late nephropathy.

  We don't know whether angiotensin II receptor blockers (ARBs), dietary protein restriction, or tight control of blood pressure reduce the risks of renal or cardiovascular disease, or improve survival, in people with early or late nephropathy.

- In people with type 2 diabetes, ACE inhibitors reduce progression from early to late nephropathy and may reduce cardiovascular events, but we don't know whether they are beneficial in late nephropathy.

  ARBs may reduce progression of nephropathy in people with early or late nephropathy.

  Lowering of diastolic blood pressure, even if not raised initially, reduces the risk of progression of early nephropathy, but we don't know whether it is effective in late nephropathy.

  We don't know whether protein restriction or tight glycaemic control are beneficial in early or late nephropathy.

DEFINITION

Diabetic nephropathy is a clinical syndrome in people with diabetes, characterised by albuminuria on at least two occasions separated by 3 to 6 months. Diabetic nephropathy is usually accompanied by hypertension, progressive rise in proteinuria, and decline in renal function. In type 1 diabetes, five stages have been proposed (see table 1, p 16). [1] [2] Of these, **stages 1 and 2** are equivalent to pre-clinical nephropathy, and are detected only by imaging or biopsy. **Stage 3** is synonymous with early nephropathy — the clinical term used in this review. **Stage 4** nephropathy is also known clinically as late nephropathy, and this term will be used for the remainder of this review. **Stage 5** represents the progression to end-stage renal disease. **Population:** For the purpose of this review, we have included people with diabetes and both early and late nephropathy. Early nephropathy presents as microalbuminuria, usually defined by albuminuria level of 30 to 300 mg a day (or albumin/creatinine ratio of 30 to 300 mg/g [3.4–34.0 mg/mmol]). Late nephropathy presents as macroalbuminuria, characterised by albuminuria greater than 300 mg a day (or albumin/creatinine ratio greater than 300 mg/g [34 mg/mmol]). The treatment of people with diabetes and end-stage renal disease is not covered in this review.

INCIDENCE/ PREVALENCE

After 20 years of type 1 or 2 diabetes, the cumulative risk of proteinuria is 27% to 28% and the overall prevalence of microalbuminuria and macroalbuminuria is 30% to 35%. [3] In addition, the incidence of diabetic nephropathy is increasing, partly due to the growing epidemic of type 2 diabetes, and because of increased life expectancies: for example, in the USA, the incidence has increased by 150% in the past decade. [4]

AETIOLOGY/ RISK FACTORS

Duration of diabetes, older age, male sex, smoking, and poor glycaemic control have all been found to be risk factors in the development of nephropathy. [5] [6] In addition, certain ethnic groups seem at greater risk (see prognosis). Microalbuminuria is less pathognomonic of nephropathy among people with type 2 diabetes because hypertension, which is a common complication of type 2 diabetes, can also cause microalbuminuria. Hypertension can also cause renal insufficiency; so, the time to development of renal insufficiency can be shorter in type 2 diabetes than in type 1. For people who have an atypical course, renal biopsy may be advisable. In addition, there are some differences in the progression of type 1 and type 2 diabetic nephropathy. In people with type 2 diabetes, albuminuria is more often present at diagnosis. Hypertension is also more common in type 2 diabetic nephropathy. Finally, microalbuminuria is less predictive of late nephropathy in people with type 2 diabetes compared with type 1. [7]

PROGNOSIS

People with microalbuminuria are at increased risk for progression to macroalbuminuria and end-stage renal disease. The natural history of diabetic nephropathy is better defined in type 1 than type 2 diabetes. In type 2 diabetes, the course can be more difficult to predict, primarily because

the date of onset of diabetes is less commonly known, and comorbid conditions can contribute to renal disease. Without specific interventions, about 80% of people with type 1 diabetes, and 20% to 40% of people with type 2 diabetes with microalbuminuria, will progress to macroalbuminuria. [8] Diabetic nephropathy is associated with poor outcomes. In the USA, diabetes accounts for 48% of all new cases of end-stage renal disease (ESRD). [9] In the UK, it is the most common cause of ESRD, accounting for 20% of cases. [10] People with type 1 diabetes and proteinuria have been found to have a 40-fold greater risk of mortality than people without proteinuria. [11] The prognostic significance of proteinuria is less extreme in type 2 diabetes, although people with proteinuria have a fourfold risk of death compared with people without proteinuria. [12] In addition, increased cardiovascular risk has been associated with albuminuria in people with diabetes. [13] African-American, Native American, and Mexican-American people have a much higher risk of developing ESRD in the setting of diabetes compared with white people. [8] [14] In the USA, African-American people with diabetes progress to ESRD at a much more rapid rate than white people with diabetes. [15] In England, the rates for initiating treatment for ESRD are 4.2 times higher for African-Caribbean people and 3.7 times higher for Indo-Asian people than for white people. [16] Native American people of the Pima tribe, in southwestern USA, have much higher rates of diabetic nephropathy than white people, and also progress to ESRD at a faster rate. [17]

AIMS OF INTERVENTION

To prevent death and complications of chronic renal failure and to prevent the need for chronic dialysis or transplantation (end-stage renal disease), with minimal adverse events.

OUTCOMES

Early nephropathy: Progression to late nephropathy (proteinuria determined by albumin excretion rate greater than 300 mg/day [34 mg/mmol]); all-cause mortality; rate of end-stage renal disease (ESRD); or rate of cardiovascular events (stroke, heart failure, and MI). **Late nephropathy:** All-cause mortality; rate of ESRD; or rate of cardiovascular events (stroke, heart failure, and MI). **Excluded outcomes:** Change or doubling of serum creatinine as a surrogate marker.

METHODS

Clinical Evidence search and appraisal November 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to November 2009, Embase 1980 to November 2009, and The Cochrane Database of Systematic Reviews 2009, Issue 4 (1966 to date of issue). An additional search within the Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded (where possible), and containing 20 or more individuals, of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. Many of the identified systematic reviews do not stratify results based on type of diabetes or stage of nephropathy. Here, we have reported systematic reviews in the question to which they are most relevant based on the participants of included trials. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 17). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of treatments to prevent progression of nephropathy in people with type 1 diabetes and early nephropathy?**

OPTION ACE INHIBITORS IN TYPE 1 DIABETES AND EARLY NEPHROPATHY

Progression to late nephropathy

Compared with placebo ACE inhibitors (captopril, lisinopril, enalapril, perindopril, and ramipril) are more effective at reducing progression to macroalbuminuria, and at increasing regression to normoalbuminuria in normotensive people with type 1 diabetes and microalbuminuria (high-quality evidence).

Note
We found no clinically important results from RCTs about ACE inhibitors compared with angiotensin II receptor blockers, or about the effects of combined ACE inhibitors plus angiotensin II receptor blockers, in people with type 1 diabetes and early nephropathy.

For GRADE evaluation of interventions for diabetic nephropathy, see table, p 17 .

