Prevention and management of chronic kidney disease in type 2 diabetes

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GUIDELINES

Blood glucose control should be optimized aiming for a general HbA1c target ≤7%. (Grade A*).

In people with type 2 diabetes and microalbuminuria or macroalbuminuria, angiotensin receptor blocker (ARB) or angiotensin-converting enzyme inhibitor ACEi antihypertensives should be used to protect against progression of kidney disease. (Grade A*).

The blood pressure (BP) of people with type 2 diabetes should be maintained within the target range. ARB or ACEi should be considered as antihypertensive agents of first choice. Multi-drug therapy should be implemented as required to achieve target blood pressure. (Grade A*)

People with type 2 diabetes should be informed that smoking increases the risk of chronic kidney disease (CKD) (Grade B*).

*Refer to Table A1: Definition of NHMRC grades of recommendation. Also refer to NHMRC ‘National Evidence Based Guidelines for Diagnosis, Prevention and Management of CKD in Type 2 Diabetes’ (see http://www.cari.org.au) for Levels of Evidence and Evidence Grading which were undertaken in accordance with the NHMRC Hierarchy of Evidence procedure.

SUGGESTIONS FOR CLINICAL CARE

- The HbA1c target may need to be individualised taking in to account history of hypoglycaemia and co-morbidities. (refer to NHMRC Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes at http://www.nhmrc.gov.au).
- Systolic blood pressure (SBP) appears to be the best indicator of the risk of CKD in type 2 diabetes. However, an optimum and safest lower limit of SBP has not been clearly defined.
- In people with type 2 diabetes antihypertensive therapy with ARB or ACEi decreases the rate of progression of albuminuria, promotes regression to normoalbuminuria, and may reduce the risk of decline in renal function.
- Due to potential renoprotective effects, the use of ACEi or ARB should be considered for the small subgroup of people with normal BP who have type 2 diabetes and microalbuminuria.
- The extent to which interventions with lipid lowering therapy reduces the development of CKD in people with type 2 diabetes is unclear. As there is limited evidence relating to effects of lipid treatment on the progression of CKD in people with type 2 diabetes, blood lipid profiles should be managed in accordance with guidelines for prevention and management of cardiovascular disease (CVD).
- Lifestyle modification (diet and physical activity) is an integral component of diabetes care (refer to the NHMRC Evidence Based Guidelines for Blood Glucose Control in Type 2 Diabetes), however, there are insufficient studies of suitable quality to enable dietary recommendations to be made with respect to prevention and/or management of CKD in people with type 2 diabetes.

BACKGROUND

Aim of the guideline

This guideline topic has been taken from the NHMRC ‘National Evidence Based Guidelines for Diagnosis, Prevention and Management of CKD in Type 2 Diabetes’ which can be found in full at the CARI website (http://www.cari.org.au). The NHMRC guideline covers issues related to the assessment and prevention of CKD in individuals with established type 2 diabetes. The NHMRC guidelines do not address the care of people with diabetes who have end-stage kidney disease or those who have a functional renal transplant. In addition, the present guideline does not provide recommendations regarding the management of individuals with established CKD, with respect to the prevention of other (non-renal) adverse outcomes, including retinopathy, hypoglycaemia, bone disease and cardiovascular disease. It is important to note however, that in an individual with type 2 diabetes, the prevention of these complications may be a more important determinant for their clinical care. Consequently, the recommendations...
made must be balanced against the overall management needs of each individual patient.

**Prevention and management of CKD in type 2 diabetes**

It should be noted that the best way to prevent CKD in individuals with diabetes is to prevent diabetes. NHMRC recommendations for the primary prevention of type 2 diabetes are available elsewhere (http://www.diabetesaustralia.com.au). These guidelines specifically target the management of individuals with established type 2 diabetes.

A risk factor analysis for kidney dysfunction in type 2 diabetes following 15 years of follow up from the UKPDS study, identified systolic blood pressure; urinary albumin excretion and plasma creatinine as common risk factors for albuminuria and kidney impairment (creatinine clearance and doubling of plasma creatinine). Additional independent risk factors for kidney impairment were female gender, decreased waist circumference, age, increased insulin sensitivity and sensory neuropathy. A cross-sectional study of 1003 Japanese hospital patients with type 2 diabetes identified large waste circumference and elevated BP as risk factors for microalbuminuria while dyslipidaemia was identified as a risk factor for decreased glomerular Filtration Rate (GFR).

In contrast to type 1 diabetes, only 20% of newly diagnosed people with type 2 diabetes are normotensive and have a normal circadian blood pressure profile. Therefore hypertension usually precedes the onset of microalbuminuria. BP control modulates the progression not only of microalbuminopathy (diabetic kidney disease and retinopathy) but also of macroangiopathy (Coronary heart disease (CHD) and stroke).

In microalbuminuric people with type 2 diabetes, observational studies have shown an association between poor glycaemic control and progression of albuminuria. A number of studies have identified a strong independent association between hyperglycaemia and the rate of development of microvascular complications. The large observational WESDR study indicated an exponential relationship between worsening glycaemic control and the incidence of nephropathy as well as retinopathy and neuropathy.

The UKPDS study clearly shown the importance of targeting glycosylated haemoglobin (HbA1c) levels close to normal (HbA1c <7.0%) in people with type 2 diabetes. A modest decrease in HbA1c over 10 years from 7.9 to 7.0% lowered the risk of microvascular endpoints with the onset of microalbuminuria being reduced by 25%. These findings are supported by a study of intensified glycaemic control in non-obese Japanese subjects with type 2 diabetes. In the UKPDS, there was no significant reduction in the risk of progression from microalbuminuria to proteinuria with intensive blood glucose control.

The AusDiab study collected information on albuminuria, measured as a spot albumin: creatinine ratio (ACR) (mg/mmol) with microalbuminuria being between 3.4 and 34 mg/mmol and macroalbuminuria at >34 mg/mol. The prevalence of albuminuria increased with increasing glycaemia. People with diabetes and impaired glucose tolerance had an increased risk for albuminuria compared with those with normal glucose tolerance, independent of other known risk factors for albuminuria (including age and sex).

Hyperglycaemia is an important determinant of the progression of normoalbuminuria to microalbuminuria in diabetes. Strict blood glucose control has been shown to delay progression from normoalbuminuria to microalbuminuria, overt kidney disease and from normo- or microalbuminuria to overt kidney disease. The influence of intensive glycaemic control is greatest in the early stages of CKD, although some observational studies suggest an association of glycaemic control with the rate of progression of overt kidney disease and even end-stage kidney disease (ESKD).

The American Heart Association (AHA) has undertaken a review of the DCCT, UKPDS, ACCORD, ADVANCE and VA Diabetes trials and on the basis of the review issued a Scientific Statement addressing intensive glycaemic control in relation to cardiovascular events. While the AHA review was focused on cardiovascular events, the statement is relevant to the consideration of the management of CKD, given the strong association between CKD and cardiovascular events. Consistent with the evidence reviewed in these guidelines (refer to following sections), the AHA note that a small but incremental benefit in microvascular outcomes (principally renal outcomes) is indicated with HbA1c values approaching normal. As a consequence the AHA statement notes that on the basis of findings from the DCCT, UKPDS and ADVANCE trials some patients may benefit (in terms of microvascular outcomes) from HbA1c goals lower than the general goal of <7%. However, the AHA also state that less stringent goals may be appropriate for patients with a history of hypoglycaemia, limited life expectancy, advanced comorbid conditions... Thus individualized glycaemic goals other than the general goal of <7% HbA1c may be appropriate for some patients.

Several studies suggest that a reduction in albuminuria as well as treatment of elevated blood pressure by the preferential use of an ACEi may lower the risk of CVD to a greater extent than with equihypotensive doses of dihydropyridine calcium channel blockade. One long-term study from Israel has shown that ACE inhibition exerts a renoprotective effect in normotensive middle-aged people with type 2 diabetes and microalbuminuria. In this 7-year study, GFR remained stable in the ACEi (enalapril) treated group, while both albuminuria and GFR deteriorated rapidly in the placebo group. However, the study did not include a third arm treated with conventional antihypertensive agents, and therefore it is not clear if the renoprotective effect was mediated by lowering of systemic BP as opposed to an intrarenal effect of the ACEi.

Antihypertensive therapy, especially with ARB’s and ACEi, has been clearly shown to reduce albumin excretion rate (AER). There are trials indicating that ACEi exert cardioprotective effects in addition to lowering of BP, even in normotensive people. Renoprotection has been demon-
strated for ARB’s in two large studies.39,40 The existence of a specific renoprotective effect of ACE inhibition in people with type 2 diabetes was not confirmed in the UKPD5 although it is possible that both captopril and atenolol exerted an equal renal protective effect, over and above lowering of systemic BP.

The term “renoprotection” is considered to denote at least three criteria:
1. Antiproteinuric effect, which has been used as a surrogate for the subsequent rate of decline in kidney function.
2. Attenuation of the rate of decline in GFR.
3. Attenuation of the rate of decline of GFR when compared with a control group treated with other antihypertensive agents in equipotent doses.

Proteinuria is a weaker basis for identifying renoprotective treatments than a reduction in the rate of decline of GFR.22

Several studies have documented the efficacy of antihypertensive therapy in lowering AER in both hypertensive21–24 and normotensive25 people with type 2 diabetes and microalbuminuria.

People with type 2 diabetes and kidney disease show a broad range of lipid abnormalities, characterized by a switch to a more atherogenic lipid profile. This becomes more pronounced with increasing proteinuria, although several factors such as glycaemic control, insulin administration, obesity and genetic factors may alter the degree of dyslipidaemia.

Increased levels of triglycerides are consistently seen in people with type 2 diabetes and microalbuminuria or overt proteinuria.26–28 The high triglyceride levels are associated with an increased proportion of atherogenic small dense LDL cholesterol particles.29 The implication is that serum triglycerides should be as low as possible to prevent atherogenic changes in LDL-cholesterol particles.30 LDL-cholesterol levels in people with type 2 diabetes have been reported to be normal in association with overt diabetic kidney disease31 whereas decreases in LDL-cholesterol levels have been reported in association with microalbuminuria.32

Higher apolipoprotein (a) levels have been reported in people with type 2 diabetes and micro- and macroalbuminuria than in control subjects, and also in people with macroalbuminuria than in those with normoalbuminuria.33 Apolipoprotein (a) levels have been related to the rates of progression of albuminuria,34 however, others have not confirmed these findings in people with diabetes and CKD.35

There is evidence to support the hypothesis that changes in lipoprotein levels may play a causal role in the initiation and progression of kidney disease, based on the finding of lipid deposits and foam cells in the glomeruli of humans with kidney disease.36

Primary or secondary intervention with statins in hypercholesterolaemic people has shown similar cardioprotective effects in diabetic and non-diabetic subjects.37–39 The absolute clinical benefit achieved by cholesterol lowering may be greater in people with CHD and diabetes than with CHD and without diabetes because people with diabetes have a higher absolute risk of recurrent CHD events and other atherosclerotic events.40

Observational studies have shown that dyslipidaemia interacts with other risk factors to increase cardiovascular risk.41,42 Microalbuminuria is a risk factor for CVD as well as overt kidney disease in people with type 2 diabetes,43,44 and dyslipidaemia is more common in microalbuminuric than normoalbuminuric people with type 2 diabetes.45 In people with type 1 or type 2 diabetes and increased AER, elevated LDL-cholesterol and triglycerides are common, whereas HDL-cholesterol may be high, low or normal. Nonetheless, studies have shown a correlation between serum cholesterol concentration and progression of CKD.46,47 Since increased AER and dyslipidaemia are each associated with an increased risk of CHD, it is logical to treat dyslipidaemia aggressively in people with increased AER. Subgroups with diabetes in large intervention studies have confirmed that correction of dyslipidaemia results in a decrease in CHD.48 However, few trials have examined the effects of treating dyslipidaemia on kidney end-points in people with type 2 diabetes and increased AER. Further studies are therefore required in people with microalbuminuria and macroalbuminuria in order to assess the effects of statins and fibrates on albuminuria and kidney function. Until the results of this type of study are known, it will not be possible to determine if correction of dyslipidaemia alone exerts renoprotective effects. Furthermore, it is not known if intervention with specific agents such as statins or fibrates exerts effects on kidney end-points over and above protection from cardiovascular events.

Dyslipidaemia is a common finding in individuals with type 2 diabetes, particularly those with CKD, in whom it is a significant risk factor for adverse cardiovascular outcomes49–52 (refer also to the NHMRC guidelines for the prevention of cardiovascular disease in type 2 diabetes). Moreover, the lowering of LDL cholesterol in individuals with type 2 diabetes leads to primary and secondary prevention of cardiovascular events and mortality.53 The absolute risk benefit of lipid lowering is much larger reflecting the increased absolute risk of adverse cardiovascular outcomes.

**SEARCH STRATEGY**

**Databases searched:** The search strategies were designed to reduce bias and ensure that most of the relevant data available on type 2 diabetes were included in the present review and were similar to those detailed in the Cochrane Collaboration Reviews Handbook (Higgins JPT et al.).48 The electronic databases searched were Medline, EMBASE, Cochrane Library, CINAHL, HTA and DARE. The detailed search strategy, research terms and yields are provided in Appendix 3 of the complete guideline document that can be found on the CARI website (http://www.cari.org.au).