Benefits:

Angiotensin-converting enzyme (ACE) inhibitors versus placebo:
We found one systematic review (search date not reported), which found that, compared with placebo, ACE inhibitors significantly reduced progression to late nephropathy and increased regression to normoalbuminuria in normotensive people with type 1 diabetes and microalbuminuria (individual patient data meta-analysis from 12 trials; 698 people; progression to macroalbuminuria: OR 0.38, 95% CI 0.25 to 0.57; P less than 0.001; regression to normoalbuminuria: OR 3.07, 95% CI 2.15 to 4.44). [18] The included ACE inhibitors were captopril, lisinopril, enalapril, perindopril, and ramipril.

ACE inhibitors versus angiotensin II receptor blockers (ARBs):
We found no systematic review or RCTs.

ACE inhibitors plus ARBs:
We found no systematic review or RCTs.

Harms:

ACE inhibitors versus placebo:
The review gave no information on adverse effects of ACE inhibitors in people with type 1 diabetes and microalbuminuria. [18]

ACE inhibitors versus ARBs:
We found no RCTs.

ACE inhibitors plus ARBs:
We found no RCTs.

Comment:

Clinical guide:
Most people with type 1 diabetes and early nephropathy should be offered initial treatment with an ACE inhibitor at a low dose, and then titrated to the maximum tolerated dose. Kidney function should be monitored during initiation of treatment and dose escalation. One expert recommends continuing the ACE inhibitor (or angiotensin II receptor blocker), unless the serum creatinine increases by greater than 30%; greater increases could lead to renal arterial stenosis. [19]

OPTION GLYCAEMIC CONTROL IN TYPE 1 DIABETES AND EARLY NEPHROPATHY

Progression to late nephropathy
Compared with conventional glycaemic control Intensive glycaemic control is more effective at reducing progression of nephropathy in people with type 1 diabetes and either normal albumin excretion or microalbuminuria (high-quality evidence).

Adverse effects: diabetic ketoacidosis
Compared with conventional glycaemic control Intensive glycaemic control seems to be associated with an increased risk of developing severe diabetic ketoacidosis (moderate-quality evidence).

Adverse effects: severe hypoglycaemia
Compared with conventional glycaemic control Intensive glycaemic control and conventional glycaemic control seem to be associated with a similar risk of developing severe hypoglycaemia (moderate-quality evidence).

For GRADE evaluation of interventions for diabetic nephropathy, see table, p 17 .

Benefits:

Intensive glycaemic control versus conventional glycaemic control:
One systematic review (search date 1991, 16 RCTs) found that, compared with conventional control, intensive glycaemic control significantly reduced progression of nephropathy in people with type 1 diabetes and either normal albumin excretion or microalbuminuria (7 RCTs, 266 people; nephropathy progression: OR 0.34, 95% CI 0.20 to 0.58; P less than 0.001). [20]

Harms:

Intensive glycaemic control versus conventional glycaemic control:
The review found no significant difference between intensive glycaemic control and conventional control in the incidence of severe hypoglycaemia (6 trials; severe hypoglycaemia increased by +9.1 episodes/100 person-years, 95% CI –1.4 episodes/100 person-years to +19.6 episodes/100 person-years). [20] The review also found a significantly higher incidence of diabetic ketoacidosis in people treated with continuous subcutaneous insulin infusion compared with conventional multiple injection treatment (3 trials, 99 people; ketoacidosis increased by 12.6 episodes/100 person-years, 95% CI 8.7 episodes/100 person-years to 16.5 episodes/100 person-years). [20]

Comment: None.

OPTION ANGIOTENSIN II RECEPTOR BLOCKERS IN TYPE 1 DIABETES AND EARLY NEPHROPATHY

We found no direct information from RCTs about angiotensin II receptor blockers in people with type 1 diabetes and early nephropathy.

For GRADE evaluation of interventions for diabetic nephropathy, see table, p 17 .

Benefits:

Angiotensin II receptor blockers (ARBs) versus placebo:
We found no systematic review or RCTs comparing the effects of ARBs with placebo in people with type 1 diabetes and early nephropathy for the outcomes of progression to late nephropathy, all-cause mortality, incidence of end-stage renal disease, or incidence of cardiovascular events (stroke, heart failure, and MI). Long-term placebo-controlled RCTs would not be ethical in people with type 1 diabetes and nephropathy, because of the established benefits of ACE inhibitors, and similarity between these two drug classes.

ARBs versus ACE inhibitors:
See benefits of ACE inhibitors in people with type 1 diabetes and early nephropathy, p 3 .

ARBs plus ACE inhibitors:
See benefits of ACE inhibitors in people with type 1 diabetes and early nephropathy, p 3 .

Harms:

ARBs versus placebo:
We found no RCTs.

ARBs versus ACE inhibitors:
See harms of ACE inhibitors in people with type 1 diabetes and early nephropathy, p 3 .

ARBs plus ACE inhibitors:
See harms of ACE inhibitors in people with type 1 diabetes and early nephropathy, p 3 .

Comment:

Clinical guide:
ARBs are appropriate for early nephropathy in type 1 diabetes for people intolerant of ACE inhibitors due to chronic cough as an adverse effect. Treatment titration dosing and precautions (greater than 30% rise in serum creatinine) are the same as for ACE inhibitors (see comment on ACE inhibitors, p 3).

OPTION PROTEIN RESTRICTION IN TYPE 1 DIABETES AND EARLY NEPHROPATHY

We found no clinically important results from RCTs about the effects of low-protein diet compared with usual diet in people with type 1 diabetes and early nephropathy.

For GRADE evaluation of interventions for diabetic nephropathy, see table, p 17 .

Benefits:

Protein restriction versus usual diet:
We found one systematic review (search date 2006) comparing low-protein diet versus usual diet. [21] The review identified two RCTs that included people with type 1 diabetes and early nephropathy; however, the RCTs did not report results on our outcomes of interest and are not discussed further.

Harms:

Protein restriction versus usual diet:
We found one systematic review, which did not report on our outcomes of interest. [21]

Comment: None.

OPTION TIGHT CONTROL OF BLOOD PRESSURE IN TYPE 1 DIABETES AND EARLY NEPHROPATHY

We found no direct information from RCTs about tight control of blood pressure compared with conventional control in people with type 1 diabetes and early nephropathy.

For GRADE evaluation of interventions for diabetic nephropathy, **see table, p 17 .**

Benefits:

Tight control of blood pressure versus conventional control:
We found no systematic review or RCTs comparing the effects of tight control of blood pressure versus conventional control in people with type 1 diabetes and early nephropathy for the outcomes of progression to late nephropathy, all-cause mortality, incidence of end-stage renal disease, or incidence of cardiovascular events (stroke, heart failure, and MI).

Harms:

Tight control of blood pressure versus conventional control:
We found no RCTs.