**Date of searches:**
- Blood Glucose – April 3, 2008
- BP – March 18, 2008
- Blood Lipids – March 27, 2008
- Dietary Factors – March 28, 2008
- Smoking Cessation – April 1, 2008.
WHAT IS THE EVIDENCE?

Role of blood glucose control

Improving glycaemic control reduces the development and progression of kidney disease in people with type 2 diabetes (Evidence Level 1 – Intervention).

The issue of the role of blood glucose control in the development and progression of kidney disease in individuals with type 2 diabetes has been addressed by a number of systematic reviews and RCTs. A summary of relevant studies is presented in Table A2 with key studies discussed in the text below. While a number of these studies have examined the use of specific antihyperglycaemic agents, it is not possible on the basis of the current evidence to provide recommendations of the use of specific agents in relation to the progression of CKD.

The systematic review by Newman et al.4 addressed the question of whether improved glycaemic control reduces the rate of development of secondary diabetic complications in people with either type 1 or type 2 diabetes and microalbuminuria. Five RCTs were identified in people with type 2 diabetes. The review considered ESKD, estimation of the Glomerular Filtration Rate (eGFR) and clinical proteinuria with the following outcomes:

- No RCT evidence was identified to show that improved glycaemic control or a different effect of rosiglitazone was considered not to be convincing. Three studies were identified in relation to improved glycaemic control and the development of clinical proteinuria and microalbuminuria, namely the Kumamoto study,47 UKPDS6 and the VA Cooperative study.46 These studies provide some evidence that intensive treatment of hyperglycaemia in normoalbuminuric people with type 2 diabetes will, in a proportion of people, prevent development of microalbuminuria and provide some evidence of a reduction in the rate of clinical proteinuria. However, the studies only included a proportion of people with microalbuminuria.

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The systematic review by Richter et al.52 assessed the effects of metformin with type 2 diabetes. The objectives of the systematic review by Saenz et al.53 were to assess the effects of metformin monotherapy on mortality, morbidity, quality of life, glycaemic control, body weight, lipid levels, blood pressure, insulinemia and albuminuria in people with type 2 diabetes. The study identified only one small trial of 51 people with type 2 diabetes with incipient nephropathy with 3 month follow up,56 which reported some benefit for microalbuminuria with metformin treatment. The authors concluded that microalbuminuria should be incorporated into the research outcomes and no overall conclusion has been made with respect to effects of metformin on diabetic kidney disease.
In addition to the studies identified by Saenz et al., the HOME trial examined the efficacy of metformin in 345 people with type 2 diabetes over a 4 month period. Metformin was associated with a 21% increase in the UAE compared with the placebo, the authors considered this to be a short-term anomaly given the association of UAE with HbAc1, however, they were unable to identify the reason for the anomaly.

The ADVANCE trial was designed to assess the effects on major vascular outcomes of lowering the HbAc1 to a target of 6.5% or less in a broad cross-section of people with type 2 diabetes with CVD or high risk of CVD. The primary endpoints were a composite of both macrovascular and microvascular events. Endpoints relevant to kidney disease included development of macroalbuminuria, doubling of serum creatinine, and the need for renal replacement therapy or death due to kidney disease. At baseline approximately 27% of the participants had a history of macroalbuminuria and 3–4% had had microalbuminuria. At the end of the follow up period the mean HbAc1 was significantly lower in the intensive group (6.5%) than the standard group (7.3%). The mean SBP was on average 1.6 mm Hg lower than the standard group.

A significant reduction (hazard ratio 0.86 CI: 0.77–0.97) in the incidence of major microvascular events occurred, while macrovascular events were not significantly different between the groups. Intensive glucose control was associated with a significant reduction in renal events including new or worsening of nephropathy (HR 0.79; CI: 0.66–0.93) predominantly due to a reduction in the development of new or worsening of nephropathy (HR 0.79; CI: 0.66–0.93) as well as the need for renal replacement therapy. The study concluded that the lack of a significant effect on major macrovascular events may be due to inadequate power to detect to such an effect given a lower than expected rate of macrovascular events. The study also noted that the lack of a significant effect on major macrovascular events may be due to inadequate power to detect such an effect given a lower than expected rate of macrovascular events. Some but not all of the overall effect on major events could be attributed to the small but significant 1.6 mm Hg lower SBP in the intensive group.

A significantly higher number of severe hypoglycaemic episodes were recorded in the intensive group compared with the standard group (2.2% vs 1.5%). The rates were 0.7 severe events per 100 people in the intensively controlled group and 0.4 severe events per 100 people in the standard control group. The rates for minor hypoglycaemic events were 8.7 per 100 people in the intensively controlled group compared with 9.0 per 100 people in the standard control group. Overall the main benefit identified by the ADVANCE study was a 5th reduction in endpoints in particular the development of macroalbuminuria.

A US study of Hispanic and African Americans assessed the efficacy of rosiglitazone in a high risk (based on ethnicity) type 2 diabetes group. The urinary ACR was collected in a secondary outcome under the general grouping of CVD markers. The study included 245 people with type 2 diabetes with FPG greater than or equal to 140 mg/dL and HbA1c greater than or equal to 7.5% who had been on a sulphonylurea monotherapy for a minimum of 2 months and were randomized to receive glyburide (GLY) plus rosiglitazone (RSG) or glyburide (GLY) plus placebo for 6 months. The urinary ACR was reduced by 26.7% in the treatment group (GLY + RSG) compared with control group (GLY + placebo). Improved insulin sensitivity and b-cell function with thiazolidinedione treatment was also noted.

The short-term trial of 223 mixed type 1 and type 2 diabetes by reported significant improvement in albuminuria in those with micro or macroalbuminuria following a 4 month high dose treatment with sulodexide. The effect was considered to be additive to the ACE inhibitory effect. The sub analysis by diabetes type produced similar results.

The multifactorial intensive treatment of the STENO2 study reduced the risk of nephropathy by 50%. This long-term study (mean 9.8 years) of 160 people with type 2 diabetes and microalbuminuria, utilized multifactorial intervention for modifiable risk factors for cardiovascular disease which included intensive treatment of blood glucose. While a no intensive treatment group achieved a significantly lower blood glucose concentration, given the multifactorial nature of the study it is not possible to determine the relative contribution that intensive blood glucose control may have had on the renal outcomes.

### ROLE OF BP CONTROL

(a) BP as a risk factor for CKD

Arterial hypertension is a key risk factor for kidney damage in people with type 2 diabetes Evidence (Level 1 – Aetiology).

Several trials have clearly shown that intensive treatment of elevated BP lowers the risk of microvascular disease, CVD and mortality in type 2 diabetes (refer to systematic reviews of). The UKPDS has been the largest long-term study to compare the effects of intensive versus less intensive BP control in hypertensive people with type 2 diabetes. In this 9-year study of 1148 people, allocated to tight BP control (n = 578) or less tight control (n = 590), mean BP was significantly reduced in the tight control group (144/82 mm Hg), compared with the group assigned to less tight control (154/87 mm Hg) (P < 0.0001). The study showed that microvascular endpoints, including the development of microalbuminuria or overt diabetic kidney disease, were reduced by 37% in the intensive control group (P < 0.01).

In this study, captopril and atenolol were used in equi-hypotensive doses and each drug attenuated the development of microvascular complications to a similar degree over 10 years.

Elevated BP was identified as one of the major risk factors associated with a decline in kidney function and increase in
albuminuria in a long-term non-interventional prospective study of 574 people with type 2 diabetes who were normoalbuminuric and microalbuminuric (based on dipstick) at the start of the study. Those with elevated BP (>95 mm Hg) had an almost 10 fold increased risk of developing microalbuminuria compared with those with lower BP over the average 8 year follow-up period. Recent analysis of the BP arm data of the ADVANCE Trial by Galan et al. has indicated that lower achieved follow-up (median 4.3 years) systolic blood pressure levels were associated with progressively lower renal event rates to below 110 mm Hg.

These studies support the concept that arterial hypertension plays a pivotal role in contributing to kidney damage in type 2 diabetes, across the range of albumin excretion from normal to micro- to macroalbuminuria. The studies also show that the rate of GFR decline can be successfully lowered in people with type 2 diabetes by effective antihypertensive therapy, however, the systematic review by considered that a 72% drop in clinical proteinuria noted in relevant trials was unlikely to be caused by the small difference in the BP between treatment groups and is consistent with renoprotective effects of ACEI.

(b) BP control for prevention and management of CKD

In people with type 2 diabetes antihypertensive therapy with ARB or ACEI decreases the rate of progression of albuminuria, promotes regression to normoalbuminuria, and may reduce the risk of decline in renal function (Evidence Level 1 – Intervention).

A large number of systematic reviews and trials have examined antihypertensive therapy using ACEi and ARBs in people with type 2 diabetes. A summary of relevant studies is shown in Table A3 with findings of key studies described in the text below.

Systematic reviews and meta-analyses:

The systematic review of RCTs up until 2002 reported by Newman et al. examined three areas relevant to consideration of the use of antihypertensive therapy that are summarized below:

1. Antihypertensive therapy and development of ESKD in people with type 2 diabetes and microalbuminuria.

   Only three RCTs were identified as being of sufficient size and length of follow-up namely ABCD, UKPDS and HOPE. Of these ABCD did not include ESKD as an endpoint.

   In the ABCD Study the prevalence of ESKD was less than 2% with a relative risk for tight control of 0.58 (95% CI: 0.15–0.53) with no significant heterogeneity between studies. No study provided information to allow assessment of regression to normoalbuminuria. The overall risk reduction was 4.5% giving a NNT of 22 patients per year to prevent one case of clinical proteinuria. The differences in BP between treatment and placebo were small and as such consider that a 72% drop in clinical proteinuria was unlikely to be caused by such a small difference and more likely that ACEI have a specific renoprotective effect.

   No appropriate trials were identified comparing antihypertensive agents in hypertensive people with type 2 diabetes and microalbuminuria. Three randomized placebo-controlled trials in normoalbuminuric people with type 2 diabetes with microalbuminuria were identified. These three trials all used the ACEi enalapril as the treatment. The overall relative risk for the development of proteinuria for the three trials was 0.28 (95% CI: 0.15–0.53) with no significant heterogeneity between studies. No study provided information to allow assessment of regression to normoalbuminuria. The overall risk reduction was 4.5% giving a NNT of 22 patients per year to prevent one case of clinical proteinuria. The differences in BP between treatment and placebo were small and as such consider that a 72% drop in clinical proteinuria was unlikely to be caused by such a small difference and more likely that ACEI have a specific renoprotective effect.

   No appropriate trials were identified comparing antihypertensive agents and intensive versus moderate BP control other than the later analysis of the ABCD trial. Intensive therapy with either enalapril or nisoldipine resulted in a lower percentage of people who progressed from normoalbuminuria and microalbuminuria to clinical proteinuria with no difference between the ACEI and CCB.

   Only one available placebo controlled study was identified for hypertensive people with type 2 diabetes with microalbuminuria. The treatment involved two dose levels
of the ARB antagonist irbesartan for 2 years. A combined relative risk for clinical proteinuria for the ARB treatments was 0.50 (95% CI: 0.0.31–0.81). This reduction in the rate of progression to clinical proteinuria was independent of BP.

Only the ABCD trial was identified as being relevant for comparing intensive versus moderate BP control in hypertensive people with type 2 diabetes with microalbuminuria. Individuals were randomized to either ACEi enalapril or the CCB antagonist nisoldipine. The percentage of patients who progressed from microalbuminuria to clinical proteinuria was not significantly different between the treatment
groups. Newman et al. noted that the results supported the observations from the UKPDS of progression to clinical proteinuria among microalbuminuric and normoalbuminuric patients with type 2 diabetes was not affected by the level of BP control, however, separation of the two groups is not possible.

Four trials were identified comparing different hypertensive agents in hypertensive people with type 2 diabetes with microalbuminuria. The trials all included an ACEi treatment compared with either a CCB antagonist or a blocker. The overall relative risk of development of clinical proteinuria for ACEi versus other hypertensive therapy was 0.74 (95% CI: 0.44–1.24) with no significant heterogeneity. Thus the ACEi reduced progression to clinical proteinuria as effectively as the other therapies. These findings were considered to be comparable with the UKPDS findings which could not separate normoalbuminuria from microalbuminuria.

The two systematic reviews addressed the use of antihypertensive agents in people with diabetes with respect to renal outcomes. The objectives of the review by Strippoli et al. were to evaluate the effects of antihypertensive agents in people with diabetes and normoalbuminuria. While the objectives of the review by Strippoli et al. were to evaluate the benefits and harms of ACEi and ARBs in preventing the progression of CKD. The reviews included studies of both type 1 and type 2 diabetes and Strippoli et al. people with either microalbuminuria or macroalbuminuria. While the reviews included both type 1 and type 2 diabetes the majority of selected trials enrolled only people with type 2 diabetes.

The overall conclusions of the two systematic reviews are summarized below:

- A significant reduction in the risk of developing microalbuminuria in normoalbuminuric patients has been demonstrated for ACEI only. This effect appears to be independent of BP, level of kidney function and type of diabetes. However, there is insufficient data to be confident that these factors do not influence the effect modifier.
- There is randomized trial evidence that ACEi versus placebo/no treatment used at the maximum tolerable dose prevent death in people with diabetic kidney disease but not so for ARB versus placebo/no treatment. Both agents prevent progression of nephropathy and promote regression to a more favorable clinical pattern of normoalbuminuria. The relative effects of ACEi and ARBs are uncertain due to a lack of head to head trials.

In relation to type 2 diabetes the following outcomes are of note:

- All-cause mortality
  - non-significant effect of ACEi versus placebo.
  - comparison between ACEi and CCB – no significant difference, however, only two studies were available where relative risk could be estimated.
  - at less than the maximum tolerable dose for ACEi versus placebo/no treatment – no significant effect.
  - at the maximum tolerable dose for ACEi versus placebo/no treatment – no significant effect in the two relevant studies both of which were mixed type 1 and type 2 diabetes populations.
  - for ARB versus placebo/no treatment – all of the studies included people with type 2 diabetes and no significant effect was noted.
- Doubling of serum creatinine
  - non-significant effect of ACEi versus placebo.
  - comparison of ACEi and CCB – no available suitable studies where relative risk was able to be estimated.
  - for ACEi versus placebo/no treatment – overall effect of marginal significance in favour of ACEi.
  - for ARB versus placebo/no Treatment – the two studies selected both included people with type 2 diabetes with an overall significant reduction for ARB compared with placebo/no treatment.
- Progression to ESKD
  - non-significant effect of ACEi versus placebo in the one mixed type 1/type 2 diabetes study only.
  - comparison between ACEi and CCB – no available suitable studies where relative risk was able to be estimated.
  - for ACEi versus placebo/no treatment – non-significant relative risk in the two studies that included people with type 2 diabetes.
  - for ARB versus placebo/no treatment – the two studies selected both included people with type 2 diabetes with an overall significant reduction in progression to ESKD for ARB compared with placebo/no treatment.
- Progression from normoalbuminuria to microalbuminuria
  - overall significant effect of ACEi versus placebo in reducing the rate of progression.
  - ACEi compared with other hypertensive agents – limited to the UKPDS study which showed no significant effect of ACEi in reducing the rate of progression.
  - normotensive patients – ACEi versus placebo – no trials identified with people with type 2 diabetes.
  - hypertensive patients – ACEi versus placebo – evidence for significant reduction in rate of progression with ACEi treatment.
  - ACEi compared with CCB – significant effect of ACEi in reducing the rate of progression.
- Progression of microalbuminuria to macroalbuminuria
  - ACEi versus placebo/no treatment – the two diabetes studies are weighted to a relative risk less than one (i.e. favoring ACEi) consistent with the overall assessment with type 2 diabetes studies accounting for approximately 70% of the total number in all selected studies.
- ARB versus placebo/no treatment – all selected studies included people with type 2 diabetes and show an overall reduction in the rate of progression in favour of ARB treatment.
- Regression from microalbuminuria to normoalbuminuria – ACEi versus placebo/no treatment – the type 2 diabetes studies are weighted to a relative risk greater than 1 (i.e., favors ACEi) consistent with the overall assessment of studies with type 2 diabetes being approximately 65% of the total number in all of the included studies.
- ARB versus placebo/no treatment – the two trials included people with type 2 diabetes and show an overall marginal increase in the rate of regression in favor of ARB treatment.
- Comparison of effect on BP – ACEi versus placebo no trials identified that included people with type 2 diabetes.
- ACEi and CCB on BP – no significant effect, however, limited to one mixed type 1/type 2 diabetes study.

The relevant trials comparing ACEi treatment with ARB treatment all included people with type 2 diabetes and no significant differences on all cause mortality, progression of microalbuminuria to macroalbuminuria or regression from microalbuminuria to normoalbuminuria were noted. However, as noted in the overall conclusion by the authors the trials were limited and provide insufficient evidence for comparison of effects.

The objectives of the systematic review was to assess the RCT evidence for the effects of different therapeutic BP goals and interventions in the normotensive range on the decline of glomerular function. The search strategy was limited to studies of people with 2 years duration of type 1 or type 2 diabetes with incipient or overt nephropathy or with or without elevated BP. The intervention was required to be treatment with one or more hypertensive agents. The review identified 5 RCTs meeting the search criteria. All of these studies have been identified and assessed. Only two studies that considered the effect of lower target BP within the normotensive range in people with type 2 diabetes were identified. Kaisil et al. considered GFR, as surrogate endpoint in the absence of a renal failure endpoint such as need for dialysis and/or transplantation. The authors noted that no trial demonstrated a beneficial effect of lower target BP values on the progression of kidney failure. In short decreases in albuminuria were not accompanied by a decrease in the rate of decline in GFR. They conclude that the available evidence does not support a beneficial effect of BP lowering within the normotensive range on progression of diabetic nephropathy as assessed by the change in GFR.

The systematic review and meta-analysis pooled analyses from the number of small studies comparing combination treatment of ACEi + ARB with ACEi alone. A total of ten studies covering both type 1 and type 2 diabetes were included in the meta-analysis. The majority of the studies were of people with type 2 diabetes. The authors concluded that the meta-analysis suggests that combined ACEi + ARB reduces 24 h proteinuria to a greater extent than ACEi alone and that this benefit is associated with small effects on GFR. However, analysis also concludes that the available studies were heterogeneous and mostly of short duration (only one study greater than 12 weeks) and the few longer term studies have not demonstrated a benefit.

Hamilton et al. conducted a meta-analysis of RCTs evaluating the efficacy of ACEi in the treatment of nephropathy in individuals with type 2 diabetes. Specifically the meta-analysis addressed the reduction in albuminuria and proteinuria and thus included only those studies that provided either geometric or arithmetic means of albuminuria. Studies reporting geometric means and arithmetic means were analysed separately. The results of the meta-analysis indicated that treatment with ACEi produced significant reductions in albuminuria in people with type 2 diabetes in studies where geometric means were used to normalize data but less clear where data was reported as arithmetic means (presumed to reflect the skewed albuminuria data). While studies were stratified on the basis of the degree of albuminuria and study duration, no distinction between normotensive or hypertensive patients have been made.

Studies with ARB for people with type 2 diabetes and overt kidney disease have shown that angiotensin receptor blockade with irbesartan attenuates the rate of doubling of serum creatinine by 20–30% over 2.7 years when compared with placebo or amlopidine, used in equipotensive doses. A study of angiotensin receptor blockade with irbesartan in hypertensive, microalbuminuric people with type 2 diabetes showed a 70% decrease in AER over 2 years. However, preservation of GFR over and above the effects of BP lowering was not demonstrated in this relatively short-term study.

**Studies not covered by Systematic Reviews**

The ADVANCE study is a multinational randomized control trial undertaken by 215 centres across 20 countries which, in addition to intensive blood glucose treatment, included a BP treatment study arm. Participants were randomized to either fixed combined perindopril indapamide or placebo. Additional antihypertensive agents were allowed for both groups as required with the exception that thiazide diuretics were not allowed and the only open labelled ACEi allowed was perindopril to a maximum dose of 4 mg a day thereby ensuring that the active treatment group did not exceed the maximum recommended dose. The active treatment resulted in a mean reduction after 4.3 years (median) in SBP and DBP of 5.6 and 2.2 mm Hg, respectively, compared with placebo. The relative risk of a major microvascular event was 7.9% in the active treatment group compared with 8.6% in the placebo group, however, this was not significant. Active treatment was associated with a borderline significant reduction in macroalbuminuria and a significant reduction in the development of microalbuminuria with a relative risk reduction of 21% (95% CI: 15–30). Further detailed analysis of the ADVANCE trial data has indicated that lower achieved follow-up systolic BP levels were associated with progressively lower renal event rates to below 110 mm Hg. Renoprotective effects of blood pres-
suring lowering with perindopril indapamide treated were noted even among the sub group with baseline BP below 120/70 mm Hg.

An open label parallel prospective randomized trial provides a comparison of the effects of a ARB (losartan) and a CCB (amlodipine) on the UAE and ACR of 87 hypertensive type 2 diabetes Japanese patients with persistent macroalbuminuria. The ARB and CCB treatments provided similar BP control (no significant difference). The ARB treatment resulted in a 30% drop in the UAE after 6 months treatment and a 16% drop in the ACR. There was no significant change in both the UAE and the ACR in the CCB treatment.

In relation to ACEi, a number of additional trials have been identified, the details and findings of which are summarized in Table A3. While the study summarized in Table A10 has examined both ACEi and ARBs either alone or in combination. A number of studies have specifically assessed the ARB valsartan. The details and findings of these studies are summarized in Table A3. Overall, the studies are consistent with the renoprotective effect of ARBs, however, they do not provide additional data allowing a direct comparison with ACEi.

The BENDICT Trial was a long-term (median 43 months) prospective multicentre RCT of 1204 people with type 2 diabetes, elevated BP and normoalbuminuria. The trial was aimed at assessing the efficacy of ACEi and CCB alone and in combination. Additional agents were permitted to achieve appropriate BP control. Trandolapril plus verapamil and trandolapril alone decreased the incidence of microalbuminuria to similar extent. Verapamil alone was found to be no different to the placebo.

The comparative effects of HCT, ACEi and ARB on UAE (as a secondary outcome) were assessed in 3 people with type 2 diabetes in the Netherlands. The people with type 2 diabetes were Caucasian with an average age in the randomized treatment groups of 68–63, hypertensive and either normoalbuminuric or persistent microalbuminuric (UAE < 100 mg/day). The trial was a 12 months duration after a 1 month run in and a 4–6 month BP titration period. All three agents achieved the aggressive BP goals equally well in the three treatment groups. The UAE was reduced by around 35% over 12 months and there was no significant difference between the three treatments. The authors note that this outcome may reflect the relatively small sample size. This additional ACEi/ARB comparative study from those reported does not provide additional evidence for the efficacy of ARB compared with ACEi in achieving regression of microalbuminuria.

The multicentric CENTRO trial of 129 Italians with type 2 diabetes compared the ARB candesartan with the ACEi enalapril with albumin excretion rate as a secondary outcome. After 6 months treatment the ARB treatment group had a reduced albumin excretion rate and ACR, while the ACEi was higher. However, the baseline conditions differed between treatment groups and the majority of individuals were normoalbuminuric thus the relevance of the outcomes for individuals with microalbuminuria is questionable.

The GEMINI trial involved 1235 people with type 2 diabetes with elevated BP under either an ACEi or ARB hypertension treatment randomized for treatment with two different β-blockers (carvedilol and metoprolol). A post hoc analysis of differential effects of the β-blockers on the progression of albuminuria indicated a greater reduction in microalbuminuria for carvedilol compared with metoprolol. In those with normoalbuminuria fewer progressed to microalbuminuria on carvedilol. These effects were not related to BP. Multivariate analysis demonstrated baseline urine ACR and treatment were significant predictors of changes in albuminuria. In a separate analysis of the presence of metabolic syndrome at baseline correlated with an OR of 2.68 (95% CI 1.36–5.30) over the duration of the study.

The DETAIL study involved 526 people with type 2 diabetes with mild to moderate hypertension and eGFR ≥ 70 mL/min per 1.73 m2 from 6 European countries. The study compared ARB and an ACEi treatment over 5 years. After 5 years the difference in eGFR between the ARB and the ACEi was −3.1 mL/min per 1.73 m2 and was insignificant. The mean annual declines in eGFR were 3.7 mL/min per 1.73 m2 for the ARB and 3.3 mL/min per 1.73 m2 for the ACEi. These results were considered by the authors to be similar to eGFR decline reported in the IRMA 2, IDNT and RENAAL studies and compare to an expected untreated type 2 diabetes annual decline in the order of 4.0 mL/min per 1.73 m2. Telmisartan was concluded to be no inferior to enalapril in providing long-term renoprotection. However, the results do not necessarily apply to more advanced nephropathy but support clinical equivalence of ARB and ACEi in persons with conditions that place them at high risk for CV events.

The large ONTARGET trial comparing ARB and ACEi of in excess of 25 000 participants included a large proportion with diabetes and microalbuminuria. Relevant secondary outcomes are kidney impairment and kidney failure requiring dialysis. The only significant differences between treatments (ACEi, ARB and ACEi + ARB) were for increased kidney impairment in the combination therapy compared with the ACEi. Further analysis of renal outcomes, indicated a significantly higher increase in ACR in the ACEi treatment group compared with the ARB and ACEi + ARB (31% vs 24% and 21%). The risk of developing new microalbuminuria was not different between ACEi and ARB treatment groups, but was significantly lower in the combination treatment group. However, in contrast to albuminuria a greater rate of decline in eGFR was noted for the combination treatment group, thus the authors concluded that there was no evidence for a renal benefit with combination therapy even though proteinuria was improved. No subgroup analysis has been undertaken with respect to diabetes or albuminuria.