Comment:

Clinical guide:
Although we found no RCTs that have investigated this clinical question, it is well known from observational studies that lower systolic blood pressure targets are associated with a decreased incidence of microvascular and macrovascular disease. Several clinical guidelines advocate a systolic blood pressure target below 130 mmHg for people with diabetes. [22] [23] [24] Once someone is initially treated with either an ACE inhibitor or angiotensin II receptor blocker, there is little evidence to direct the choice of subsequent antihypertensives to reach the blood pressure target.

QUESTION What are the effects of treatments to prevent progression of nephropathy in people with type 1 diabetes and late nephropathy?

OPTION ACE INHIBITORS IN TYPE 1 DIABETES AND LATE NEPHROPATHY

Mortality
Compared with placebo Captopril seems more effective at reducing the combined outcome of renal transplant, end-stage renal disease, or death over 3 years in people with type 1 diabetes and late nephropathy (moderate-quality evidence).

Note
We found no direct information from RCTs about ACE inhibitors compared with angiotensin II receptor blockers, or about the effects of ACE inhibitors combined with angiotensin II receptor blockers, in people with type 1 diabetes and late nephropathy.

For GRADE evaluation of interventions for diabetic nephropathy, **see table, p 17 .**

Benefits:

Angiotensin-converting enzyme (ACE) inhibitors versus placebo:
We found one RCT, [25] which found that captopril significantly reduced the combined outcome of renal transplant, end-stage renal disease, or death over 3 years compared with placebo (1 RCT, 409 people; combined outcome of renal transplant, end-stage renal disease, or death: 23/207 [11%] with captopril *v* 42/202 [21%] with placebo; RR 0.50, 95% CI 0.18 to 0.70). [25] Diabetic nephropathy was defined as a urinary protein excretion rate greater than 500 mg a day and serum creatinine of 2.5 mg/dL (221 micromol/L) or less. [25]

ACE inhibitors versus angiotensin II receptor blockers (ARBs):
We found no systematic review or RCTs.

ACE inhibitors plus ARBs:
We found no systematic review or RCTs.

Harms:

ACE inhibitors versus placebo:
One RCT found that, in people with type 1 diabetes and early nephropathy, hyperkalaemia occurred in three (1.5%) people taking ACE inhibitors and in none of the people taking placebo. [25]

ACE inhibitors versus ARBs:
We found no RCTs.

ACE inhibitors plus ARBs:
We found no RCTs.

Comment: **Clinical guide:**
Most people should be offered initial treatment with an ACE inhibitor at a low dose, and then titrated to the maximum tolerated dose. Kidney function should be monitored during initiation of treatment and dose escalation. One expert has recommended continuing the ACE inhibitor (or angiotensin II receptor blocker), unless the serum creatinine increases by greater than 30%; greater increases could lead to renal arterial stenosis. [19]

OPTION ANGIOTENSIN II RECEPTOR BLOCKERS IN TYPE 1 DIABETES AND LATE NEPHROPATHY

We found no clinically important results from RCTs about angiotensin II receptor blockers in people with type 1 diabetes and late nephropathy.

For GRADE evaluation of interventions for diabetic nephropathy, see table, p 17 .

Benefits: **Angiotensin II receptor blockers (ARBs) versus placebo:**
We found no systematic review or RCTs comparing effects of ARBs versus placebo in people with type 1 diabetes and late nephropathy for the outcomes of interest. Long-term placebo-controlled RCTs would not be ethical in people with type 1 diabetes and nephropathy because of the established benefits of ACE inhibitors, and similarity between these two drug classes.

ARBs versus ACE inhibitors:
See benefits of ACE inhibitors in people with type 1 diabetes and late nephropathy, p 6 .

ARBs plus ACE inhibitors:
See benefits of ACE inhibitors in people with type 1 diabetes and late nephropathy, p 6 .

Harms: **ARBs versus placebo:**
We found no RCTs.

ARBs versus ACE inhibitors:
See harms of ACE inhibitors in people with type 1 diabetes and late nephropathy, p 6 .

ARBs plus ACE inhibitors:
See harms of ACE inhibitors in people with type 1 diabetes and late nephropathy, p 6 .

Comment: **Clinical guide:**
Angiotensin II receptor blockers are appropriate for late nephropathy in type 1 diabetes for people intolerant of ACE inhibitors due to chronic cough as an adverse effect. Treatment titration dosing and precautions (greater than 30% rise in serum creatinine) are the same as for ACE inhibitors (see comment on ACE inhibitors, p 6).

OPTION GLYCAEMIC CONTROL IN TYPE 1 DIABETES AND LATE NEPHROPATHY

We found no direct information from RCTs about intensive glycaemic control compared with conventional glycaemic control in people with type 1 diabetes and late nephropathy.

For GRADE evaluation of interventions for diabetic nephropathy, see table, p 17 .

Benefits: **Glycaemic control versus conventional control:**
We found no systematic review or RCTs comparing the effects of intensive glycaemic control versus conventional glycaemic control in people with type 1 diabetes and late nephropathy on the outcomes of all-cause mortality, incidence of end-stage renal disease, or incidence of cardiovascular events (stroke, heart failure, and MI).

Harms: **Glycaemic control versus conventional control:**
We found no RCTs.

Comment: None.

OPTION PROTEIN RESTRICTION IN TYPE 1 DIABETES AND LATE NEPHROPATHY

Mortality
Compared with usual diet A low-protein diet may be more effective at reducing the cumulative incidence of end-stage renal disease or death over 4 years in people with type 1 diabetes and late nephropathy (low-quality evidence).

For GRADE evaluation of interventions for diabetic nephropathy, see table, p 17 .

Benefits:

Protein restriction versus usual diet:
We found one systematic review. [21] The review (search date 2006, 7 RCTs in people with diabetes type 1 and late nephropathy) pooled data but did not report on any outcome of interest to our review. [21] One RCT identified by the review met our reporting criteria, and is reported separately here. [26] The RCT found that, compared with usual protein intake, a low-protein diet significantly reduced the cumulative incidence of end-stage renal disease or death over 4 years in people with type 1 diabetes and late nephropathy (1 RCT, 82 people aged 18–60 years; cumulative incidence of end-stage renal disease or death: 4/41 [10%] with low-protein diet *v* 11/41 [27%] with usual protein intake; RR 0.23, 95% CI 0.07 to 0.72). The causes of death were heart failure or MI. [26] This RCT was small, and neither participants nor study investigators could be blinded to the randomisation owing to the nature of the intervention.

Harms:

Protein restriction versus usual diet:
The RCT gave no information on adverse effects of protein restriction in people with type 1 diabetes and late nephropathy. [26]

Comment:

None.

OPTION TIGHT CONTROL OF BLOOD PRESSURE IN TYPE 1 DIABETES AND LATE NEPHROPATHY

We found no direct information from RCTs about the effects of tight blood pressure control compared with conventional control in people with type 1 diabetes and late nephropathy.

For GRADE evaluation of interventions for diabetic nephropathy, **see table, p 17 .**

Benefits:

Tight control of blood pressure versus conventional control:
We found no systematic review or RCTs comparing the effects on our outcomes of interest of tight control of blood pressure versus conventional control in people with type 1 diabetes and early or late nephropathy.

Harms:

Tight control of blood pressure versus conventional control:
We found no RCTs.

Comment:

Clinical guide:
Although we found no RCTs that investigated this clinical question, it is well known from observational studies that lower systolic blood pressure targets are associated with a decreased incidence of microvascular and macrovascular disease. Several clinical guidelines advocate a systolic blood pressure target below 130 mmHg for people with diabetes. [22] [23] [24] Once someone is initially treated with either an ACE inhibitor or angiotensin II receptor blocker, there is little evidence to direct the choice of subsequent antihypertensives to reach the blood pressure target.

QUESTION What are the effects of treatments to prevent progression of nephropathy in people with type 2 diabetes and early nephropathy?

OPTION ACE INHIBITORS IN TYPE 2 DIABETES AND EARLY NEPHROPATHY

Mortality
Compared with placebo We don't know whether ramipril is more effective at reducing mortality in people with early nephropathy and type 2 diabetes (very low-quality evidence).

Compared with angiotensin II receptor blockers We don't know how ACE inhibitors and angiotensin II receptor blockers compare at reducing mortality (low-quality evidence).

Progression to late nephropathy
Compared with placebo Enalapril seems more effective at reducing progression to late nephropathy in people with diabetes and microalbuminuria at 5 years (moderate-quality evidence).

Compared with angiotensin II receptor blockers We don't know how ACE inhibitors and angiotensin II receptor blockers compare at reducing progression to late nephropathy (low-quality evidence).

End-stage renal disease
Compared with placebo Low dose ramipril (1.25 mg) seems no more effective at reducing rate of end-stage renal disease in people with type 2 diabetes and early nephropathy but the dose assessed was below that typically used in clinical practice (moderate-quality evidence).

Cardiovascular events

Compared with placebo We don't know whether ramipril is more effective at reducing cardiovascular events in people with type 2 diabetes (very low-quality evidence)

Compared with angiotensin II receptor blockers We don't know how ACE inhibitors and angiotensin II receptor blockers compare at reducing cardiovascular events or a composite outcome of MI, stroke, or cardiovascular death (low-quality evidence).

Note
We found no direct information from RCTs about the effects of ACE inhibitors plus angiotensin II receptor blockers in people with type 2 diabetes and early nephropathy.

For GRADE evaluation of interventions for diabetic nephropathy, **see table, p 17 .**

Benefits:

ACE inhibitors versus placebo:
We found no systematic review specifically in people with type 2 diabetes and early nephropathy. We found four RCTs (5 publications). [27] [28] [29] [30] [31]

The first RCT (94 people with type 2 diabetes and with microalbuminuria; reported in 2 publications) found that enalapril 10 mg significantly reduced the risk of progression to late nephropathy at 5 years compared with placebo (6/49 [12%] with enalapril *v* 19/45 [42%] with placebo; ARR 30%, 95% CI 15% to 45%). [27] [28]

The second RCT (120 people with type 2 diabetes and microalbuminuria) found that enalapril 10 mg daily significantly reduced the risk of progression to late nephropathy at 5 years compared with placebo (4/52 [8%] with enalapril *v* 12/51 [24%] with placebo; ARR 15.8%, CI not reported; P less than 0.001). [29]

The third RCT found that ramipril 10 mg significantly reduced the combined outcomes of MI, stroke, or cardiovascular death compared with placebo (subgroup analysis with diabetes and early nephropathy, 1140 people; specific ORs not reported). [30] The outcome of total mortality was not reported separately for people with diabetes and early nephropathy. However, the RCT found that ramipril 10 mg reduced mortality in the diabetes subgroup compared with placebo (196/1808 [11%] with ramipril *v* 248/1769 [14%] with placebo; P = 0.004).

The fourth RCT (4912 people with type 2 diabetes and early nephropathy) found no significant difference in mortality; end-stage renal disease; or incidence of stroke, heart failure, or MI between low-dose ramipril (1.25 mg/day) and placebo at a median of 4 years (mortality: 334/2443 [14%] with ramipril *v* 324/2469 [13%] with placebo; RR 1.04, 95% CI 0.90 to 1.20; end-stage renal disease: 4/2443 [0.2%] with ramipril *v* 10/2469 [0.4%] with placebo; RR 0.40, 95% CI 0.13 to 1.30; stroke: 89/2443 [4%] with ramipril *v* 84/2469 [3%] with placebo; RR 1.07, 95% CI 0.80 to 1.44; heart failure: 76/2443 [3%] with ramipril *v* 91/2469 [4%] with placebo; RR 0.84, 95% CI 0.62 to 1.14; MI: 52/2443 [2.1%] with ramipril *v* 59/2469 [2.4%] with placebo; RR 0.89, 95% CI 0.61 to 1.29). [31] The dose of ramipril used in this trial is below that typically used in current clinical practice.

ACE inhibitors versus angiotensin II receptor blockers (ARBs):
See benefits of ARBs in people with type 2 diabetes and early nephropathy, p 10 .

ACE inhibitors plus ARBs:
See benefits of ARBs in people with type 2 diabetes and early nephropathy, p 10 .

Harms:

ACE inhibitors versus placebo:
Two RCTs gave no information on adverse effects. [27] [28] [29]

The third RCT found a greater incidence of cough with ramipril 10 mg (133/1808 [7%] with ramipril *v* 37/1769 [2%] with placebo; P value not reported). [30]

The fourth RCT found an increased incidence of cough on low-dose ramipril 1.25 mg daily (80/2443 [3%] with low-dose ramipril *v* 21/2469 [1%] with placebo; P value not reported). [31]

ACE inhibitors versus ARBs:
See harms of ARBs in people with type 2 diabetes and early nephropathy, p 10 .

ACE inhibitors plus ARBs:
See harms of ARBs in people with type 2 diabetes and early nephropathy, p 10 .

Comment:

None.

OPTION ANGIOTENSIN II RECEPTOR BLOCKERS IN TYPE 2 DIABETES AND EARLY NEPHROPATHY

Mortality
Compared with ACE inhibitors We don't know how angiotensin II receptor blockers and ACE inhibitors compare at reducing mortality in people with type 2 diabetes and early nephropathy (low-quality evidence).

Progression to late nephropathy
Compared with placebo Irbesartan (an angiotensin II receptor blocker) is more effective at reducing progression to late nephropathy in people with type 2 diabetes, hypertension, and microalbuminuria (high-quality evidence).

Compared with ACE inhibitors We don't know how angiotensin II receptor blockers compare with ACE inhibitors at reducing progression to late nephropathy (low-quality evidence).

Cardiovascular events
Compared with ACE inhibitors We don't know how angiotensin II receptor blockers and ACE inhibitors compare at reducing cardiovascular events (low-quality evidence).