The short-term (6 month) study examined the renoprotective effects in people with type 2 diabetes with albuminuria of treatment with a direct renin inhibitor (aliskiren) in addition to maximal treatment with an ARB (losartan). Treatment with 300 mg of aliskiren was demonstrated to reduce the ACR by 18% compared with the placebo group and to increase the number of people with an albuminuria
reduction of greater than 50% over the treatment period. These effects were independent of changes in BP and therefore considered to indicate renoprotective effects of the treatment. The rationale behind the trial was provision of further benefit by use of a direct renin inhibitor in addition to maximal use of an angiotensin II receptor antagonist.

Table A3 provides a summary of studies that provide evidence in relation to use of antihypertensive agents in people with type 2 diabetes and the progression of CKD. Included are details of a number of studies conducted prior to 2000 that have not been discussed above that are provided as an overview of the collective evidence in relation to the role of BP control in the progression of CKD.\(^{100-103}\)

(iii) Role of blood lipid modification

The extent to which interventions with lipid lowering therapy reduces the development of CKD is unclear (Evidence Level I – Intervention).

As detailed below there are some trials that show that, over and above the cardio-protective actions, lipid-lowering may also exert beneficial effects on the development and progression of kidney disease in individuals with type 2 diabetes, as determined by albuminuria and/or GFR. However, there are no RCT studies in which renal outcomes including ESKD or doubling of serum creatinine have been used. It is unlikely that these studies will ever be performed given the overwhelming benefit of lipid lowering in terms of cardio-protection. Clinical trials in cardiovascular disease studying agents targeting dyslipidaemia have commonly excluded subjects with late stage CKD. Moreover, the significant cardiovascular benefits of these agents cannot confound associations between lipid effects and renal function outcomes. Consequently, conclusions regarding their potential as reno-protective agents must be limited by reliance on early, surrogate markers of kidney disease and its progression.

An overall summary of relevant studies is provided in Table A4 with findings from key studies described in the text below.

Systematic reviews and meta-analyses

Sandhu et al.\(^{104}\) conducted a systematic review and meta-analysis to determine the effect of statins on the rate of kidney function loss and proteinuria in individuals with CKD (with and without diabetes). They included 27 eligible studies with 39,704 participants (21 with data for eGFR and 20 for proteinuria or albuminuria). Overall, the change in the eGFR was slower in statin recipients (by approximately 1.2 mL/min per year). In addition, treatment with statins resulted in a significant reduction in baseline albuminuria and/or proteinuria. However, the magnitude of cholesterol reduction from baseline was not significantly associated with the described renal benefit of statins in meta-regression. In the smaller studies specifically performed in people with type 2 diabetes and kidney disease \((n = 3)\) the change in eGFR was unaffected by statins, although the modest magnitude of the effect observed in the other (larger) trials, if translated to these smaller studies, would mean the latter were underpowered to detect an eGFR difference.

Keating & Croom\(^{105}\) specifically addressed the pharmacological properties and efficacy of the fibric acid derivative, fenofibrate, in the treatment of dyslipidaemia in individuals with type 2 diabetes. The review included consideration of the effects on albuminuria in the two major RCTs (FIELD and DAIS, see below). In both trials fenofibrate, reduced the rate of progression from normoalbuminuria to microalbuminuria and microalbuminuria to macroalbuminuria and increased the rate of regression, when combined with treatment with placebo. This effect was modest in size. For example, the proportion of people developing microalbuminuria was significantly reduced in the FIELD trial (10% compared with 11%) and in the DAIS trial (8% compared with 18%).

Strippoli et al.\(^{106}\) examined data on 50 trials (30,144 people), 15 of which evaluated the potential renoprotective effect of statins. Most of these studies enrolled people with early or late stages of CKD and with a history of coronary heart disease. These studies did not include people with moderate CKD but without known cardiovascular disease. In the small number of studies reporting urinary protein excretion (g/24 h) in individuals with CKD (6 randomized controlled trials, 311 people), statins modestly reduced albuminuria and/or proteinuria. However, in contrast to findings of other meta-analyses, no significant effect was observed on creatinine clearance (11 randomized controlled trials, 548 people). This review was unable to distinguish a specific response in individuals with diabetes.

Fried et al.\(^{107}\) conducted a meta-analysis of trials of effects of lipid lowering therapy on nephropathy. A total 12 trials were included following systematic review, with all but one being a RCT. Of the 12 trials, the cause of kidney disease was stated as being due to diabetes (no distinction between type 1 or type 2 diabetes) in 7 of the 12 trials. Meta-analysis indicated that lipid reduction had a beneficial effect on the decline in GFR. The reduction in GFR from lipid-lowering therapy was 1.9 mL/min per year. There was no significant heterogeneity and no indication of publication bias. Regression analysis showed no relationship between effect of treatment and age, gender, cause of kidney disease and the type of lipid lowering therapy. No clear conclusions were possible with respect to the effect of lipid lowering therapy on proteinuria due to significant heterogeneity. Overall the authors concluded that meta-analysis suggests that lipid lowering therapy may help slow the rate of kidney disease progression. However, the applicability to type 2 diabetes is less clear as no sub group analysis was conducted.

Randomized clinical trials using statins

Statins are the most widely used class of drug for lipid lowering in individuals with type 2 diabetes. Currently in Australian practice at least two thirds of patients seeing their GP are receiving a statin. This reflects the clear and incon-
troverifiable evidence that lowering of LDL cholesterol in individuals with type 2 diabetes is associated with reduced cardiovascular events and mortality. Moreover, when results were adjusted for baseline risk, people with diabetes benefited more in both primary and secondary prevention. In addition, a number of studies have looked at the effects of statins on renal parameters, including GFR, creatinine clearance and urinary albumin excretion. However, no trials report endpoints such as end stage kidney disease or doubling of creatinine as an outcome. The following trials provide evidence in relation to the use of statins in people with type 2 diabetes and that also include renal outcomes.

A number of major statin trials have been conducted, which have included individuals with type 2 diabetes. In post hoc analyses of these large studies, beneficial effects on renal functional parameters have been examined in the subgroup of participants with diabetes.

- In the MRC/BHF heart protection study subgroup of participants with diabetes, renal functional parameters have been examined in the subgroup of participants with diabetes. In these trials, the use of statins has been associated with a significant decrease in urinary albumin excretion, however, the study did not include separate analysis for type 2 diabetes.

- In the Aggressive Lipid-Lowering Study (ALLIANCE) showed beneficial effects on GFR in individuals with type diabetes, however, the study did not separately identify or assess type 2 diabetes.

There have also been a number of studies examining the effects of statins on albuminuria and or creatinine clearance in individuals with type 2 diabetes, however, most of these are small (i.e. less than 50). The following two studies have been identified:

- A multicentric double blind parallel group RCT of type 2 diabetes Swedish patients with dyslipidaemia (fasting LDL-C > 3.3 mmol/L) compared the statin treatments (rosuvastatin and atorvastatin) over a 16 week treatment period. The primary endpoints were UAE and GFR which were measured/calculated at baseline and at 8 and 16 weeks into the treatment period. The treatment goal (achieved by titration) was an LDL-C <3.0 mmol/L. As noted by the authors, the short duration of the study allows only conclusions to be made with respect to 'acute or subacute changes' in UAE and estimated GFR. The overall conclusion of the authors is that both drugs were well tolerated and 'show no evidence of short-term detriment on the renal endpoints of UAE and GFR over a 4 month treatment period.' An absence of clinically important changes in albuminuria was noted for both treatments.

- Nakamura et al. studied the effect of cerivastatin on urinary albumin excretion in people with type 2 diabetes, microalbuminuria and dyslipidaemia. Sixty participants were enrolled in a double-blind study for 6 months, receiving either cerivastatin (0.15 mg/day) or placebo. At the endpoint, cerivastatin treatment resulted in a significant decrease in UAE (P < 0.01).

Randomized clinical trials using fibrates

Fibrates are effective in raising HDL cholesterol levels in individuals with type 2 diabetes and in improving LDL cholesterol quality. Two recent large studies have examined the effect of fenofibrate on renal outcomes in individuals with type 2 diabetes. The efficacy of this drug class has not been tested in individuals with renal impairment. There is also an increased potential for side-effects in this subgroup.

- A subgroup analysis of the Diabetic Atherosclerosis Intervention Study (DAIS), examined the effects of fenofibrate treatment (vs placebo) in people with type 2 diabetes (Canada and Europe) with mild to moderate lipid abnormalities and normo to microalbuminuria. The study length was a minimum of 3 years. Regression of albuminuria (defined as micro to normal albuminuria or macro to microalbuminuria) was significantly higher in the treatment group (13%) compared with the placebo group (11%), while progression of albuminuria was significantly lower in the treatment group (18%) compared with the placebo group (18%). Slightly more people showed no change in albuminuria in the treatment group (79%) compared with the placebo group (71%). The use of ACEI and ARBs increased during the course of the study; however, the use at the end of the trial was not significantly different between the groups at the end of the trial. The differences between groups in the progression and regression of albuminuria remained significant after controlling for baseline BP and HbA1c. The final urinary albumin was significantly correlated with either HbA1c level or BP. A significant correlation was observed between urinary albumin and baseline fasting triglyceride (TG) levels. After fenofibrate treatment urinary albumin levels correlated significantly with HDL-C levels but not with changes in TG. The study was not able to assess the persistence of the reduction to microalbuminuria after cessation of treatment.

Keech et al. and Radermecker & Scheen report the large (9795) multinational Fenofibrate Intervention and event Lowering in Diabetes (FIELD) study, which included assessment of progression and regression of albuminuria. Fenofibrate was associated with a significantly lower progression and significantly higher regression of albuminuria, however, the overall differences were relatively small (in the order of 2%). Albuminuria was a secondary outcome of the study.

In the only study to compare statins and fibrates, head to head, in 71 individuals with type 2 diabetes both benzafibrate and pravastatin prevented increase in the urinary albumin excretion rate over 4 years, with no difference observed between drug classes.

Randomized clinical trials using other lipid lowering agents

A number of other agents have clinically useful effects on dyslipidaemia in individuals with type 2 diabetes, including
The effects of probucol treatment on the progression of diabetic nephropathy was evaluated in a randomized open study of 102 people with type 2 diabetes with clinical albuminuria (UAE > 300 mg/g Cr). The mean follow up period was 28.5 months for all patients and 18.6 months for advanced patients (defined as those having serum Cr > 2.0 mg/dL). The mean interval to initiation of haemodialysis was significantly longer in probucol patients. In advanced cases treated with probucol, increases in serum creatinine and urinary protein were significantly suppressed and the haemodialysis-free rate was significantly higher. The study concluded that probucol may suppress the progression of diabetic nephropathy as a consequence of the antioxidant effect of the drug.

The multifactorial intensive treatment of the STENO2 reduced the risk of nephropathy by 50%. This long-term study (mean 7.8 years) of 160 people with type 2 diabetes and microalbuminuria, utilized multifactorial interventions for modifiable risk factors for cardiovascular disease which included blood lipid control with statins and fibrates. While the intensive treatment group achieved a significantly lower blood glucose concentration, given the multifactorial nature of the study it is not possible to determine the relative contribution of the intensive lipid treatment they may have had.

(iv) Role of diet modification

There are insufficient studies of suitable quality to enable dietary recommendations to be made with respect to CKD in people with type 2 diabetes (Evidence Level II – Intervention).

Lifestyle modification (diet and physical activity) is an integral component of diabetes care (refer to the guidelines for Blood Glucose Control in type 2 diabetes). However, there are few studies that have specifically addressed kidney related outcomes in type 2 diabetes and as such it is not possible to currently make recommendations specific to the management of CKD. The following sections summarize the current evidence in relation to alternate diets, protein restriction, and salt.

Role of dietary fats

The Diabetes and Nutrition Clinical Trial (DCNT) is a population based prospective, observational multicentre study designed to evaluate the nutritional pattern of people with diabetes in Spain and associations with diabetic complications. The study (total 192) included a mix of people with type 2 diabetes (99) and type 1 diabetes (93). Nephropathy progression was indicated by change from normoalbuminuria to microalbuminuria and microalbuminuria to macroalbuminuria. Regression was indicated by change from microalbuminuria to normalalbuminuria. The nutritional pattern of people with nephropathy regression was characterized by greater polyunsaturated fatty acid (PUFA) and smaller saturated fatty acid (SFA) than those with nephropathy, whereas the PUFA to SFA and monounsaturated fatty acid (MUFA) to SFA ratios were preserved. An opposite pattern was observed for progression of nephropathy.

The authors note that the findings of the studies are consistent with CVD studies and the role that SFAs may play in insulin sensitivity and other factors affecting diabetes control. Nonetheless, the authors consider that control of BP and blood glucose and cessation of smoking should remain the therapeutic objectives for modifiable risk factors. When these objectives are obtained, other measures such as encouraging PUFA and MUFA over SFA may help prevent micro and macroalbuminuria.

Table A5 presents a summary of the relevant studies found by the search strategy in relation to dietary fat. With the exception of the study by Cardenas et al., discussed above, these studies are either of short duration and thus provide little useful evidence for the role of dietary fat in the progression of CKD. Relevant details of the studies are provided in Table A12. In summary, there are insufficient reliable studies to support a recommendation in relation to the prevention and management of CKD in people with type 2 diabetes.

Protein restriction

Intake of protein in the usual range does not appear to be associated with the development of CKD. However, long-term effects of consuming >20% of energy as protein on development of CKD has not been determined. Although diets high in protein and low in carbohydrate may produce short-term weight loss and improved glycaemic control, it has not been established that weight loss is maintained in the long term. There have been few prospective controlled studies of low protein diets in people with type 2 diabetes and kidney disease. The studies that have been performed have generally been deficient in experimental design, in methods for measuring kidney function and/or in duration of follow-up. Furthermore, the level of compliance with a low protein diet has not always been assessed objectively by urinary urea nitrogen excretion. A particular criticism is that changes in the creatinine pool and creatinine intake seen in low protein diet studies render measurements of creatinine clearance or the reciprocal of serum creatinine unreliable for the assessment of GFR.

The objective of the systematic review was to assess the effects of dietary protein restriction on the progression of diabetic nephropathy in people with diabetes (type 1 and type 2 diabetes). The review identified 11 studies (9 RCTs and 2 before and after trials) where diet modifications were followed for at least 4 months. Before and after trials were
included as it was considered that people could act as their own controls. Of these studies 8 were of people with type 1 diabetes, one type 2 diabetes and two included both type 1 and type 2 diabetes. Overall the total number of participants in the trials was 585 with 263 being people with type 2 diabetes. Protein modified diets of all types lasting a minimum of 4 months were considered with protein intake ranging from 0.3 to 0.8 g/kg per day.

Overall protein restriction appeared to slow progression of CKD, but not by much on average. Individual variability suggests some may benefit more than others. Results of meta analysis imply that patients can delay dialysis by, on average around one or 2 months. Positive but non-significant correlation between improvement in GFR and level of protein restriction is evident. There were insufficient studies to recommend a level of protein intake. Furthermore, problems of non-compliance remain a significant issue. The review also considered different sources of protein (e.g. red meat, chicken, fish, vegetarian); however, relevant studies are of short duration only. The authors consider that the available information supports further research in this area. The number of studies that include people with type 2 diabetes are limited.

The study by Dussol et al.121 was the only other RCT identified that was not reviewed by Robertson et al.122 This 2 year single centre RCT of type 1 and type 2 diabetes indicated that the low-protein diet did not alter the course of GFR or of AER in people with diabetes with incipient or overt nephropathy.

Table A6 includes a summary of studies identified by the search strategy. The studies are characterized by being small and of short duration. Relevant details are provided below, however, as for dietary fat, there are insufficient reliable studies that provide evidence to support a recommendation in relation protein restriction in the prevention and management of CKD in people with type 2 diabetes.

**Restricted salt intake**

When considering the evidence related to salt intake and CKD in people with type 2 diabetes, the following points made based on a literature review for preparation of a Cochrane Protocol are noteworthy:122

- Dietary salt is important in BP control in both hypertensives and non-hypertensives (supported by meta-analyses) and therefore it may be protective in the development and progression of CKD.
- High dietary salt suppresses the renin-angiotensin system (RAS). Salt sensitivity in people with diabetes may be increased due to less responsive RAS. Low salt intake enhances high salt intake reduces the antiproteinuric effect of ACE inhibition.
- Urinary albumin excretion is reduced by lowering dietary salt.
- Changes in dietary salt may have a beneficial influence on TGF b production, affecting the progression of CKD.

Table A7 presents a summary of studies identified by the search strategy in relation to the assessment of the role of restricted salt intake. As for protein restriction the studies are small and of short duration. Details of the studies are included in Table A7; however, it is concluded that there are insufficient reliable studies that provide evidence to support a recommendation in relation to restriction of dietary salt and the prevention and management of CKD in people with type 2 diabetes.

**(v) Role of smoking cessation**

Smoking increases the risk of the development and progression of CKD in people with type 2 diabetes (Evidence Level II – Aetiology).

Interventional studies to assess the effects of smoking cessation have not been performed, but it has been calculated from the cause-specific, all-cause mortality data of the subjects screened for the Multiple Risk Factor Intervention Trial (MRFIT) that stopping smoking is the most (cost-) effective risk factor intervention in people with diabetes. Smoking cessation would prolong life by a mean of 4 years in a 45-year old man and by 3 years in a diabetic man, whereas aspirin and antihypertensive treatment would provide approximately 1 year of additional life expectancy.123 The following cohort studies summarized in the text below and in Table A15 have included assessment of renal outcomes.

Smoking has been found to be an independent risk factor for progression of AER in people with type 2 diabetes. In a prospective 9-year follow-up study of 108 people with type 2 diabetes and normal AER after a duration of diabetes of 9 years, there was an over-representation of smokers (55% vs 27%; P = 0.01) in people who progressed to micro- or macroalbuminuria versus those who did not progress.125

A number of prospective cohort studies were identified by the search strategy that have considered smoking in people with type 2 diabetes in relation to kidney function. Relevant details of these studies are summarized in Table A15. All of these studies showed an association between smoking and albuminuria. Only one cohort study was found which included an assessment of smoking as a risk factor for eGFR.126 Of the 7 prospective cohort studies identified only one small study reported no significant association between smoking and the progress of albuminuria.127

Chuaahirun & Wesson128 prospectively sought predictors of renal function decline in 33 people with type 2 diabetes, successfully targeting a mean BP goal of 92 mm Hg (about 125/75 mm Hg) with antihypertensives including ACEi. Initial plasma creatinine was <1.4 mg/dL, follow-up 64.0 ± 1.1 months. Regression analysis showed that smoking was the only examined parameter that significantly predicted renal function decline. In the 13 smokers, serum Cr increased from 1.05 ± 0.04 mg/dL to 1.78 ± 0.20 mg/dL although MAP was the same. The 20 non-smokers had a lesser Cr rise at 1.08 ± 0.03 mg/dL to 1.32 ± 0.04 mg/dL.

The 6 month prospective cohort studies concluded that cigarette smoking exacerbates renal injury despite adequate BP control with ACEi.129 Smoking cessation by those with
microalbuminuria was associated with amelioration of the progressive renal injury caused by continual smoking. The smaller but long-term study concluded that smoking and increased UAE are interrelated predictors of nephropathy progression and that smoking increases UAE in patients despite improved BP control and ACE inhibition.130

The prospective cohort study included 6513 people with type 2 diabetes with 5 year follow up period.131 Smoking was identified as an independent risk factor for established microalbuminuria and for the development of microalbuminuria. Similarly the retrospective cohort study,136 used logistic to show that smoking was the most important risk factor for progression of nephropathy. The authors concluded that quitting smoking should be part of the prevention therapy. The OR for smoking and development of microalbuminuria in a prospective cohort study of 930 people with type 2 diabetes and high cholesterol was 3.19 (95% CI: 1.02–9.96).132

The large cohort study of people with type 2 diabetes receiving dialysis treatment, concluded that dialysis patients with a history of smoking had the highest all cause mortality.133

In addition to the prospective cohort studies, a number of cross sectional studies were identified by the search strategy. These provide a lower level of evidence for the assessment of smoking as a risk factor for CKD. A total of 11 cross sectional studies have been identified the details of which are summarized in Table A8. All of the studies identified smoking to be associated with or to be an independent risk factor indicators of CKD.

SUMMARY OF THE EVIDENCE

- Given the strong association between type 2 diabetes and ESKD, strategies aimed at prevention of type 2 diabetes are also relevant to the prevention of CKD.
- Effective control of blood glucose has been shown to reduce the progression of CKD in people with type 2 diabetes. There is some evidence to suggest that HbA1c targets below that recommended for the management of type 2 diabetes may have beneficial outcomes with respect to CKD. However, the same evidence suggests that lower targets may have adverse outcomes or at best no effect on cardiovascular events, which are a key focus in the management of type 2 diabetes. Furthermore, lower blood glucose targets are also associated with an increase in serious hypoglycaemic events.
- Elevated BP is strongly associated with the development of albuminuria in people with type 2 diabetes. Management of elevated BP has been shown to influence the rate of progression of CKD as well as CVD and is thus a major focus of both prevention and management.
- There is evidence to indicate that antihypertensive agents that act on the renin-angiotensin system (i.e. ACEi and ARB) have a renoprotective effect over and above that resulting from the effect on BP. As a consequence use of these agents is favored in the treatment of elevated BP in type 2 diabetes and has also lead to their use in normotensive people with type 2 diabetes.
- Abnormal blood lipid profiles are strongly associated with the progression and severity of CKD in people with type 2 diabetes. Given the strong association between dyslipidaemia and CVD, management of blood lipid in type 2 diabetes is recommended irrespective of the presence of indicators of CKD. There is no evidence to suggest alternate management strategies are required for management of CKD. Nor is there evidence to show that lipid lowering prevents development or rate of progression of CKD in individuals with type 2 diabetes.
- There is limited evidence demonstrating a long-term effect of dietary interventions on the progression of CKD in type 2 diabetes. There is some evidence to suggest that protein restriction may affect the rate of progression of CKD, however, the clinical application of these interventions are questionable. Diet and lifestyle advice, however, important for the management of type 2 diabetes and CVD risk and thus likely to form a component of the overall management of an individual's risk profile irrespective of CKD.

WHAT DO THE OTHER GUIDELINES SAY?

KDQI: Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease, AJKD, Suppl 2. 49(2):S46, February 2007. (Note covers both type 1 and type 2 diabetes)
- Hyperglycemia, the defining feature of diabetes, is a fundamental cause of vascular target-organ complications, including kidney disease. Intensive treatment of hyperglycemia prevents DKD and may slow progression of established kidney disease.
- Target HbA1c for people with diabetes should be <7.0%, irrespective of the presence or absence of CKD.
- Clinicians should encourage the adoption of a healthy lifestyle in their patients; this includes sound nutrition, weight control, exercise and smoking cessation.
- In patients with type 2 diabetes, therapeutic lifestyle changes (diet, exercise, and weight loss, when appropriate) should be the initial interventions for hyperglycemia.
- Most people with diabetes and CKD have hypertension. Treatment of hypertension slows the progression of CKD.
- Hypertensive people with diabetes and CKD stages 1–4 should be treated with an ACE inhibitor or an ARB, usually in combination with a diuretic.
- Target BP in diabetes and CKD stages 1–4 should be <130/80 mm Hg.
- Normotensive people with diabetes and macroalbuminuria should be treated with an ACE inhibitor or an ARB.
- Treatment with an ACE inhibitor or an ARB may be considered in normotensive people with diabetes and microalbuminuria.
- Albuminuria reduction may be considered a treatment target in DKD.
• Dyslipidemia is common in people with diabetes and CKD. The risk of CVD is greatly increased in this population. People with diabetes and CKD should be treated according to current guidelines for high-risk groups.
• Target low-density lipoprotein cholesterol (LDL-C) in people with diabetes and CKD stages 1–4 should be <100 mg/dL; <70 mg/dL is a therapeutic option.
• People with diabetes, CKD stages 1–4, and LDL-C >100 mg/dL should be treated with a statin.
• Target dietary protein intake for people with diabetes and CKD stages 1–4 should be the recommended daily allowance (RDA) of 0.8 g/kg body weight per day.

**UK Renal Association:** No recommendation.

**Canadian Society of Nephrology:** No recommendation.

**European Best Practice Guidelines:** No recommendation.


- Start ACE inhibitors with the usual precautions and titrate to full dose in all individuals with confirmed raised creatinine.

**Guideline for management in primary and secondary care of chronic conditions. Type 2 diabetes: National Clinical Guidelines for Diagnosis, Prevention and Management of Chronic Kidney Disease in Type 2 Diabetes** was undertaken by CARI in collaboration with The Diabetes Unit, Menzies Centre for Health Policy at the University of Sydney.