Note
We found no direct information from RCTs about the effects of combined angiotensin II receptor blockers plus ACE inhibitors in people with type 2 diabetes and early nephropathy.

For GRADE evaluation of interventions for diabetic nephropathy, see table, p 17 .

Benefits:

Angiotensin II receptor blockers (ARBs) versus placebo:
We found one RCT, which found that irbesartan 300 mg significantly reduced progression to late nephropathy over 2 years compared with placebo in people with type 2 diabetes, hypertension, and microalbuminuria. [32] It found no significant decrease with irbesartan 150 mg compared with placebo (1 RCT, 590 people; progression from early to late nephropathy: 10/194 [5%] with irbesartan 300 mg *v* 30/201 [15%] with placebo; HR 0.30, 95% CI 0.14 to 0.61; P less than 0.001; 19/195 [10%] with irbesartan 150 mg *v* 30/201 [15%] with placebo; HR 0.61, 95% CI 0.34 to 1.08; P = 0.08). Early nephropathy (microalbuminuria) was defined as an albumin excretion rate of 20 to 200 micrograms/minute and late nephropathy as albumin excretion rate greater than 200 micrograms/minute. [32]

ARBs versus ACE inhibitors:
We found one RCT (250 people with type 2 diabetes and early nephropathy), which found no significant difference in change in glomerular filtration rate, mortality, stroke, heart failure, and MI between telmisartan 80 mg and enalapril 20 mg in people with type 2 diabetes and early nephropathy over 5 years of follow-up (change in glomerular filtration rate: –17.9 mL/minute/1.73 m^2 with telmisartan *v* –14.9 mL/minute/1.73 m^2 with enalapril; treatment difference: –3.0 mL/minute/1.73 m^2, 95% CI –7.6 mL/minute/1.73 m^2 to +1.6 mL/minute/1.73 m^2; mortality: 6/120 [5.0%] with telmisartan *v* 6/130 [4.6%] with enalapril; RR 1.04, 95% CI 0.58 to 1.87; stroke: 6/120 [5.0%] with telmisartan *v* 6/130 [4.6%] with enalapril; RR 1.04, 95% CI 0.58 to 1.87; heart failure: 9/120 [8%] with telmisartan *v* 7/130 [5%] with enalapril; RR 1.39, 95% CI 0.54 to 3.62; MI: 9/120 [8%] with telmisartan *v* 6/130 [5%] with enalapril; RR 1.63, 95% CI 0.60 to 4.43). [33] Although this study found no difference between the two drugs, the results could have been biased, as telmisartan was at maximum dose, whereas enalapril was not.

ARBs plus ACE inhibitors:
We found no systematic review or RCTs.

Harms:

ARBs versus placebo:
The RCT found no significant difference in the proportion of people permanently discontinuing medication (590 people; 15% with combined doses of irbesartan *v* 19% with placebo; P = 0.21). [32]

ARBs versus ACE inhibitors:
The RCT found no significant difference in the proportion of people discontinuing telmisartan or enalapril (20/120 [17%] with telmisartan *v* 30/130 [23%] with enalapril; P = 0.21). [33]

ARBs plus ACE inhibitors:
We found no RCTs.

Comment:

None.

OPTION TIGHT CONTROL OF BLOOD PRESSURE IN TYPE 2 DIABETES AND EARLY NEPHROPATHY

Progression to late nephropathy

Compared with moderate diastolic blood pressure target A lower diastolic blood pressure target (10 mmHg below baseline) seems more effective at reducing progression from microalbuminuria to overt albuminuria over 5 years compared with a moderate diastolic blood pressure target (80–89 mmHg) in people with type 2 diabetes, early nephropathy, and baseline blood pressure within the normal range (moderate-quality evidence).

For GRADE evaluation of interventions for diabetic nephropathy, **see table, p 17** **.**

Benefits:

Tight control of blood pressure versus moderate diastolic blood pressure target:
We found no systematic review but found one RCT. [34] The RCT found that, in people with type 2 diabetes, early nephropathy, and baseline blood pressure within the normal range, a lower diastolic blood pressure target significantly reduced progression from microalbuminuria to overt albuminuria over 5 years compared with a moderate diastolic blood pressure target (480 people aged 40–74 years; P = 0.02; results presented graphically). [34] The lower diastolic blood pressure target was 10 mmHg below baseline diastolic blood pressure and moderate diastolic blood pressure target was 80 mmHg to 89 mmHg.

Harms:

Tight control of blood pressure versus moderate diastolic blood pressure target:
The RCT did not evaluate adverse effects of lower target diastolic blood pressure compared with moderate target diastolic blood pressure in people with type 2 diabetes and baseline blood pressure within the normal range. [34]

Comment:

None.

OPTION GLYCAEMIC CONTROL IN TYPE 2 DIABETES AND EARLY NEPHROPATHY

We found no direct information from RCTs about the effects of glycaemic control in people with type 2 diabetes and early nephropathy.

For GRADE evaluation of interventions for diabetic nephropathy, **see table, p 17** **.**

Benefits:

We found no systematic review or RCTs evaluating the effects of glycaemic control in people with type 2 diabetes and early nephropathy on our outcomes of interest.

Harms:

We found no RCTs.

Comment:

Clinical guide:
Results from one large RCT (11,140 people with type 2 diabetes predominantly without a diagnosis of nephropathy) suggest that, compared with standard glucose control, intensive glycaemic control (modified-release gliclazide plus other drugs as required to achieve a glycated haemoglobin value of 6.5% or less) could be key in slowing onset or progression of renal complications of diabetes. [35] The RCT comprised predominantly people with type 2 diabetes and either no nephropathy or early nephropathy (early nephropathy: 1423/5569 [26%] in the standard group *v* 1434/5571 [26%] in the intensive-control group; late nephropathy: 215/5569 [3.9%] in the standard group *v* 189/5571 [3.4%] in the intensive-control group) and did not did carry out a subgroup analysis of people with nephropathy. However, as the authors of the RCT highlight that the observed benefits of intensive glucose control on reducing major macrovascular and microvascular events were primarily the result of a reduction in renal complications, we thought it important to report the data.

A primary outcome assessed was a composite of major microvascular events, which included new or worsening nephropathy. [35] The RCT found that intensive glucose control significantly reduced the risk of new or worsening nephropathy compared with standard control (230/5571 [4%] with intensive control *v* 292/5569 [5%] with standard control; HR 0.79, 95% CI 0.66 to 0.93; P = 0.006). The RCT found that the reduction in development of macroalbuminuria made the largest contribution to the observed reduction in renal complications (3% with intensive control *v* 4% with standard control; HR 0.70, 95% CI 0.57 to 0.85; P less than 0.001; absolute numbers not reported). There was a non-significant reduction in the composite outcome of need for renal-replacement therapy or death from renal causes (0.4% with intensive control *v* 0.6% with standard control; HR 0.64, 95% CI 0.38 to 1.08; P = 0.09; absolute numbers not reported). The reduction in risk of renal complications was balanced by potential harms, including a significantly higher rate of admission to hospital for any cause (2501/5571 [45%] with intensive control *v* 2381/5569 [43%] with standard control; HR 1.07, 95% CI 1.01 to 1.03; P = 0.03).