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APPENDIX

Table A1 Definition of NHMRC grades of recommendation

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Body of evidence can be trusted to guide practice.</td>
</tr>
<tr>
<td>B</td>
<td>Body of evidence can be trusted to guide practice in most situations.</td>
</tr>
<tr>
<td>C</td>
<td>Body of evidence provides some support for recommendations(s) but care should be taken in its application.</td>
</tr>
<tr>
<td>D</td>
<td>Body of evidence is weak and recommendation must be applied with caution.</td>
</tr>
<tr>
<td>Study ID</td>
<td>Study description</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>Multicentre (215 across 20 countries) Type 2 diabetes diagnosed ≥ 30 years or older. Age ≥ 55 years at the start of the study. History of major microvascular disease or at least one other risk factor for cardiovascular disease.</td>
</tr>
<tr>
<td>Amador-Licona</td>
<td>Type 2 diabetes, incipient nephropathy, &lt;65, normotensive n = 51</td>
</tr>
<tr>
<td>Bakris et al.</td>
<td>RCT, open label, cardiac safety Multicentre, US Type 2 diabetes 40 to 80 years, no ACEi ARB beta-blockers or CCB n = 203</td>
</tr>
<tr>
<td>Davidson et al.</td>
<td>RCT, double blind, placebo controlled US Multicentre (38), US Hispanic and African American Type 2 diabetes, FPG ≥ 140 mg/dL and HbA1c ≥ 7.5%, monotherapy with sulfonyl urea for a minimum of 2 months n = 245.</td>
</tr>
<tr>
<td>De Jager et al.</td>
<td>RCT Netherlands – 3 centres Type 2 diabetes n = 345</td>
</tr>
<tr>
<td>Gasèe et al.</td>
<td>RCT Type 2 diabetes, microalbuminuria n = 160</td>
</tr>
</tbody>
</table>

This Guideline is OUT OF DATE & has been ARCHIVED
<table>
<thead>
<tr>
<th>Authors/Study</th>
<th>Design Type</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gambaro et al. (2002)</td>
<td>RCT, double blind, placebo</td>
<td>Suloflaxide vs Placebo</td>
<td>UAE</td>
<td>4</td>
</tr>
<tr>
<td>Hanefeld et al. (2004)</td>
<td>RCT, double blind</td>
<td>Pioglitazone plus SU vs Metformin plus SU</td>
<td>ACR</td>
<td>12</td>
</tr>
<tr>
<td>Johnston et al. (1998)</td>
<td>RCT</td>
<td>Miglitol vs Placebo</td>
<td>ACR</td>
<td>12</td>
</tr>
<tr>
<td>Johnston et al. (1998)</td>
<td>RCT</td>
<td>Miglitol vs Placebo</td>
<td>ACR</td>
<td>12</td>
</tr>
<tr>
<td>Lebovitz et al. (2001)</td>
<td>RCT</td>
<td>Rosiglitazone (2 or 4 mg/day) vs Placebo</td>
<td>UAE, ACR</td>
<td>7</td>
</tr>
<tr>
<td>Levin et al. (2000)</td>
<td>RCT</td>
<td>Intensive (HbA1c goal 7.1%) vs Standard (HbA1c goal 9.1%)</td>
<td>UAE, ACR</td>
<td>24</td>
</tr>
<tr>
<td>Matthews et al. (2005)</td>
<td>RCT, double blind</td>
<td>Metformin plus pioglitazone vs Metformin plus gliclazide</td>
<td>ACR</td>
<td>12</td>
</tr>
<tr>
<td>Ohkubo et al. (1995)</td>
<td>RCT</td>
<td>Multiple Insulin Treatment (MIT) vs Conventional Insulin Treatment (CIT)</td>
<td>UAE, ACR</td>
<td>60</td>
</tr>
<tr>
<td>Schernthaner et al. (2004)</td>
<td>RCT, double-blind</td>
<td>Pioglitazone vs Metformin</td>
<td>ACR</td>
<td>8</td>
</tr>
<tr>
<td>Shichiri et al. (2007)</td>
<td>RCT</td>
<td>MIT vs CIT</td>
<td>Albuminuria</td>
<td>96</td>
</tr>
</tbody>
</table>

Significantly reduced albuminuria in people with both type 1 and type 2 diabetes.

Clinically equivalent improvements in glycemic control. Pioglitazone plus SU resulted in a reduction of ACR. Overall differences from baseline ACR small (i.e. <15%).

Miglitol had 'just non-significant' reduction of ACR.

Minor reduction in ACR with miglitol.

ACR decreased significantly in both 2 and 4 mg/day RSG. Compared with an insignificant increase from baseline of the placebo. For subgroup with microalbuminuria, both doses of RSG gave reduction in ACR from baseline of around 40%. Only a small percentage of patients were receiving antihypertensive therapy – suggests effect is a result of improved glycemic control or a different effect of RSG.

Intensive glycaemic control retarded microalbuminuria, but may not lessen the progressive deterioration of glomerular function.

Mean ACR reduced by 10% in met plus piog group. Potential benefits are indicated.

Intensive glycaemic control can delay the onset and progression of nephropathy. The cumulative percentages of the development and progression in nephropathy after 6 years were 7.7% for the MIT group and 28.0% for the CIT group in the primary-prevention cohort (P = 0.032).

Pioglitazone – 19% decrease in ACR compared with 1% in metformin group. BP not statistically different between groups. Consistent with previous studies that troglitazone but not metformin or glibenclamide reduced urinary albumin excretion rate.

Intensive glycaemic control (MIT) – cumulative percentages of worsening in nephropathy were significant lower.
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study Description</th>
<th>Intervention</th>
<th>Outcome relevant to CKD</th>
<th>Follow up (months)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANCE (2007) and de Galan (2009)</td>
<td>RCT</td>
<td>Perindopril plus indapamide vs placebo</td>
<td>Worsening nephropathy i.e. development of macroalbuminuria, doubling of serum creatinine, need for renal replacement therapy or death due to kidney disease.</td>
<td>52 (median)</td>
<td>Active treatment mean reduction in SBP and DBP of 5.6 and 2.2 mm Hg respectively, compared with placebo. The relative risk of a major microvascular event was 7.9% in the active treatment group compared with 8.6% in the placebo group (non-significant). Active treatment was associated with a borderline significant reduction in macroalbuminuria and a significant reduction in the development of microalbuminuria with a relative risk reduction of 21% (95% CI: 15–30).</td>
</tr>
<tr>
<td>Agardh et al. (1996)</td>
<td>RCT, double blind</td>
<td>Lisinopril vs Nifedipine</td>
<td>UAE, creatinine clearance</td>
<td>12</td>
<td>Significantly more beneficial effect on UAE, however creatinine clearance did not change significantly with either treatment.</td>
</tr>
<tr>
<td>Ahmad et al. (1997)</td>
<td>RCT single blind</td>
<td>ACEi vs Placebo</td>
<td>AER</td>
<td>60</td>
<td>After 5 years ACEi treated patients experienced significantly less progression of microalbuminuria to clinical albuminuria.</td>
</tr>
<tr>
<td>Baba &amp; MIND Study Group (2001)</td>
<td>RCT – intent to treat analysis</td>
<td>ACEi vs CCB</td>
<td>UAE</td>
<td>24</td>
<td>CCB and ACEi had a similar effect on nephropathy in hypertensive people with type 2 diabetes without overt proteinuria.</td>
</tr>
<tr>
<td>Bakris et al. (2005)</td>
<td>RCT</td>
<td>Metoprolol (maintain ACEi/ARB) vs Carvedilol (maintain ACEi/ARB)</td>
<td>Albuminuria (spot ACR)</td>
<td>5 after reaching target BP</td>
<td>Pre-specified and post hoc analyses of the GEMINI trial. Greater reduction in microalbuminuria was observed for carvedilol. Those with normal albuminuria fewer progressed to micro or macroalbuminuria. This effect was not related to BP. Multivariate analysis in albuminuria change demonstrated only baseline urine ACR and treatment were significant predictors. In a separate analysis – the presence of metabolic syndrome at baseline corresponded with an OR of 2.68 (95% CI: 1.36–5.30) over the duration of the study.</td>
</tr>
<tr>
<td>Barnett et al. (2004)</td>
<td>RCT, double blind</td>
<td>ARB (telmisartan – 40 mg/day up to 80 mg/day for BP control) vs ACEi (enalapril – 10 mg/day up to 20 mg/day for BP control) (Additional hypertensive allowed as required)</td>
<td>GFR (calculated from serum creatinine), UAE</td>
<td>60</td>
<td>The difference in GFR between the ARB and the ACEi was 3.1 mL/min per 1.73 m² and was significant. The annual declines in GFR were 3.7 mL/min per 1.73 m² for the ARB and 3.3 mL/min per 1.73 m² for the ACEi. The results similar to GFR decline reported in IRMA-2, IDNT, and RENAAL studies. Compare to untreated type 2 diabetes annual decline of 10 mL/min per 1.73 m². Telmisartan was non-inferior to enalapril in providing long-term renoprotection. Does not necessarily apply to more advanced nephropathy – but support clinical equivalence of ARBs and ACEi in persons with conditions that place them at high risk for CV events.</td>
</tr>
<tr>
<td>Study Description</td>
<td>Study Design</td>
<td>Type 2 Diabetes</td>
<td>Hypertensive</td>
<td>n</td>
<td>Treatment</td>
</tr>
<tr>
<td>-------------------</td>
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<tr>
<td>Chan et al. (2000)</td>
<td>RCT</td>
<td>Type 2 diabetes</td>
<td>Hypertensive</td>
<td>102</td>
<td>ACEi vs CCB</td>
</tr>
<tr>
<td>Estacio (2006)</td>
<td>RCT</td>
<td>Type 2 diabetes</td>
<td>Normotensive</td>
<td>129</td>
<td>Intensive BP control (valsartan + other as required) vs Moderate BP control (placebo plus others as required)</td>
</tr>
<tr>
<td>ABCD Estacio et al. (2000)</td>
<td>RCT prospective</td>
<td>Type 2 diabetes</td>
<td>Normotensive (DBP between 80 and 89 mm/Hg, not receiving antihypertensives)</td>
<td>470</td>
<td>ACEi vs CCB</td>
</tr>
<tr>
<td>Fogari et al. (2000)</td>
<td>RCT</td>
<td>Type 2 diabetes (well controlled), 60 to 75 years, hypertensive</td>
<td>n = 147</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galle et al. (2008)</td>
<td>RCT</td>
<td>Multicentric</td>
<td>Type 2 diabetes with hypertension, proteinuria and serum creatinine ≤3.0 mg/dl</td>
<td>n = 855</td>
<td>Telmisartan vs valsartan, (additional non-ACEi/ARB antihypertensives permitted as necessary)</td>
</tr>
<tr>
<td>Hollenberg et al. (2007)</td>
<td>RCT</td>
<td>Multicentric</td>
<td>Type 2 diabetes with hypertension and albuminuria (AER 20–700 μg/min)</td>
<td>n = 391</td>
<td>valsartan 160 mg/day vs 320 mg/day vs 640 mg/day (add on medications for BP control as required)</td>
</tr>
<tr>
<td>Jermyn et al. (2004)</td>
<td>RCT prospective open, blinded endpoint</td>
<td>Type 2 diabetes</td>
<td>n = 77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacourciere et al. (1993)</td>
<td>RCT double blind</td>
<td>Caucasian (45 to 75 years)</td>
<td>Type 2 diabetes</td>
<td>n = 109</td>
<td>ACEi vs CCB</td>
</tr>
</tbody>
</table>