OPTION PROTEIN RESTRICTION IN TYPE 2 DIABETES AND EARLY NEPHROPATHY

We found no clinically important results from RCTs about the effects of protein restriction in people with type 2 diabetes and early nephropathy.

For GRADE evaluation of interventions for diabetic nephropathy, **see table, p 17 .**

Benefits: We found one systematic review (search date 2006) evaluating the effects of protein restriction in people with type 2 diabetes and early nephropathy. [21] The review did not pool data on our outcomes of interest, and is not discussed further. The RCTs identified by the review did not meet our reporting criteria and are not discussed further.

Harms: We found no RCTs.

Comment: None.

QUESTION What are the effects of treatments to prevent progression of nephropathy in people with type 2 diabetes and late nephropathy?

OPTION ANGIOTENSIN II RECEPTOR BLOCKERS IN TYPE 2 DIABETES AND LATE NEPHROPATHY

Mortality
Compared with placebo Angiotensin II receptor blockers seem no more effective at decreasing all-cause mortality in people with mainly late-stage nephropathy and type 2 diabetes (moderate-quality evidence).

Compared with ACE inhibitors We don't know how angiotensin II receptor blockers and ACE inhibitors compare at reducing mortality in people with mainly late-stage nephropathy and type 2 diabetes (low-quality evidence).

End-stage renal disease
Compared with placebo Angiotensin II receptor blockers seem more effective at reducing the risk of end-stage renal disease in people with type 2 diabetes with late-stage nephropathy (moderate-quality evidence).

Note
We found no direct information from RCTs about the effects of combined angiotensin II receptor blockers plus ACE inhibitors in people with type 2 diabetes and late nephropathy.

For GRADE evaluation of interventions for diabetic nephropathy, **see table, p 17 .**

Benefits:

Angiotensin II receptor blockers (ARBs) versus placebo:
We found one systematic review (search date 2005, 5 RCTs, 3409 people) comparing ARBs versus placebo for end-stage renal disease (ESRD) and all-cause mortality. [36] It combined RCTs of early and late nephropathy and RCTs in people with type 1 and type 2 diabetes. In the analysis of the effects of ARBs, all RCTs included in the meta-analysis were in people with type 2 diabetes and most had late-stage nephropathy. The review found no significant difference in all-cause mortality between ARBs and placebo (5 RCTs, 3409 people; 248/1813 [14%] with ARBs *v* 249/1596 [16%] with placebo; RR 0.99, 95% CI 0.85 to 1.17). The review also found that ARBs significantly reduced ESRD compared with placebo (3 RCTs, 3251 people; 229/1719 [13%] with ARBs *v* 295/1532 [19%] with placebo; RR 0.78, 95% CI 0.67 to 0.91). Most people included in the review were from two RCTs.

ARBs versus ACE inhibitors:
We found one systematic review (search date 2005, 3 RCTs, 307 people). [36] The review included RCTs of early and late nephropathy and people with type 1 and type 2 diabetes. In the analysis of the effects of ARBs versus ACE inhibitors, all RCTs included in the meta-analysis were in people with type 2 diabetes and most had late-stage nephropathy. The review found no significant difference in all-cause mortality between ARBs and ACE inhibitors (6/157 [3.8%] with ARBs *v* 6/150 [4.0%] with ACE inhibitors; RR 0.92, 95% CI 0.31 to 2.78). [36] Given this wide confidence interval, this review cannot exclude large differences between the two drug classes.

ARBs plus ACE inhibitors:
We found no systematic review or RCTs.

Harms:

ARBs versus placebo:
The review reported a significant increase in the risk of hyperkalaemia with ARBs compared with placebo (2 RCTs, 2287 people; 22/1153 [2%] with ARBs *v* 4/1134 [0.4%] with placebo; RR 5.41, 95% CI 1.87 to 15.65). [36]

ARBs versus ACE inhibitors:
The review gave no information on adverse effects for this comparison. [36]

ARBs plus ACE inhibitors:
We found no RCTs.

Comment: None.

OPTION ACE INHIBITORS IN TYPE 2 DIABETES AND LATE NEPHROPATHY

Mortality
Compared with angiotensin II receptor blockers We don't know how ACE inhibitors and angiotensin II receptor blockers compare at reducing mortality in people with mainly late-stage nephropathy and type 2 diabetes (low-quality evidence).

Note
We found no direct information from RCTs about the effects of ACE inhibitors versus placebo or angiotensin II receptor blockers in people with type 2 diabetes and late nephropathy.

For GRADE evaluation of interventions for diabetic nephropathy, see table, p 17 .

Benefits:

ACE inhibitors versus placebo:
We found no systematic review or RCTs comparing the effects of ACE inhibitors versus placebo in people with type 2 diabetes and late nephropathy that assessed our outcomes of interest.

ACE inhibitors versus angiotensin II receptor blockers (ARBs):
See benefits of ARBs in people with type 2 diabetes and late nephropathy, p 12 .

ACE inhibitors plus ARBs:
See benefits of ARBs in people with type 2 diabetes and late nephropathy, p 12 .

Harms:

ACE inhibitors versus placebo:
We found no RCTs.

ACE inhibitors versus ARBs:
See harms of ARBs in people with type 2 diabetes and late nephropathy, p 12 .

ACE inhibitors plus ARBs:
See harms of ARBs in people with type 2 diabetes and late nephropathy, p 12 .

Comment: None.

OPTION GLYCAEMIC CONTROL IN TYPE 2 DIABETES AND LATE NEPHROPATHY

We found no direct information from RCTs about the effects of glycaemic control in people with type 2 diabetes and late nephropathy.

For GRADE evaluation of interventions for diabetic nephropathy, see table, p 17 .

Benefits: We found no systematic review or RCTs evaluating the effects of glycaemic control in people with type 2 diabetes and late nephropathy on our outcomes of interest.

Harms: We found no RCTs.

Comment: See comments section of glycaemic control in people with type 2 diabetes and early nephropathy, p 11 .

OPTION PROTEIN RESTRICTION IN TYPE 2 DIABETES AND LATE NEPHROPATHY

We found no clinically important results from RCTs about the effects of protein restriction in people with type 2 diabetes and late nephropathy.

For GRADE evaluation of interventions for diabetic nephropathy, see table, p 17 .

Benefits: We found one systematic review (search date 2006) comparing low-protein diet versus usual diet in people with late nephropathy type 2 diabetes. [21] The review did not pool data on our outcomes

of interest, and is not discussed further. The RCTs identified by the review did not meet our reporting criteria and are not discussed further.

Harms: We found no RCTs.

Comment: None.