**Summary:**
- Treatment with ACEi associated with greater reduction in albuminuria than with CCB in the entire patient group and especially in those with microalbuminuria. In macromalbuminuria, rate of deterioration in renal function was also attenuated with ACEi.
- Blood pressure control of 138/86 or 138/78 mm/Hg with either ACEi or CCB as the initial hypertensive agent appeared to stabilize renal function in hypertensive people with type 2 diabetes without overt albuminuria over a 5 year period. More intensive BP control decreased all cause mortality. Intensive BP control in normotensive type 2 diabetes slowed progression to incident and overt nephropathy, decreased progression of retinopathy and diminished the incidence of stroke. Study indicates BP control as being the important factor rather than ACEi vs CCB.
- At 24 months UAE significantly decreased in both treatments. Creatinine clearance unaffected by ACEi, but increased by CCB.
- Mean reduction in proteinuria 33% (same for both treatments). Greater renoprotection seen among patients with better blood pressure control.
- High dose valsartan above 160 mg/day – greater reduction from baseline AER with greater number (12%) regressing to normoalbuminuria.
- Long-term control of blood pressure with ACEi or CCB stabilizes AER and attenuates GFR decline in proportion to MAP in non-hypertensive people with type 2 diabetes and microalbuminuria.
- Treatment with captopril decreased albuminuria and reduced the development of macroalbuminuria in those with persistent microalbuminuria.
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study description</th>
<th>Intervention</th>
<th>Outcome relevant to CKD</th>
<th>Follow up (months)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacourciere et al. (2000)&lt;sup&gt;19&lt;/sup&gt;</td>
<td>RCT prospective multicentre Canada Type 2 diabetes Hypertensive Early nephropathy n = 92</td>
<td>ACEi vs ARB</td>
<td>Renal biomarkers</td>
<td>12</td>
<td>Treatment with either ACEi or ARB significantly reduced UAE. Reduction in UAE with each treatment was similarly related to decrements in ABP. Rate of decline in GFR was similar in both treatment groups.</td>
</tr>
<tr>
<td>Lebovitz et al. (1994)&lt;sup&gt;21&lt;/sup&gt;</td>
<td>RCT, double blind Type 2 diabetes Hypertensive n = 121</td>
<td>ACEi vs Placebo</td>
<td>UAE, protein, urea, nitrogen, creatinine, GFR</td>
<td>36</td>
<td>ACEi preserved GFR better in patients with sub-clinical proteinuria at baseline better than other antihypertensives without ACEi. Smaller percentage proceeded to clinical albuminuria.</td>
</tr>
<tr>
<td>Marre et al. (2004)&lt;sup&gt;11&lt;/sup&gt;</td>
<td>RCT double blind, parallel group Multicentre, primary care, 16 European and North African Type 2 diabetes &gt;50 years Persistent microalbuminuria or proteinuria n = 4912</td>
<td>ACEi (vs placebo of usual treatment) vs Placebo</td>
<td>ESKD Secondary – UAE, urinary protein</td>
<td>72 (median)</td>
<td>Low dose ramipril once daily has no effect on CVD and kidney outcomes (type 2 diabetes and albuminuria) despite slight decrease in blood pressure and UAE.</td>
</tr>
<tr>
<td>Muirhead et al. (1999)&lt;sup&gt;10&lt;/sup&gt;</td>
<td>RCT, double blind, placebo Multicentre, Caucasian Type 2 diabetes, normotensive, microalbuminuria n = 122</td>
<td>ACEi ARB vs Placebo</td>
<td>UAE</td>
<td>12</td>
<td>The ARB slowed progressive rise of UAE compared with the ACEi.</td>
</tr>
<tr>
<td>Nakamura et al. (2002)&lt;sup&gt;16&lt;/sup&gt;</td>
<td>RCT, Type 2 diabetes, normotensive, microalbuminuria n = 60</td>
<td>ACEi ARB ACEi + ARB vs Placebo</td>
<td>UAE</td>
<td>18</td>
<td>Data suggest the combination of ARB/ACEi has an additive effect. On the reduction of microalbuminuria.</td>
</tr>
<tr>
<td>ONTARGET (2008)&lt;sup&gt;5&lt;/sup&gt; and Mann et al. (2008)&lt;sup&gt;99&lt;/sup&gt;</td>
<td>RCT Heart disease, included 38% with diabetes (type 1 and type 2) and 13% with microalbuminuria n = 25 000</td>
<td>ACEi (Ramipril) vs ARB (Telmisartan) vs Combination</td>
<td>eGFR, UAE Secondary- Renal impairment based on clinical investigators report Renal failure requiring dialysis.</td>
<td>56 (median)</td>
<td>No subgroup analysis has been presented including diabetes and microalbuminuria. Therefore not generalisable to type 2 diabetes. Overall, no significant differences noted between treatments except for renal impairment. Combination treatment resulted in lower ACR and lower onset of new microalbuminuria at the end of the follow up period, however greater rate of decline in eGFR.</td>
</tr>
<tr>
<td>Parving et al. (2001)&lt;sup&gt;12&lt;/sup&gt; and Brenner et al. (2001)&lt;sup&gt;13&lt;/sup&gt;</td>
<td>RCT, double blind Multicentre, multinational Type 2 diabetes n = 1513</td>
<td>ARB 150 mg/day ARB 300 mg/day vs Placebo (and conventional hypertensive treatment)</td>
<td>Serum creatinine doubling, ESKD, death, proteinuria, progression of kidney disease</td>
<td>40 (mean)</td>
<td>Losartan conferred significant renal benefits in type 2 diabetes with neuropathy and was generally well tolerated.</td>
</tr>
<tr>
<td>Parving et al. (2008)&lt;sup&gt;99&lt;/sup&gt;</td>
<td>RCT, double blind, placebo controlled Multicentre, multinational Type 2 diabetes, nephropathy. Excluded – known non-diabetic nephropathy; ACR &gt;300 mg/g, eGFR &lt;30 mL/min, chronic UTI, severe hypertension, cardiovascular disease within the previous 6 months. n = 599</td>
<td>Aliskiren (direct renin inhibitor) 150 mg for 3 months 300 mg for 3 months. vs Placebo Both – maximal losartan (100 mg) plus additional hypertensive to achieve optimal BP (i.e. target of 130/80 mm Hg).</td>
<td>Urinary ACR, eGFR.</td>
<td>6</td>
<td>No adjustment for changes from baseline in systolic or diastolic blood pressure. The aliskiren treatment reduced the mean urinary ACR by 18% compared with the placebo. The treatment group had a greater number of patients where albuminuria reductions were greater than 50% (24.7% vs 12.5%). The benefit of aliskiren appeared to be independent of differences in blood pressure.</td>
</tr>
</tbody>
</table>
This Guideline in OUT OF DATE & has been ARCHIVED
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study description</th>
<th>Intervention</th>
<th>Outcome relevant to CKD</th>
<th>Follow up (months)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>The HOPE Study Group (2000)&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Multicentre CVD or diabetes plus high CVD risk (98% type 2 diabetes) n = 3577</td>
<td>Ramipril vs Placebo</td>
<td>Albuminuria (secondary outcome)</td>
<td>54</td>
<td>Significant reduction in risk of overt nephropathy in ramipril treatment group. No difference in risk of new microalbuminuria.</td>
</tr>
<tr>
<td>Trevisan &amp; Tiengo (1995)&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Italy – multicentre Type 2 diabetes Normal or mild hypertension n = 122</td>
<td>ACEi vs Placebo</td>
<td>AER</td>
<td>6</td>
<td>Low dose ACEi can arrest the progressive rise in albuminuria in type 2 diabetes with persistent microalbuminuria.</td>
</tr>
<tr>
<td>UKPDS (1998)&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Multicentre UK 20 hospital clinics Type 2 diabetes Hypertensive n = 1148</td>
<td>ACEi vs Beta blocker</td>
<td>UAE</td>
<td>100 (median)</td>
<td>BP lowering with captopril was similarly effective in reducing the incidence of diabetic complications.</td>
</tr>
<tr>
<td>UKPDS (1998)&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Multicentre UK 20 hospital clinics Type 2 diabetes Hypertensive n = 1148</td>
<td>ACEi vs Beta blocker</td>
<td>UAE</td>
<td>100 (median)</td>
<td>Tight blood pressure control in patients with hypertension and type 2 diabetes achieves a clinically important reduction in the risk of deaths related to diabetes, complications related to diabetes, progression of diabetic retinopathy, and deterioration in visual acuity.</td>
</tr>
<tr>
<td>Viberti (2002)&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Type 2 diabetes with microalbuminuria n = 332</td>
<td>Valsartan vs amlodipine (additional agents used to meet BP target of 135/80 mm/Hg)</td>
<td>UAE</td>
<td>6</td>
<td>More patients reverted to normoalbuminuria with losartan 29.9% vs 14.5%). BP reductions were similar.</td>
</tr>
<tr>
<td>Yasuda et al. (2005)&lt;sup&gt;79&lt;/sup&gt;</td>
<td>Open-label parallel prospective RCT Japan Type 2 diabetes, Overt nephropathy (UAE between 300 and 3000 mg/day), 31 and 80 years (average 44), hypertensive n = 87</td>
<td>ARB – losartan 25 up to 100 mg/d CCB – amlodipine 2.5 up to 10 mg/d</td>
<td>UAE, ACR</td>
<td></td>
<td>ARB – UAE reduced from 810 mg/day to 570 mg/day (P &lt; 0.001). CCB no drop. Similar for ACR significant drop for ARB vs for CCB. No correlation between BP and UAE or ACR. Both ARB and CCB decreased BP to the same degree. Results suggest that regulating 24 h blood pressure alone is inadequate to reduce macroalbuminuria and additional effects of ARB (losartan) are crucial for antiproteinuric action.</td>
</tr>
</tbody>
</table>
### Table A4 Summary of studies relevant to the role of blood lipid profiles in CKD in individuals with type 2 diabetes

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study description</th>
<th>Intervention</th>
<th>Outcome (relevant to CKD)</th>
<th>Follow up (months)</th>
<th>Comments/conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ansquer et al. (2005)</td>
<td>113 RCT</td>
<td>Fenofibrate vs Placebo</td>
<td>UAE (secondary to main study)</td>
<td>38 (average)</td>
<td>Improvement in lipid profiles was associated with reduced progression from normal to microalbuminuria, higher regression and larger number of patients with unchanged albuminuria. The persistence of effect after treatment was not assessed.</td>
</tr>
<tr>
<td>Endo et al. (2006)</td>
<td>RCT, open study, Single centre, Japan Type 2 diabetes, clinical albuminuria (UAE &gt; 300 mg/g Cr). 102 defined as advanced cases on the basis of serum Cr &gt; 2.0 mg/dL.</td>
<td>Probucol (500 mg/day). Protein restriction diet. Blood glucose control to HbA1c (≤ 6.5%). Blood pressure control with CCB or alpha-blocker vs No treatment</td>
<td>UAE</td>
<td>36 (max)</td>
<td>Mean interval to initiation of haemodialysis was significantly longer in probucol patients. In advanced cases increases in serum creatinine and urinary protein were significantly suppressed. In advanced cases the haemodialysis-free rate was significantly higher in probucol group. Suggest probucol may suppress the progression of diabetic nephropathy.</td>
</tr>
<tr>
<td>Gaede et al. (2003)</td>
<td>Type 2 diabetes, microalbuminuria</td>
<td>Multifactorial intensive treatment vs Standard treatment</td>
<td>UAE</td>
<td>94 (mean)</td>
<td>Target driven long-term intensified treatment aimed at multiple risk factors reduced nephropathy by about 50%.</td>
</tr>
<tr>
<td>Keech et al. (2005)</td>
<td>RCT</td>
<td>Fenofibrate vs Placebo</td>
<td>UAE</td>
<td>60 (average)</td>
<td>Rate of progression to albuminuria was significantly reduced by fenofibrate and rate of regression was significantly increased. However, the differences in terms of numbers of patients was small (in the order of 2%).</td>
</tr>
<tr>
<td>Nishimura et al. (2001)</td>
<td>RCT, double blind Type 2 diabetes, normo and microalbuminuria</td>
<td>Cerivastatin vs Placebo</td>
<td>UAE</td>
<td>6</td>
<td>BP, HbA1c not significantly affected. Total chl and LDL chl reduced and concomitant decrease in UAE.</td>
</tr>
<tr>
<td>Sorof et al. (2006)</td>
<td>RCT, double blind, parallel group Multicentre, Sweden Type 2 diabetes, dyslipidaemia (fasting LDL-C &gt; 3.3 mmol/L) &gt; 18 years (actual 65 years average), exclusions included – nephrotic syndrome, severe renal dysfunction, uncontrolled hypertension.  n = 344</td>
<td>Rosuvastatin – 10 mg with titration up to 40 mg vs Atorvastatin – 10 mg with possible titration to 80 mg</td>
<td>UAE, GFR</td>
<td>4 months treatment</td>
<td>No change from baseline UAE for either treatment group, no significant change in GFR for either treatment group.</td>
</tr>
<tr>
<td>The Heart Protection Study (2003)</td>
<td>RCT Multicentre, UK Type 1 diabetes (10%) and type 2 diabetes (90%) 5963 – Diabetes 11307 – No diabetes</td>
<td>Simvastatin (40 mg/day) vs Placebo</td>
<td>Plasma creatinine, eGFR (retrospectively)</td>
<td>60</td>
<td>A reduction to simvastatin was associated with a significantly smaller fall in eGFR over the trial period (2.6 ml/min vs 6.7 ml/min) and was slightly better among those with diabetes.</td>
</tr>
</tbody>
</table>
Table A5  Summary of studies relevant to the assessment of the role of dietary fat

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study description</th>
<th>Intervention</th>
<th>Outcome (relevant to CKD)</th>
<th>Follow up (months)</th>
<th>Comments/conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barnard et al. (2006)</td>
<td>RCT Type 2 diabetes n = 99</td>
<td>Low Fat Vegan vs ADA diet</td>
<td>UAE</td>
<td>5</td>
<td>UAE greater reduction in vegan diet. Also improved glycaemic and lipid control.</td>
</tr>
<tr>
<td>Cardenas et al. (2004)</td>
<td>Prospective cohort Population based, multicentre Type 1 diabetes, type 2 diabetes n = 192</td>
<td></td>
<td>ACR</td>
<td>84</td>
<td>Normal albuminuria and nephropathy regression in well-controlled diabetes in people with long term diabetes duration are associated with greater PUFA consumption and lesser SFA consumption, specifically higher PUFA/SFA and MUFA/SFA ratios – the opposite pattern is associated with progression of neuropathy.</td>
</tr>
<tr>
<td>Nicholson et al. (1999)</td>
<td>RCT Type 2 diabetes n = 11</td>
<td>Low fat vegan vs Conventional low fat</td>
<td>UAE</td>
<td>3</td>
<td>No significant effect on UAE.</td>
</tr>
<tr>
<td>Nielsen et al. (1995)</td>
<td>Before and after non-randomized trial. Pseudo randomized trial. Type 2 diabetes, persistent microalbuminuria n = 10</td>
<td>Diet rich in MUF vs Recommended high carbohydrate diet</td>
<td>UAE</td>
<td>3 weeks</td>
<td>No effect on UAE. However a potential beneficial effect on LDL/HDL ratio was detected.</td>
</tr>
<tr>
<td>Shimizu et al. (1995)</td>
<td>Before and after non-randomized trial. Comparative study using patients grouped according to albuminuric status. Type 2 diabetes n = 115</td>
<td>Eicosapentaenoic acid ethyl (EPA-E) (present in cod liver oil)</td>
<td>ACR</td>
<td>12</td>
<td>Improved increased albumin excretion in type 2 diabetes with nephropathy and the effects were sustained at least 12 months after the start of treatment.</td>
</tr>
</tbody>
</table>

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### Table A6 Summary of studies relevant to the assessment of the role of protein restriction

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Intervention</th>
<th>Outcome (relevant to CKD)</th>
<th>Follow up (months)</th>
<th>Comments/conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barsotti et al. (1998)</td>
<td>RCT</td>
<td>Type 1 diabetes, type 2 diabetes with chronic renal failure n = 32</td>
<td>Low protein diet vs Free</td>
<td>Residual renal function</td>
<td>Study confirms the protective effect of low protein diets on nephropathy in the absence of any sign of protein malnutrition.</td>
</tr>
<tr>
<td>de Mello et al. (2006)</td>
<td>Before and after – random order of diet Crossover Type 2 diabetes, macroalbuminuric n = 17</td>
<td>Chicken (CD) Lactovegetarian Low Protein (LPD) vs Usual (UD)</td>
<td>GFR, UAE</td>
<td>4 wk for each diet</td>
<td>Withdrawing red meat from diet reduces UAE rate.</td>
</tr>
<tr>
<td>Dussol et al. (2005)</td>
<td>RCT (unblinded)</td>
<td>Single centre Type 1 diabetes and type 2 diabetes Incipient or overt nephropathy and mild renal failure, Strict BP control using ACEi or ARB n = 63</td>
<td>Low protein vs Usual protein (provided not greater than 0.8 g/kg per day)</td>
<td>GFR, UAE</td>
<td>24</td>
</tr>
<tr>
<td>Gross et al. (2002)</td>
<td>RCT, cross over Type 2 diabetes, normo or microalbuminuric n = 28</td>
<td>Low protein Chicken (no red meat) vs Usual diet</td>
<td>GFR, UAE</td>
<td>1/1 with 1 washout between</td>
<td>Normal albuminuric – both LP and chicken reduced UAE compared with normal diet. Microalbuminuric – only chicken reduced UAE compared with normal diet.</td>
</tr>
<tr>
<td>Meloni et al. (2004)</td>
<td>RCT, prospective Nephrology out patients, 80 with DKD (24 type 1 diabetes, 56 type 2 diabetes) n = 169</td>
<td>Low protein diet vs Free protein diet</td>
<td>Renal function</td>
<td>12</td>
<td>Significant slowing of the progression of kidney damage was only observed in non-diabetics.</td>
</tr>
<tr>
<td>Pijs et al. (1999)</td>
<td>RCT Type 2 diabetes, microalbuminuria n = 121</td>
<td>Counselling on protein restriction vs Usual advice</td>
<td>UAE</td>
<td>6 and 12</td>
<td>At 6 months experimental group had significantly lower protein intake and significantly lower UAE. At 12 months differences between groups had decreased.</td>
</tr>
<tr>
<td>Pijs et al. (2002)</td>
<td>RCT Type 2 diabetes, microalbuminuria n = 131</td>
<td>Dietary counselling – protein restriction vs Usual dietary advice</td>
<td>GFR, UAE</td>
<td>28 ± 7</td>
<td>Protein intake between groups at follow up at 6 months differed by only 0.08 g/kg per day. No difference by end of trial. Within the intervention group individuals with reduction of at least 0.2 mg/kg per day protein compared with controls with no change – showed no-significantly difference in GFR. Conclude that protein restriction is neither feasible or efficacious.</td>
</tr>
<tr>
<td>Pomerleau et al. (1993)</td>
<td>RCT, cross over Type 2 diabetes, normotensive n = 12</td>
<td>3 week moderate protein vs 3 week high protein</td>
<td>UAE, GFR, creatinine clearance</td>
<td>3 week/6 weeks</td>
<td>Moderate diet reduced the UAE, GFR, proteinuria and creatinine clearance without adversely affecting glycemic control. High protein diet induced small changes in renal function.</td>
</tr>
<tr>
<td>Teixeira et al. (2004)</td>
<td>Before and after cross over. Random order of interventions Type 2 diabetes n = 14</td>
<td>Isolated soy protein vs Casein</td>
<td>UAE</td>
<td>2/2 with 1 lead in and wash out</td>
<td>UAE significantly reduced in ISP compared with casein.</td>
</tr>
<tr>
<td>Wheeler et al. (2002)</td>
<td>RCT, cross over Type 2 diabetes, microalbuminuric n = 17</td>
<td>Plant based protein vs Animal based protein</td>
<td>GFR, UAE</td>
<td>1.5/1.5</td>
<td>No protein difference between GFR and UAE.</td>
</tr>
</tbody>
</table>
Table A7 Summary of studies relevant to the assessment of the role of restricted salt intake

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Intervention</th>
<th>Outcome (relevant to CKD)</th>
<th>Follow up (months)</th>
<th>Comments/conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Houlihan et al. (2000)149</td>
<td>RCT – w.r.t losartan and placebo Type 2 diabetes, hypertensive, microalbuminuric</td>
<td>Low sodium vs Normal sodium</td>
<td>UAE</td>
<td>1/1</td>
<td>Low salt amplified both anti-hypertensive and anti-proteinuric effects of losartan and no significant effect in the placebo.</td>
</tr>
<tr>
<td>Houlihan et al. (2002)150</td>
<td>RCT Type 2 diabetes, UAE 10–200 μg/day, hypertension</td>
<td>Losartan + low and high salt vs Placebo + low and high salt</td>
<td>TGF-beta (urine), UAE</td>
<td>1/1</td>
<td>The ARB not sodium restriction reduced urinary TGF-beta.</td>
</tr>
<tr>
<td>Houlihan et al. (2002)151</td>
<td>RCT Type 2 diabetes, UAE 10–200 μg/day</td>
<td>Losartan + low and high salt vs Placebo + low and high salt</td>
<td>ACR</td>
<td>1/1</td>
<td>ACR in losartan group decreased significantly with low salt. No significantly changes in placebo group. Demonstrated a low-sodium diet potentiates the antihypertensive and antiproteinuric effects of losartan.</td>
</tr>
<tr>
<td>Imanishi et al. (2001)152</td>
<td>Before and after cross over Type 2 diabetes – normo to macroalbuminuria, normal levels of serum creatinine</td>
<td>Sodium restricted diet vs Normal sodium diet.</td>
<td>UAE</td>
<td>1 week/1 week</td>
<td>Sodium sensitivity of blood pressure appears before hypertension and is related to albuminuria.</td>
</tr>
<tr>
<td>Vedovato et al. (2004)153</td>
<td>Before and after Type 2 diabetes Case – microalbuminuria Control – normoalbuminuria</td>
<td>Reduced salt vs High salt</td>
<td>UAE</td>
<td>1 week</td>
<td>High salt increased BP and UAE.</td>
</tr>
<tr>
<td>Yoshioka et al. (1998)154</td>
<td>Cross over randomization is limited to the order of diet Type 2 diabetes, normo to macroalbuminuria.</td>
<td>Sodium restricted diet vs Normal sodium diet.</td>
<td>Calculated IgG and albumin fractional clearances.</td>
<td>1 week/1 week</td>
<td>Charge selectivity is lost before size selectivity as diabetic nephropathy progresses.</td>
</tr>
</tbody>
</table>
### Table A8 Summary table of studies of smoking as risk factor for the development and progression of CKD in people with type 2 diabetes

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Outcome (relevant to CKD)</th>
<th>Follow up (months)</th>
<th>Comments/conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anan et al. (2007)</td>
<td>Cross sectional. Type 2 diabetes premenopausal women, n = 355 (Smokers/non-smokers)</td>
<td>UAE</td>
<td></td>
<td>UAE was independently associated with current smoking suggesting smoking as a risk factor for development of increased UAE.</td>
</tr>
<tr>
<td>Baggio et al. (2002)</td>
<td>Cross sectional Type 2 diabetes with abnormal AER, n = 96</td>
<td>UAE, GFR, GBM width</td>
<td></td>
<td>Smoking affects glomerular structure and function in type 2 diabetes and may be an important factor for the onset and progression of diabetic nephropathy.</td>
</tr>
<tr>
<td>Baines et al. (2005)</td>
<td>Prospective cohort Type 2 diabetes, high cholesterol, n = 930</td>
<td>Albuminuria</td>
<td>24</td>
<td>OR for smoker and development of microalbuminuria 3.19 (1.02–9.96).</td>
</tr>
<tr>
<td>Bruno et al. (1996)</td>
<td>Cross sectional Type 2 diabetes, n = 1574</td>
<td>UAE</td>
<td></td>
<td>Smoking habits are independently related to both micro and macroalbuminuria.</td>
</tr>
<tr>
<td>Cederholm et al. (2005)</td>
<td>Prospective cohort Type 2 diabetes and type 1 diabetes, 4097 (type 1 diabetes) 6513 (type 2 diabetes)</td>
<td>Albuminuria</td>
<td>60</td>
<td>Smoking identified as an independent risk factor for established microalbuminuria and for the development of microalbuminuria.</td>
</tr>
<tr>
<td>Chuahirun et al. (2003)</td>
<td>Prospective cohort Type 2 diabetes undergoing BP control, n = 84</td>
<td>Plasma creatinine, UAE</td>
<td>64</td>
<td>Smoking and increased UAE are interrelated predictors of nephropathy progression and smoking increases UAE in patients despite improved BP control and ACE inhibition.</td>
</tr>
<tr>
<td>Chuahirun et al. (2004)</td>
<td>Prospective cohort Type 2 diabetes with and without microalbuminuria, Smoking cessation in type 2 diabetes, n = 237</td>
<td>Urine excretion of TGFbeta, UAE</td>
<td>6</td>
<td>Cigarette smoking exacerbates renal injury despite BP control and ACEi – cessation by those with microalbuminuria ameliorates the progressive renal injury caused by continual smoking.</td>
</tr>
<tr>
<td>Corradi et al. (1993)</td>
<td>Cross sectional Type 2 diabetes, hypertensive, males, n = 90</td>
<td>UAE</td>
<td></td>
<td>The determinants of a decrease in UAE after lisinopril treatment were the duration of hypertension in non-smokers and daily tobacco consumption and duration of smoking in smokers. Smoking may be an independent determinant of microalbuminuria in hypertensive individuals.</td>
</tr>
<tr>
<td>Dean et al. (1994)</td>
<td>Cross sectional Type 2 diabetes, normotensive, n = 87</td>
<td>UAE</td>
<td></td>
<td>Relationship if any between smoking and UAE not stated in abstract.</td>
</tr>
<tr>
<td>Study ID</td>
<td>Study design</td>
<td>Outcome (relevant to CKD)</td>
<td>Follow up (months)</td>
<td>Comments/conclusions</td>
</tr>
<tr>
<td>----------</td>
<td>--------------</td>
<td>---------------------------</td>
<td>--------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Forsblom et al. (1998)</td>
<td>Retrospective cohort Type 2 diabetes</td>
<td>UAE</td>
<td>108</td>
<td>There was an over-representation of smokers (55% vs 27%; ( P = 0.01 )) in people who progressed to micro- or macroalbuminuria vs those who did not progress.</td>
</tr>
<tr>
<td>Gambaro et al. (2001)</td>
<td>Retrospective cohort Italy Type 2 diabetes</td>
<td>AER, serum creatinine</td>
<td>36</td>
<td>Logistic regression – smoking was the most important risk factor for progression of nephropathy. Quitting smoking should be part of the prevention therapy.</td>
</tr>
<tr>
<td>Gatling et al. (1988)</td>
<td>Cross sectional Type 2 diabetes</td>
<td>UAE, ACR</td>
<td></td>
<td>Significant association found between UAE and smoking category.</td>
</tr>
<tr>
<td>Ikeda et al. (1997)</td>
<td>Cross sectional Type 2 diabetes – men</td>
<td>ACR</td>
<td></td>
<td>OR for the prevalence of micro/macralbuminuria was significantly higher for smokers than ex smokers.</td>
</tr>
<tr>
<td>Nilsson et al. (2004)</td>
<td>Cross sectional Type 1 diabetes and type 2 diabetes Hospitals, primary health care</td>
<td>Albuminuria</td>
<td></td>
<td>Smoking was associated with poor glycaemic control and microalbuminuria.</td>
</tr>
<tr>
<td>Pijls et al. (2001)</td>
<td>Cross sectional Type 2 diabetes – primary care patients</td>
<td>ACR</td>
<td></td>
<td>Smoking independently associated with ACR.</td>
</tr>
<tr>
<td>Savage et al. (1995)</td>
<td>Cross sectional Type 2 diabetes with appropriate BP control</td>
<td>UAE</td>
<td></td>
<td>The most significant predictors of micro and macroalbuminuria were systolic hypertension, BMI, HDL, insulin use and smoking pack years.</td>
</tr>
<tr>
<td>Smulders et al. (1997)</td>
<td>Prospective cohort Type 2 diabetes with microalbuminuria</td>
<td>ACR</td>
<td>24</td>
<td>Smoking was not a significant predictor of the progress of albuminuria.</td>
</tr>
<tr>
<td>Thomas et al. (2006)</td>
<td>Cross section Type 2 diabetes Chinese males</td>
<td>ACR</td>
<td></td>
<td>ACR elevated in smokers. Smoking was associated with a more adverse metabolic profile and peripheral vascular disease. Male smokers compared with never smokers had lower HDL-cholesterol levels (1.12 ± 0.31 vs 1.20 ± 0.30 mmol/L, ( P = 0.006 )), and elevated albumin-to-creatinine ratio (3.57 (2.68–4.75) vs 2.47 (1.99–3.05) mg/mmol, ( P = 0.006 )).</td>
</tr>
</tbody>
</table>