OPTION TIGHT CONTROL OF BLOOD PRESSURE IN TYPE 2 DIABETES AND LATE NEPHROPATHY

We found no direct information from RCTs about the effects of tight blood pressure control in people with type 2 diabetes and late nephropathy.

For GRADE evaluation of interventions for diabetic nephropathy, **see table, p 17 .**

Benefits: We found no systematic review or RCTs evaluating the effects of tight blood pressure control in people with type 2 diabetes and late nephropathy on our outcomes of interest.

Harms: We found no RCTs.

Comment: **Clinical guide:**
The Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure advocates a blood pressure target of less than 130/80 mmHg for people with diabetes and for people with macroalbuminuria. [37]

GLOSSARY

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

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

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

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Glycaemic control in early nephropathy, type 2 diabetes One large RCT added to the comments section found that intensive glucose control reduced renal complications (new or worsening nephropathy) compared with standard control in people with type 2 diabetes, most of whom did not have a diagnosis of nephropathy. [35] The RCT did not carry out a subgroup analysis of people with early or late nephropathy and small numbers of this subgroup mean that the overall results of the trial may not be generalisable to our population of interest. Therefore we have not reported the RCT in full in our benefits and harms sections. Categorisation unchanged (Unknown effectiveness).

REFERENCES

1. Fioretto P, Steffes MW, Brown DM, et al. An overview of renal pathology in insulin-dependent diabetes mellitus in relationship to altered glomerular hemodynamics. *Am J Kidney Dis* 1992;20:549–558.[PubMed]
2. Eknoyan G, Hostetter T, Bakris GL, et al. Proteinuria and other markers of chronic kidney disease: a position statement of the national kidney foundation (NKF) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). *Am J Kidney Dis* 2003;42:617–622.[PubMed]
3. Parving HH, Osterby R, Ritz E. Diabetic nephropathy. In: Brenner BM, ed. *The kidney*. Philadelphia: WB Saunders, 2000:1731–1773.
4. Remuzzi G, Schieppati A, Ruggenenti P. Clinical practice. Nephropathy in patients with type 2 diabetes. *N Engl J Med* 2002;346:1145–1151.[PubMed]
5. Marcantoni C, Ortalda V, Lupo A, et al. Progression of renal failure in diabetic nephropathy. *Nephrol Dial Transplant* 1998;13(suppl 8):16–19.
6. Ballard DJ, Humphrey LL, Melton LJ, 3rd, et al. Epidemiology of persistent proteinuria in type II diabetes mellitus. Population-based study in Rochester, Minnesota. *Diabetes* 1988;37:405–412.[PubMed]
7. Powers A. Diabetes mellitus. In: Braunwald E, Fauci AS, Kasper DL, et al eds. *Harrison's principles of internal medicine*. New York: McGraw-Hill, 2001.
8. Molitch ME, DeFronzo RA, Franz MJ, et al. Nephropathy in diabetes. *Diabetes Care* 2004;27(suppl 1):S79–S83.
9. USRDS. *2000 annual data report*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2000.
10. Ansell D, Feest T. *UK renal registry report*. Bristol: UK Renal Registry, 2001.
11. Borch-Johnsen K, Andersen PK, Deckert T. The effect of proteinuria on relative mortality in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 1985;28:590–596.[PubMed]
12. Morrish NJ, Stevens LK, Head J, et al. A prospective study of mortality among middle-aged diabetic patients (the London Cohort of the WHO Multinational Study of Vascular Disease in Diabetics) I: causes and death rates. *Diabetologia* 1990;33:538–541.[PubMed]
13. Mogensen CE. Microalbuminuria, blood pressure and diabetic renal disease: origin and development of ideas. *Diabetologia* 1999;42:263–285.[PubMed]
14. Mokdad AH, Ford ES, Bowman BA, et al. Diabetes trends in the US: 1990–1998. *Diabetes Care* 2000;23:1278–1283.[PubMed]
15. Hsu CY, Lin F, Vittinghoff E, Shlipak MG. Racial differences in the progression from chronic renal insufficiency to end-stage renal disease in the United States. *J Am Soc Nephrol* 2003;14:2902–2907.[PubMed]
16. Roderick PJ, Raleigh VS, Hallam L, Mallick NP. The need and demand for renal replacement therapy in ethnic minorities in England. *J Epidemiol Community Health* 1996;50:334–339.[PubMed]
17. Lemley KV. A basis for accelerated progression of diabetic nephropathy in Pima Indians. *Kidney Int Suppl* 2003:S38–S42.
18. ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. *Ann Intern Med* 2001;134:370–379. Search date not reported.[PubMed]
19. Bakris GL. A practical approach to achieving recommended blood pressure goals in diabetic patients. *Arch Intern Med* 2001;161:2661–2667.[PubMed]
20. Wang PH, Lau J, Chalmers TC. Meta-analysis of effects of intensive blood-glucose control on late complications of type I diabetes. *Lancet* 1993;341:1306–1309. Search date 1991.[PubMed]
21. Robertson L, Waugh N, Robertson A. Protein restriction for diabetic renal disease. In: The Cochrane Library, Issue 4, 2009. Chichester, UK: John Wiley & Sons, Ltd. Search date 2006.
22. Chobanian AV, Bakris GL, Henry R. et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42:1206–1252.[PubMed]
23. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2005;28:S4–S36. [Erratum in: *Diabetes Care* 2005;28:990]

24. Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis* 2004;43:S1–S290.[PubMed]
25. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med* 1993;329:1456–1462.[PubMed]
26. Hansen HP, Tauber-Lassen E, Jensen BR, et al. Effect of dietary protein restriction on prognosis in patients with diabetic nephropathy. *Kidney Int* 2002;62:220–228.[PubMed]
27. Ravid M, Savin H, Jutrin I, et al. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients.*Ann Intern Med* 1993;118:577–581.[PubMed]
28. Ravid M, Savin H, Jutrin I, et al. Long-term effects of ACE inhibition on development of nephropathy in diabetes mellitus type II. *Kidney Int Suppl* 1994;45:S161–S164. [PubMed]
29. Ahmad J, Siddiqui MA, Ahmad H. Effective postponement of diabetic nephropathy with enalapril in normotensive type 2 diabetic patients with microalbuminuria. *Diabetes Care* 1997;20:1576–1581.[PubMed]
30. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000;355:253–259.[PubMed]
31. Marre M, Lievre M, Chatellier G, et al. Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: randomised, double blind, placebo controlled trial (the DIABHYCAR study). *BMJ* 2004;328:495. [Erratum in *BMJ* 2004;328:686]
32. Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001;345:870–878.[PubMed]
33. Barnett AH, Bain SC, Bouter P, et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 2004;351:1952–1961. [PubMed]
34. Schrier RW, Estacio RO, Esler A, et al. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney Int* 2002;61:1086–1097.[PubMed]
35. ADVANCE Collaborative Group, Patel A, MacMahon S, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560–2572.[PubMed]
36. Strippoli GFM, Bonifati C, Craig M, et al. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. In: The Cochrane Library, Issue 4, 2009. Chichester, UK: John Wiley & Sons, Ltd. Search date 2005.
37. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *JAMA* 2003;289:2560–2572. [Erratum in: *JAMA* 2003;290:197]

Michael Shlipak
Associate Professor of Medicine
Epidemiology & Biostatistics
San Francisco VA Medical Center
San Francisco
USA

Competing interests: MS declares that he has no competing interests.

Disclaimer

TABLE 1 **Stages of progression of nephropathy in type 1 diabetes.**

Stage 1	Characterised by renal hypertrophy and hyperfiltration, and is present at the time of diagnosis of type 1 diabetes. [1]
Stage 2	Typically asymptomatic, lasting for an average of 10 years. The earliest notable changes are renal hypertrophy seen on renal ultrasound, and an increase in the glomerular filtration rate due to hyperfiltration. At this stage, the kidneys show typical histological abnormalities, including diffuse thickening of the glomerular and tubular basement membranes. Glomerular and tubuloepithelial cell hypertrophy are also evident. About one third of people who develop these changes will develop microalbuminuria.
Stage 3	Develops an average of 10 years after the onset of diabetes. People develop microalbuminuria (defined as a urine albumin excretion greater than 30 mg/day but less than 300 mg/day). The development of microalbuminuria is the earliest clinically detectable evidence of diabetic nephropathy. At this stage, serum creatinine level is typically normal. About 80% of people who develop microalbuminuria will progress to overt proteinuria. This proportion may be decreasing in the current era as a result of aggressive early treatment with ACE inhibitors and angiotensin II receptor blockers. Microalbuminuria is well correlated with renal biopsy findings, particularly nodular glomerulosclerosis. The diagnosis of microalbuminuria is traditionally made with a 24-hour urine collection to measure urine albumin using radioimmunoassay or enzyme-linked immunosorbent assays. An alternative and easier method of detecting microalbuminuria is measurement of the albumin/creatinine ratio in a spot urine specimen. A ratio between 0.03 and 0.30 (mg albumin/mg creatinine) or 30/300 mg/g (mg albumin/g creatinine [3.4/34.0 mg/mmol]) is well correlated with 24-hour collections, and is now the preferred screening test for diabetic nephropathy. [2]
Stage 4	Late-stage nephropathy occurs 15 to 20 years after the onset of diabetes. Urine albumin increases beyond microalbuminuria to macroalbuminuria (greater than 300 mg/day or greater than 200 micrograms/minute). It is at this stage that glomerular filtration rate declines and urine protein excretion increases to greater than 500 mg/day. The glomerular filtration rate declines on average between 0.5 and 1.0 mL/minute/month. Blood pressure also rises, probably reflecting renal parenchymal disease in sodium retention. Histologically, renal fibrosis becomes more evident. Mesangial expansion develops, resulting in diffuse and nodular glomerulosclerosis. The degree of mesangial expansion correlates well with increases in urine albumin excretion, and loss of renal function.
Stage 5	The development of end-stage renal disease, which occurs a median of 7 years from the development of persistent proteinuria.

TABLE **GRADE evaluation of interventions for diabetic nephropathy (preventing progression)**

Important outcomes	Mortality, progression to late nephropathy, end-stage renal disease, cardiovascular events, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments to prevent progression of nephropathy in people with type 1 diabetes and early nephropathy?									
12 (698) [18]	Progression to late nephropathy	ACE inhibitors *v* placebo	4	0	0	0	+1	High	Effect-size point added for OR less than 0.5
7 (266) [20]	Progression to late nephropathy	Intensive glycaemic control *v* conventional control	4	0	0	0	+1	High	Effect-size point added for OR less than 0.5
3 (99) [20]	Adverse effects: diabetic ketoacidosis	Intensive glycaemic control *v* conventional control	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
6 (number of people unclear) [20]	Severe hypoglycaemia	Intensive glycaemic control *v* conventional control	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results (number of people in analysis not clear)
What are the effects of treatments to prevent progression of nephropathy in people with type 1 diabetes and late nephropathy?									
1 (409) [25]	Mortality	ACE inhibitors *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for use of a composite outcome
1 (82) [26]	Mortality	Protein-restricted diet *v* usual-protein diet	4	–2	0	–1	+1	Low	Quality points deducted for sparse data and lack of blinding. Directness point deducted for use of a composite outcome. Effect-size point added for RR less than 0.5
What are the effects of treatments to prevent progression of nephropathy in people with type 2 diabetes and early nephropathy?									
2 (6052) [30] [31]	Mortality	ACE inhibitors *v* placebo	4	0	–1	–2	0	Very low	Consistency point deducted for conflicting results. Directness points deducted for inclusion of people with type 2 diabetes without nephropathy and for dose assessed in one RCT being less than that used clinically
2 (197) [27] [28] [29]	Progression to late nephropathy	ACE inhibitors *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (4912) [31]	End-stage renal disease	ACE inhibitors *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for dose assessed being less than that used clinically
2 (6052) [30] [31]	Cardiovascular events	ACE inhibitors *v* placebo	4	–2	–1	–2	0	Very low	Quality points deducted for subgroup analysis in one RCT and incomplete reporting of results. Consistency point deducted for conflicting results. Directness points deducted for use of a composite outcome in one RCT and for dose assessed being less than that used clinically in another RCT
1 (590) [32]	Progression to late nephropathy	ARBs *v* placebo	4	0	+1	–1	0	High	Consistency point added for dose response. Directness point deducted for restricted population
1 (250) [33]	Mortality	ARBs *v* ACE inhibitors	4	–1	0	–1	0	Low	Quality point deducted for dose inconsistency between interventions. Directness point deducted for low number of comparators

Important outcomes	Mortality, progression to late nephropathy, end-stage renal disease, cardiovascular events, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (250) [33]	Progression to late nephropathy	ARBs *v* ACE inhibitors	4	–1	0	–1	0	Low	Quality point deducted for dose inconsistency between interventions. Directness point deducted for low number of comparators
1 (250) [33]	Cardiovascular events	ARBs *v* ACE inhibitors	4	–1	0	–1	0	Low	Quality point deducted for dose inconsistency between interventions. Directness point deducted for low number of comparators
1 (480) [34]	Progression to late nephropathy	Tight blood pressure control *v* moderate diastolic blood pressure target	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
What are the effects of treatments to prevent progression of nephropathy in people with type 2 diabetes and late nephropathy?									
5 (3409) [36]	Mortality	ARBs *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of range of disease severity
3 (3251) [36]	End-stage renal disease	ARBs *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of range of disease severity
3 (307) [36]	Mortality	ARBs *v* ACE inhibitors	4	–1	0	–1	0	Low	Quality point deducted for uncertainty about significance of result. Directness point deducted for inclusion of people with early-stage nephropathy

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion. Consistency: similarity of results across studies. Directness: generalisability of population or outcomes. ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker