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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 individualized 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,[1] 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[2] 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.[3] BP control modulates the progression not only of microangiopathy (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.[4] The large observational WESDR study[5] indicated an exponential relationship between worsening glycaemic control and the incidence of nephropathy as well as retinopathy and neuropathy.

The UKPDS has 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%.[6] These findings are supported by a study of intensified glycaemic control in non-obese Japanese subjects with type 2 diabetes.[7] In the UKPDS, there was no significant reduction in the risk of progression from microalbuminuria to proteinuria with intensive blood glucose control.[8]

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.[9] 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 the progression from normoalbuminuria to microalbuminuria or overt kidney disease[6] and from normo- or microalbuminuria to overt kidney disease.[7] 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).[10]

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.[11] While the AHA review is focused on cardiovascular events, the statement is relevant to the consideration of the management of CKD given the strong association between CKD and CVD in people with type 2 diabetes. 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 microvascular or macrovascular complications, or extensive comorbid conditions . . .*'. Thus individualized glycaemic goals other than the general goal of <7% HbA1c may be appropriate for some patients.[11]

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.[12,13] 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.[12,14,15] 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).[16,17] There are trials indicating that ACEi exert cardioprotective effects in addition to lowering of BP, even in normotensive people.[18] Renoprotection has been demonstrated for ARB's in two large studies.[19,20] The existence of a specific renoprotective effect of ACE inhibition in people with type 2 diabetes was not confirmed in the UKPDS[8] 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 equihypotensive doses.

Proteinuria is a weaker basis for identifying renoprotective treatments than a reduction in the rate of decline of GFR.[21]

Several studies have documented the efficacy of antihypertensive therapy in lowering AER in both hypertensive[22–24] and normotensive[25] 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] HDL cholesterol levels in people with type 2 diabetes have been reported to be normal in association with overt diabetic kidney disease[28] whereas decreased HDL cholesterol levels have been reported in association with microalbuminuria.[27] 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 with normoalbuminuria.[31] Apolipoprotein (a) levels have been related to the rates of progression of albuminuria,[32] however, others have not confirmed these findings in people with diabetes and CKD.[28]

There is evidence to support the hypothesis that changes in lipid profiles 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.[33]

Primary or secondary intervention with statins in hypercholesterolaemic people has shown similar cardioprotective effects in diabetic and non-diabetic subjects.[34–36] 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.[34]

Observational studies have shown that dyslipidaemia interacts with other risk factors to increase cardiovascular risk.[37,38] Microalbuminuria is a risk factor for CVD as well as overt kidney disease in people with type 2 diabetes,[39,40] and dyslipidaemia is more common in microalbuminuric than normoalbuminuric people with type 2 diabetes.[27] 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. Nearly all studies have shown a correlation between serum cholesterol concentration and progression of CKD.[41,42] 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.[43] 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 outcomes[27,37,38] (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.[44] 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.*).[45] 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 I – 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 has any effect on the development of ESKD. The most relevant study is the UKPDS from which further information may come from long-term follow up.
- Evidence from the VA Cooperative study[46] indicate that intensified glycaemic control has little if any effect on the rate of GFR decline.
- Three studies were identified in relation to improved glycaemic control and the development of clinical proteinuria and microalbuminuria, namely the Kumamoto study,[47] UKPDS[6] 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. The VA study examined as a sub group the effect of glycaemic control in those with microalbuminuria, however, the study was relatively small and of limited duration.

The systematic review by Richter *et al.*[48] assessed the effects of pioglitazone in the treatment of type 2 diabetes. The relevant outcomes for these guidelines are mortality (kidney disease) and morbidity (nephropathy). Overall the evidence for a positive patient-oriented outcome for the use of pioglitazone was considered not to be convincing. Three studies were identified that included endpoints relevant to the assessment of kidney disease namely, Hanefeld *et al.*,[49] Matthews *et al.*[50] and Schernthaner *et al.*[51] The Hanefeld *et al.*[49] study compared pioglitazone plus sulfonyl urea with metformin plus sulphonyl urea over 12 months in 649 people with type 2 diabetes with a history of poorly controlled diabetes. The pioglitazone treatment resulted in a 15% reduction in the urinary ACR compared with a 2% increase in the metformin group with both treatments giving clinically equivalent glycaemic control. The Matthews *et al.*[50] study compared pioglitazone plus metformin with glicazide plus metformin in 630 people with poorly managed type 2 diabetes over 12 months. The pioglitazone treatment gave a 10% reduction in the ACR compared with a 6% increase in the glicazide group with no significant difference in HbA1c.

The Schernthaner *et al.*[51] study included 1199 people with type 2 diabetes inadequately treated by diet alone (HbA between 7.5% and 11%) and aged between 35–75 years from 167 centres located across 11 European countries. Pioglitazone treatment resulted in a 19% decrease in ACR compared with 1% in the metformin group. Blood pressure was not statistically different between groups. The results were considered to be consistent with previous studies that troglitazone but not metformin or glibenclamide reduced urinary albumin excretion rate.

The systematic review by Richter *et al.*[52] assessed the effects of rosiglitazone in the treatment of type 2 diabetes. The study by Lebovitz *et al.*[53] was identified as including an outcome measure relevant to kidney disease. The study examined the use of rosiglitazone as a monotherapy in 493 people with type 2 diabetes over a 7 month period. Urinary albumin excretion was decreased significantly compared with the placebo. For the subgroup of people with microalbuminuria, both doses of rosiglitazone gave a reduction in ACR from baseline of around 40%. Only a small percentage of patients were receiving antihypertensive therapy which the authors suggested indicates the effect to be a result of improved glycaemic control or a different effect of rosiglitazone. The measurement of urinary ACR was a secondary prospective outcome of the study of 203 people with type 2 diabetes by Bakris *et al.*[54] comparing rosiglitazone with glyburide in a randomized controlled trial. RSG significantly reduced ACR from baseline and strongly correlated with changes in blood pressure and little relation to changes in FPG or HbA1c. Given similar levels of glucose control, the mean reduction in ACR was greater for rosiglitazone than glyburide and a greater proportion of participants in the RSG treatment group with baseline microalbuminuria achieved normalization of the ACR by the 12 months. However, the power of the study in relation to the secondary outcome ACR was low and the differences in between the groups was not statistically significant, thus the suggested potential benefit of RSG cannot be determined from this study.

The objectives of the systematic review by Saenz *et al.*[55] were to assess the effects of metformin monotherapy on mortality, morbidity, quality of life, glycaemic control, body weight, lipid levels, blood pressure, insulinaemia and albuminuria in people with type 2 diabetes. The review 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.*,[55] the HOME trial[57] 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[58] 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 microalbuminuria and 3–4% had macroalbuminuria. 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 macroalbuminuria and new onset microalbuminuria (0.91 CI: 0.85–0.98). A trend towards a reduction in the need for renal replacement therapy was also noted. The study concluded 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.[58]

A significantly higher number of severe hypoglycaemic episodes were recorded in the intensive group compared with the standard group (2.7% *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 120 per 100 people in the intensively controlled group compared with 90 per 100 people in the standard control group. Overall the main benefit identified by the ADVANCE study was a one fifth reduction in kidney complications in particular the development of macroalbuminuria.[58]

A US study of Hispanic and African Americans assessed the efficacy of rosiglitazone in a high risk (based on ethnicity) type 2 diabetes group.[59] The urinary ACR was collected as 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 sulphonyl urea 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 treatments was also noted.

US studies on the long-term effectiveness of miglitol have been conducted by Johnston *et al.* for 385 Hispanic Americans with type 2 diabetes and 345 African Americans with type 2 diabetes.[60,61] ACR was included as an 'efficacy parameter' in both studies. The duration of the studies was 12 months. Miglotol treatment was associated with a minor reduction in ACR in both studies.

The short-term trial of 223 mixed type 1 and type 2 diabetes by,[62] 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[63] 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 intensive treatment of blood glucose. 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 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 I – 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.[4,16,17,64]

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 ($n = 758$) or less tight control ($n = 390$), 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 ($P < 0.01$).[8] In this study, captopril and atenolol were used in equihypotensive doses and each drug attenuated the development of microvascular complications to a similar degree over 10 years.[65]

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 normotensive and normoalbuminuric (based on dipstick) at the start of the study.[66] 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[67] by Galan *et al.*[68] 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[4] 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 I – 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.*[4] 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 UKPDS study the prevalence of ESKD was less than 2% with a relative risk for tight control of 0.58 (95% CI: 0.015–2.21) with similar results for death from kidney failure.[8]

The HOPE Study demonstrated that there was a non-significant relative risk reduction for the requirement for renal dialysis among people treated with ramipril.[18]

As a consequence of the above two trials, Newman *et al.*[4] concluded that there was no evidence of a beneficial effect of antihypertensive therapy on the development of ESKD.

2. Antihypertensive therapy and change in GFR in people with type 2 diabetes and microalbuminuria.

Three placebo controlled trials in normotensive people were identified.[14,25,69] Newman *et al.*[4] considers the data are inconclusive. No appropriate trials comparing different antihypertensive agents and intensive *versus* moderate BP control were identified. However, later analysis of the ABCD trial[70] indicated a significant effect of intensive therapy on the progression from microalbuminuria to clinical proteinuria, however, there was no change in creatinine clearance and no difference between ACEi and CCB.

Two placebo controlled trials in hypertensive people were identified.[71,72] Newman *et al.*[4] concludes that the limited evidence indicates kidney function to remain stable in hypertensive people with type 2 diabetes with microalbuminuria treated with ACEi compared with a decline in the placebo group (36 month follow up). The Parving *et al.*[72] study also indicated a significant reduction in the rate of progression to clinical proteinuria with ARB treatment however, this was not associated with a significant decline in creatinine clearance.

Two trials were identified that compared intensive and moderate BP control in hypertensive people with type 2 diabetes with microalbuminuria.[8,73] However, the UKPDS study was unable to differentiate between normoalbuminuric and microalbuminuric subgroups. In the large ABCD study no significant difference in creatinine clearance was found in either normoalbuminuric or microalbuminuric subgroups.

Three appropriate trials were identified comparing different antihypertensive agents in hypertensive people with type 2 diabetes with microalbuminuria.[73–75] None of these trials showed significant differences in GFR or creatinine clearance.

3. Antihypertensive therapy and development of clinical proteinuria in people with type 2 diabetes and microalbuminuria.

Three randomized placebo-controlled trials in normotensive people with type 2 diabetes with microalbuminuria were identified.[14,25,69] 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.[4]

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.[73]

Only one available placebo controlled study was identified for hypertensive people with type 2 diabetes with microalbuminuria.[71] 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.[73] Individuals were randomized to either ACEi enalapril or the CCB antagonist nisoldipine. The percentage of people who progressed from microalbuminuria to clinical proteinuria was not significantly different between the treatment groups. Newman *et al.*[4] noted that the results supported the observations from the UKPDS of progression to clinical proteinuria among microalbuminuric and normoalbuminuric people 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.[12,74–76] The trials all included an ACEi treatment compared with either a CCB antagonist or b 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.[16,17] The objectives of the review by Strippoli *et al.*[16] were to evaluate the effects of antihypertensive agents in people with diabetes and normoalbuminuria. While the objectives of the review by Strippoli *et al.*[17] were to evaluate the benefits and harms of ACEi and ARBs in preventing the progression of CKD. Both reviews included studies of both type 1 and type 2 diabetes and Strippoli *et al.*[17] 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 and, kidney function and type of diabetes. However, there is insufficient data to be confident that these factors are not important effects modifiers.[16]
- 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.[17]

In relation to type 2 diabetes the following outcomes are of note:[16,17]

- 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.[18]
  - – 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 or macroalbuminuria
  - – 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 type 2 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.[17] 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.[64] 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 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.[4,16,17] Only two studies that considered the effect of BP targets within the normotensive range in people with type 2 diabetes were identified.[70,73]

Kaiser *et al.*[64] 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 any 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.[77] 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.*[78] 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 or 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 is reported as arithmetic means (presumed to reflect the skewing of the 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's in 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 amlodipine, used in equihypotensive doses.[19] 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.[72] 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.[67] 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.[68] Renoprotective effects of blood pressuring 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 (amlidopine) on the UAE and ACR of 87 hypertensive type 2 diabetes Japanese patients with persistent macroalbuminuria.[79] 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.[80–83] While the study summarized in Table A10 has examined both ACEi and ARBs either alone of in combination.[84] A number of studies have specifically assessed the ARB valsartan.[85–90] The details and findings of these studies are summarized in Table A3 below. 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.[91,92] 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 70 people with type 2 diabetes in the Netherlands.[93] The people with type 2 diabetes were Caucasian with an average age in the randomized treatment groups of 60–63, hypertensive and either normoalbuminuric or early microalbuminuric (UAE < 100 mg/day). The trial was of 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.[17]

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.[94] 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).[95] 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 only baseline urine ACR and treatment were significant predictors of changes in albuminuria. 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.

The DETAIL study involved 250 people with type 2 diabetes with mild to moderate hypertension and eGFR ≥ 70 mL/min per 1.73 m^2 from 6 European countries.[96] The study compared an 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 m^2 and was insignificant. The mean annual declines in eGFR were 3.7 mL/min per 1.73 m^2 for the ARB and 3.3 mL/min per 1.73 m^2 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 10 mL/min per 1.73 m^2. Telmisartan was concluded to be not 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.[97] 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,[98] 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).[99] 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 a 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 could 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 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 compared 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 incontrovertible evidence that lowering of LDL cholesterol in individuals with type 2 diabetes is associated with reduced cardiovascular events and mortality.[44] 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[108] subgroup analysis for participants with diabetes, allocation to simvastatin (40 mg/day) significantly decreased the rise in SCr values. Subjects were excluded from entering the trial if their serum creatinine was above 200 μmol/L, reflecting that those with late stage CKD were not studied.
- In the Greek atorvastatin and coronary heart disease evaluation (GREACE) treatment with atorvastatin was associated with a significant decrease in urinary albumin excretion, however, the study did not include separate analysis for type 2 diabetes.[109]
- The Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) showed beneficial effects on GFR in individuals with type diabetes, however, the study did not separately identify or assess type 2 diabetes.[110]

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 two statin treatments (rosuvastatin and atorvastatin) over a 16 week treatment period.[111] 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 trial was 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.*[112] 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 Diabetes Atherosclerosis Intervention Study (DAIS), examined the effects of fenofibrate treatment (*vs* placebo) in 314 people with type 2 diabetes (Canada and Europe) with mild to moderate lipid abnormalities and normo to microalbuminuria.[113] The study length was a minimum of 3 years. Regression of albuminuria (defined as micro to normoalbuminuria 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 (8%) compared with the placebo group (18%). Significantly 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.*[114] and Radermecker & Scheen[115] 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.[116]

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 probucol and glitazones. However, their other primary actions, on oxidative stress and glucose lowering make it impossible to gauge the contribution of lipid lowering to their efficacy. Currently available glitazones do vary in their impact on lipid profiles, indicating sub-class variations in effect. Nonetheless, both agents appear to have effects on the development and progression of kidney disease in individuals with type 2 diabetes.

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).[117] 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 anti-oxidative effect of the drug.

The multifactorial intensive treatment of the STENO2 reduced the risk of nephropathy by 50%.[63] 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 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.[118] 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 normoalbuminuria. 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 greater. An opposite pattern was observed for progression of nephropathy.

The authors note that the findings of the study 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.[118]

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.*[118] discussed above, the 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.[119]

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).[120] 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.*[120] 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 normotensives (supported by meta-analyses) and therefore expect that this could 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 and 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 10-year 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.[123,124] 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]

Chuahirun & Wesson[128] 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 +/ to 0.08 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,[126] 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 progress of CKD in type 2 diabetes. There is some evidence to suggest that protein restriction may affect the rate of progress of CKD, however, the clinical application of these interventions are questionable. Diet and lifestyle are, 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 individuals risk profile irrespective of CKD.
- In observational studies, smoking has been identified as a independent risk factor in the progression of CKD, and given the role of smoking as a strong risk factor in a range of other outcomes including CVD, an individuals smoking cessation is an important recommendation irrespective of CKD.

WHAT DO THE OTHER GUIDELINES SAY?

KDOQI: 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.

NICE Guidelines: National Collaborating Centre for Chronic Conditions. type 2 diabetes: national clinical guideline for management in primary and secondary care (update). London: Royal College of Physicians, 2008.

• Start ACE inhibitors with the usual precautions and titrate to full dose in all individuals with confirmed raised albumin excretion rate (>2.5 mg/mmol for men, >3.5 mg/mmol for women).
• Substitute an angiotensin II-receptor antagonist for an ACE inhibitor for a person with an abnormal albumin : creatinine ratio if an ACE inhibitor is poorly tolerated.
• For a person with an abnormal albumin : creatinine ratio, maintain BP below 130/80 mm Hg.

American Diabetes Association: Standards of Medical Care in Diabetes – 2008. Diabetes Care: 31, S1 JANUARY 2008. (Note covers both type 1 and type 2 diabetes)

• To reduce the risk or slow the progression of nephropathy, optimize glucose control.
• To reduce the risk or slow the progression of nephropathy, optimize BP control.
• In the treatment of the nonpregnant patient with micro- or macroalbuminuria, either ACE inhibitors or ARBs should be used.
• In patients with type 2 diabetes, hypertension, and microalbuminuria, both ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria.
• In patients with type 2 diabetes, hypertension, macroalbuminuria, and renal insufficiency (serum creatinine – 1.5 mg/dL), ARBs have been shown to delay the progression of nephropathy.
• If one class is not tolerated, the other should be substituted.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

No recommendation.

CONFLICT OF INTEREST

Non-identified.

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REFERENCES

1. Retnakaran R, Cull CA, Thorne KI *et al.* Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. *Diabetes*. 2006; **55**: 1832–39.
2. Hanai K, Babazono T, Iwamoto Y. Renal manifestations of metabolic syndrome in type 2 diabetes. *Diabetes. Res. Clin. Prac.* 2008; **79**: 318–24.
3. Mogensen CE, Christensen CK, Vittinghus E. The stages in diabetic renal disease. With emphasis on the stage of incipient diabetic nephropathy. *Diabetes*. 1983; **32** (Suppl 2): 64–78.
4. Newman DJ, Mattock MB, Dawnay AB *et al.* Systematic review on urine albumin testing for early detection of diabetic complications. *Health. Technology. Assessment*. 2005; **9**: iii–vi.xiii–163.
5. Klein R, Klein BE, Moss SE. Relation of glycemic control to diabetic microvascular complications in diabetes mellitus. *Ann. Intern. Med.* 1996; **124**: 90–6.
6. UKPDS. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998; **352**: 837–53.
7. Ohkubo Y, Kishikawa H, Araki E *et al.* Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: A randomized prospective 6-year study. *Diabetes. Res. Clin. Prac.* 1995; **28**: 103–17.
8. UKPDS. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ*. 1998; **317**: 703–13.
9. Tapp RJ, Shaw JE, Zimmet PZ *et al.* Albuminuria is evident in the early stages of diabetes onset: Results from the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). *Am. J. Kid. Dis.* 2004; **44**: 792–98.
10. Morioka T, Emoto M, Tabata T *et al.* Glycemic control is a predictor of survival for diabetic patients on hemodialysis. *Diabetes. Care*. 2001; **24**: 909–13.
11. Skyler JS, Bergenstal R, Bonow RO *et al.* Intensive glycemic control and the prevention of cardiovascular events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials: A position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Circulation*. 2009; **119**: 351–57.
12. Estacio RO, Schrier RW. Antihypertensive therapy in type 2 diabetes: Implications of the appropriate blood pressure control in diabetes (ABCD) trial. *Am. J. Cardiol.* 1998; **82**: 9R–14R.
13. Tatti P, Pahor M, Byington RP *et al.* Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. *Diabetes. Care*. 1998; **21**: 597–603.
14. Ravid M, Savin H, Jutrin I *et al.* Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine

and on proteinuria in normotensive type II diabetic patients. *Ann. Intern. Med.* 1993; **118**: 577–81.
15. Ravid M, Lang R, Rachmani R *et al.* Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus. A 7-year follow-up study. *Arch. Intern. Med.* 1996; **156**: 286–89.
16. Strippoli GF, Craig M, Craig JC. Antihypertensive agents for preventing diabetic kidney disease. *Cochrane. Database. Syst. Rev.* 2005; **4**: CD004136.
17. Strippoli GF, Bonifati C, Craig M *et al.* Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. *Cochrane. Database. Syst. Rev.* 2006; **4**: CD006257.
18. The HOPE Study Group. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. *Lancet.* 2000; **355**: 253–59.
19. Brenner BM, Cooper ME, de Zeeuw D *et al.* Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N. Eng. J. Med.* 2001; **345**: 861–69.
20. Lewis EJ, Hunsicker LG, Clarke WR *et al.* Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N. Eng. J. Med.* 2001; **345**: 851–60.
21. Mogensen CE. Microalbuminuria, blood pressure and diabetic renal disease: Origin and development of ideas. *Diabetologia.* 1999; **42**: 263–85.
22. Chan JC, Cockram CS, Nicholls MG *et al.* Comparison of enalapril and nifedipine in treating non-insulin dependent diabetes associated with hypertension: One year analysis. *BMJ.* 1992; **305**: 981–85.
23. Ferder L, Daccordi H, Martello M *et al.* Angiotensin converting enzyme inhibitors versus calcium antagonists in the treatment of diabetic hypertensive patients. *Hypertension.* 1992; **19**: 237–42.
24. Slataper R, Vicknair N, Sadler R *et al.* Comparative effects of different antihypertensive treatments on progression of diabetic renal disease. *Arch. Intern. Med.* 1993; **153**: 973–80.
25. Ahmad J, Siddiqui MA, Ahmad H. Effective postponement of diabetic nephropathy with enalapril in normotensive type 2 diabetic patients with microalbuminuria. *Diabetes. Care.* 1997; **20**: 1576–81.
26. Bruno G, Cavallo-Perin P, Bargero G *et al.* Association of fibrinogen with glycemic control and albumin excretion rate in patients with non-insulin-dependent diabetes mellitus. *Ann. Intern. Med.* 1996; **125**: 653–57.
27. Mattock MB, Morrish NJ, Viberti G *et al.* Prospective study of microalbuminuria as predictor of mortality in NIDDM. *Diabetes.* 1992; **41**: 736–41.
28. Nielsen S, Schmitz O, Moller N *et al.* Renal function and insulin sensitivity during simvastatin treatment in type 2 (non-insulin-dependent) diabetic patients with microalbuminuria. *Diabetologia.* 1993; **36**: 1079–86.
29. Lahdenpera S, Syvanne M, Kahri J *et al.* Regulation of low-density lipoprotein particle size distribution in NIDDM and coronary disease: Importance of serum triglycerides. *Diabetologia.* 1996; **39**: 453–61.
30. Groop L, Ekstrand A, Forsblom C *et al.* Insulin resistance, hypertension and microalbuminuria in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia.* 1993; **36**: 642–47.
31. Jenkins AJ, Steele JS, Janus ED *et al.* Plasma apolipoprotein (a) is increased in type 2 (non-insulin-dependent) diabetic patients with microalbuminuria. *Diabetologia.* 1992; **35**: 1055–59.
32. Jerums G, Allen TJ, Tsalamandris C *et al.* Relationship of progressively increasing albuminuria to apoprotein(a) and blood pressure in type 2 (non-insulin-dependent) and type 1 (insulin-dependent) diabetic patients. *Diabetologia.* 1993; **36**: 1037–44.
33. Keane WF, Kasiske BL, O'Donnell MP. Lipids and progressive glomerulosclerosis. A model analogous to atherosclerosis. *Am. J. Nephrol.* 1988; **8**: 261–71.
34. Pyorala K, Pedersen TR, Kjekshus J *et al.* Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study. *Diabetes. Care.* 1997; **20**: 614–20.
35. Sacks FM, Pfeffer MA, Moye LA *et al.* The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N. Eng. J. Med.* 1996; **335**: 1001–09.
36. Shepherd J, Cobbe SM, Ford I *et al.* Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N. Eng. J. Med.* 1995; **333**: 1301–07.
37. Kannel WB. Cardioprotection and antihypertensive therapy: The key importance of addressing the associated coronary risk factors (the Framingham experience). *Am. J. Cardiol.* 1996; **77**: B6–B11.
38. Stamler J, Vaccaro O, Neaton JD *et al.* Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes. Care.* 1993; **16**: 434–44.
39. Mogensen CE, Christensen CK. Predicting diabetic nephropathy in insulin-dependent patients. *N. Eng. J. Med.* 1984; **311** (2): 89–93.
40. Schmitz A, Vaeth M. Microalbuminuria: A major risk factor in non-insulin-dependent diabetes. A 10-year follow-up study of 503 patients. *Diabetic. Med.* 1988; **5**: 126–34.
41. Parving HH. Renoprotection in diabetes: Genetic and non-genetic risk factors and treatment. *Diabetologia.* 1998; **41**: 745–59.
42. Smulders YM, van Eeden AE, Stehouwer CD *et al.* Can reduction in hypertriglyceridaemia slow progression of microalbuminuria in patients with non-insulin-dependent diabetes mellitus? *Euro. J. Clin. Invest.* 1997; **27**: 997–1002.
43. National Heart Foundation of Australia. Lipid Management Guidelines. *Med. J. Aust.* 2001; (9 Suppl): S57–S88.
44. Costa J, Borges M, David C *et al.* Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients: Meta-analysis of randomised controlled trials. *BMJ.* 2006; **332**: 1115–24.
45. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions. V 5.0.0. The Cochrane Collaboration 2008.* [Cited April 2008.] Available from URL: http://www.cochrane-handbook.org
46. Levin SR, Coburn JW, Abraira C *et al.* Effect of intensive glycemic control on microalbuminuria in type 2 diabetes. *Diabetes. Care.* 2000; **23**: 1478–85.
47. Shichiri M, Kishikawa H, Ohkubo Y *et al.* Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. *Diabetes. Care.* 2000; **23** (2 Suppl): B21–B29.
48. Richter B, Bandeira-Echtler E, Bergerhoff K *et al.* Pioglitazone for type 2 diabetes mellitus. *Cochrane. Database. Syst. Rev.* 2006; **4**.
49. Hanefeld M, Brunetti P, Schernthaner GH *et al.* One-year glycemic control with a sulfonylurea plus pioglitazone versus a sulfonylurea plus metformin in patients with type 2 diabetes. *Diabetes. Care.* 2004; **27**: 141–47.
50. Matthews DR, Charbonnel BH, Hanefeld M *et al.* Long-term therapy with addition of pioglitazone to metformin compared with the addition of gliclazide to metformin in patients with type

2 diabetes: A randomized, comparative study. *Diabetes/Metabolism. Res. Rev.* 2005; **21**: 167–74.
51. Schernthaner G, Matthews DR, Charbonnel B *et al.* Efficacy and safety of pioglitazone versus metformin in patients with type 2 diabetes mellitus: A double-blind, randomized trial. *J. Clin. Endocrinol. Metabol.* 2004; **89**: 6068–76.
52. Richter B, Bandeira-Echtler E, Bergerhoff K *et al.* Rosiglitazone for type 2 diabetes mellitus. *Cochrane. Database. Syst. Rev.* 2007; **3**.
53. Lebovitz HE, Dole JF, Patwardhan R *et al.* Rosiglitazone monotherapy is effective in patients with type 2 diabetes. *J. Clin. Endocrinol. Metabol.* 2001; **86**: 280–88.
54. Bakris G, Viberti G, Weston WM *et al.* Rosiglitazone reduces urinary albumin excretion in type II diabetes. *J. Hum. Hypertens.* 2003; **17**: 7–12.
55. Saenz A, Fernandez-Esteban I, Mataix A *et al.* Metformin monotherapy for type 2 diabetes mellitus. *Cochrane. Database. Syst. Rev.* 2005; **3**.
56. Amador-Licona N, Guizar-Mendoza J, Vargas E *et al.* The short-term effect of a switch from glibenclamide to metformin on blood pressure and microalbuminuria in patients with type 2 diabetes mellitus. *Arch. Med. Res.* 2000; **31**: 571–75.
57. De Jager J, Kooy A, Lehert P *et al.* Effects of short-term treatment with metformin on markers of endothelial function and inflammatory activity in type 2 diabetes mellitus: A randomized, placebo-controlled trial. *J. Intern. Med.* 2005; **257**: 100–09.
58. ADVANCE Collaborative Group, Patel A, MacMahon S *et al.* Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N. Eng. J. Med.* 2008; **358**: 2560–72.
59. Davidson JA, McMorn SO, Waterhouse BR *et al.* A 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and tolerability of combination therapy with rosiglitazone and sulfonylurea in African American and Hispanic American patients with type 2 diabetes inadequately controlled with sulfonylurea monotherapy. *Clin. Ther.* 2007; **29**: 1900–14.
60. Johnston PS, Feig PU, Coniff RF *et al.* Long-term titrated-dose alpha-glucosidase inhibition in non-insulin-requiring Hispanic NIDDM patients. *Diabetes. Care.* 1998; **21**: 409–15.
61. Johnston PS, Feig PU, Coniff RF *et al.* Chronic treatment of African-American type 2 diabetic patients with alpha-glucosidase inhibition. *Diabetes. Care.* 1998; **21**: 416–22.
62. Gambaro G, Kinalska I, Oksa A *et al.* Oral sulodexide reduces albuminuria in microalbuminuric and macroalbuminuric type 1 and type 2 diabetic patients: The Di.N.A.S. randomized trial. *J. Am. Soc. Nephrol.* 2002; **13**: 1615–25.
63. Gaede P, Vedel P, Larsen N *et al.* Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N. Eng. J. Med.* 2003; **348**: 383–93.
64. Kaiser T, Florack C, Stephan U *et al.* Should BP targets be lower in diabetic patients with microalbuminuria or nephropathy: A systematic review of randomised controlled trials (Provisional record). *Br. J. Diabetes. Vasc. Dis.* 2003; **3**: 278–81.
65. UKPDS. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. *BMJ.* 1998; **317**: 713–20.
66. Ravid M, Brosh D, Ravid-Safran D *et al.* Main risk factors for nephropathy in type 2 diabetes mellitus are plasma cholesterol levels, mean blood pressure, and hyperglycemia. *Arch. Intern. Med.* 1998; **158**: 998–1004.
67. Patel A, ADVANCE Collaborative Group, MacMahon S *et al.* Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): A randomised controlled trial. *Lancet.* 2007; **370**: 829–40.
68. de Galan B, Perkovic V, Ninomiya T *et al.* Lowering blood pressure reduces renal events in Type 2 diabetes. *J. Am. Soc. Nephrol.* 2009; **20**: 883–92.
69. Sano T, Hotta N, Kawamura T *et al.* Effects of long-term enalapril treatment on persistent microalbuminuria in normotensive type 2 diabetic patients: Results of a 4-year, prospective, randomized study. *Diabetic. Medicine.* 1996; **13**: 120–24.
70. Schrier RW, Estacio RO, Esler A *et al.* Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney. Int.* 2002; **61**: 1086–97.
71. Lebovitz HE, Wiegmann TB, Cnaan A *et al.* Renal protective effects of enalapril in hypertensive NIDDM: Role of baseline albuminuria. *Kidney. Int.* 1994; **45**: S150–S55.
72. Parving HH, Lehnert H, Brochner-Mortensen J *et al.* The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N. Eng. J. Med.* 2001; **345**: 870–78.
73. Estacio RO, Jeffers BW, Gifford N *et al.* Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes. Care.* 2000; **23** (Suppl 2): B54–B64.
74. Agardh CD, Garcia-Puig J, Charbonnel B *et al.* Greater reduction of urinary albumin excretion in hypertensive type II diabetic patients with incipient nephropathy by lisinopril than by nifedipine. *J. Hum. Hypertens.* 1996; **10**: 185–92.
75. Lacourciere Y, Nadeau A, Poirier L *et al.* Captopril or conventional therapy in hypertensive type II diabetics. Three-year analysis. *Hypertension.* 1993; **21**: 786–94.
76. Chan JC, Ko GT, Leung DH *et al.* Long-term effects of angiotensin-converting enzyme inhibition and metabolic control in hypertensive type 2 diabetic patients. *Kidney. Int.* 2000; **57**: 590–600.
77. Jennings DL, Kalus JS, Coleman CI *et al.* Combination therapy with an ACE inhibitor and an angiotensin receptor blocker for diabetic nephropathy: A meta-analysis. *Diabetic. Med.* 2007; **24**: 486–93.
78. Hamilton RA, Kane MP, Demers J. Angiotensin-converting enzyme inhibitors and type 2 diabetic nephropathy: A meta-analysis. *Pharmacotherapy.* 2003; **23**: 909–15.
79. Yasuda G, Ando D, Hirawa N *et al.* Effects of losartan and amlodipine on urinary albumin excretion and ambulatory blood pressure in hypertensive type 2 diabetic patients with overt nephropathy. *Diabetes. Care.* 2005; **28**: 1862–68.
80. Jerums G, Allen TJ, Campbell DJ *et al.* Melbourne Diabetic Nephropathy Study Group. Long-term renoprotection by perindopril or nifedipine in non-hypertensive patients with Type 2 diabetes and microalbuminuria. *Diabetic. Med.* 2004; **21**: 1192–99.
81. Marre M, Lievre M, Chatellier G *et al.* Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: Randomised, double blind, placebo controlled trial (the DIABHYCAR study). *BMJ.* 2004; **328**.
82. Baba S, MIND Study Group. Nifedipine and enalapril equally reduce the progression of nephropathy in hypertensive type 2 diabetics. *Diabetes. Res. Clin. Prac.* 2001; **54**: 191–201.
83. Fogari R, Zoppi A, Corradi L *et al.* Long-term effects of amlodipine versus fosinopril on microalbuminuria in elderly hypertensive patients with type 2 diabetes mellitus. *Curr. Ther. Res. Clin. Exp.* 2000; **61**: 163–73.
84. Lacourciere Y, Belanger A, Godin C *et al.* Long-term comparison of losartan and enalapril on kidney function in hypertensive

type 2 diabetics with early nephropathy. *Kidney. Int.* 2000; **58**: 762–69.
85. Estacio RO, Coll JR, Tran ZV *et al.* Effect of intensive blood pressure control with valsartan on urinary albumin excretion in normotensive patients with type 2 diabetes. *Am. J. Hypertens.* 2006; **19**: 1241–48.
86. Galle J, Schwedhelm E, Pinnetti S *et al.* Antiproteinuric effects of angiotensin receptor blockers: Telmisartan versus valsartan in hypertensive patients with type 2 diabetes mellitus and overt nephropathy. *Nephrol. Dial. Transplant.* 2008; **23**: 3174–83.
87. Hollenberg NK, Parving HH, Viberti G *et al.* Albuminuria response to very high-dose valsartan in type 2 diabetes mellitus. *J. Hypertens.* 2007; **25**: 1921–26.
88. Shiga Microalbuminuria Reduction Trial (SMART) Group, Uzu T, Sawaguchi M, Maegawa H, Kashiwagi A. Reduction of microalbuminuria in patients with type 2 diabetes: The Shiga Microalbuminuria Reduction Trial (SMART). *Diabetes. Care.* 2007; **30**: 1581–83.
89. Tan KC, Chow WS, Ai VH *et al.* Effects of angiotensin II receptor antagonist on endothelial vasomotor function and urinary albumin excretion in type 2 diabetic patients with microalbuminuria. *Diabetes. Metabol. Res. Rev.* 2002; **18**: 71–6.
90. Viberti G, Wheeldon NM. MicroAlbuminuria Reduction with VALsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: A blood pressure-independent effect. *Circulation.* 2002; **106**: 672–78.
91. Ruggenenti P, Gambara V, Perna A *et al.* The nephropathy of non-insulin-dependent diabetes: Predictors of outcome relative to diverse patterns of renal injury. *J. Am. Soc. Nephrol.* 1998; **9**: 2336–43.
92. Remuzzi G, Macia M, Ruggenenti P. Prevention and treatment of diabetic renal disease in type 2 diabetes: The BENEDICT study. *J. Am. Soc. Nephrol.* 2006; **17**: S90–S97.
93. Schram MT, van Ittersum FJ, Spoelstra-de Man A *et al.* Aggressive antihypertensive therapy based on hydrochlorothiazide, candesartan or lisinopril as initial choice in hypertensive type II diabetic individuals: Effects on albumin excretion, endothelial function and inflammation in a double-blind, randomized clinical trial. *J. Hum. Hypertens.* 2005; **19**: 429–37.
94. Rosei EA, Rizzoni D, Muiesan ML *et al.* CENTRO (CandEsartaN on aTherosclerotic Risk factors) study investigators. Effects of candesartan cilexetil and enalapril on inflammatory markers of atherosclerosis in hypertensive patients with non-insulin-dependent diabetes mellitus. *J. Hypertens.* 2005; **23**: 435–44.
95. Bakris GL, Fonseca V, Katholi RE *et al.* Differential effects of beta-blockers on albuminuria in patients with type 2 diabetes. *Hypertension.* 2005; **46**: 1309–15.
96. Barnett AH, Bain SC, Bouter P *et al.* Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N. Eng. J. Med.* 2004; **351**: 1952–61.
97. ONTARGET. Ramipril, or both in patients at high risk for vascular events. *N. Eng. J. Med.* 2008; **358**: 1547–59.
98. Mann JF, Schmieder RE, McQueen M *et al.* Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): A multicentre, randomised, double-blind, controlled trial. *Lancet.* 2008; **372**: 547–53.
99. Parving HH, Persson F, Lewis JB *et al.* Aliskiren combined with losartan in type 2 diabetes and nephropathy. *N. Eng. J. Med.* 2008; **358**: 2433–46.
100. Muirhead N, Feagan BF, Mahon J *et al.* The effects of valsartan and captopril on reducing microalbuminuria in patients with type 2 diabetes mellitus: A placebo-controlled trial. *Curr. Ther. Res. Clin. Exp.* 1999; **60**: 650–60.
101. Ravid M, Brosh D, Levi Z *et al.* Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus. A randomized, controlled trial. *Ann. Intern. Med.* 1998; **128**: 982–88.
102. Sano T, Kawamura T, Matsumae H *et al.* Effects of long-term enalapril treatment on persistent micro-albuminuria in well-controlled hypertensive and normotensive NIDDM patients. *Diabetes. Care.* 1994; **17**: 420–24.
103. Trevisan R, Tiengo A. Effect of low-dose ramipril on microalbuminuria in normotensive or mild hypertensive non-insulin-dependent diabetic patients. North-East Italy Microalbuminuria Study Group. *Am. J. Hypertens.* 1995; **8**: 876–83.
104. Sandhu S, Wiebe N, Fried L *et al.* Statins for improving renal outcomes: A meta-analysis. *J. Am. Soc. Nephrol.* 2006; **17**: 2006–16.
105. Keating GM, Croom KF. Fenofibrate: A review of its use in primary dyslipidaemia, the metabolic syndrome and type 2 diabetes mellitus. *Drugs.* 2007; **67**: 121–53.
106. Strippoli G, Navaneethan S, Johnson D *et al.* Effects of statins in patients with chronic kidney disease: Meta-analysis and meta-regression of randomised controlled trials. *BMJ.* 2008; **336**: 645–51.
107. Fried LF, Orchard TJ, Kasiske BL. Effect of lipid reduction on the progression of renal disease: A meta-analysis. *Kidney. Int.* 2001; **59**: 260–69.
108. The Heart Protection Study. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 5963 people with diabetes: A randomised placebo-controlled trial. *Lancet.* 2003; **361**: 2005–16.
109. Athyros VG, Mikhailidis DP, Papageorgiou AA *et al.* The effect of statins versus untreated dyslipidaemia on renal function in patients with coronary heart disease. A subgroup analysis of the Greek atorvastatin and coronary heart disease evaluation (GREACE) study. *J. Clin. Pathol.* 2004; **57**: 728–34.
110. Koren MJ. Statin use in a 'real-world' clinical setting: Aggressive lipid lowering compared with usual care in the Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) trial. *Am. J. Med.* 2005; **118** (Suppl 12A): 16–21.
111. Sorof J, Berne C, Siewert-Delle A *et al.* Effect of rosuvastatin or atorvastatin on urinary albumin excretion and renal function in type 2 diabetic patients. *Diabetes. Res. Clin. Prac.* 2006; **72**: 81–7.
112. Nakamura T, Ushiyama C, Hirokawa K *et al.* Effect of cerivastatin on urinary albumin excretion and plasma endothelin-1 concentrations in type 2 diabetes patients with microalbuminuria and dyslipidemia. *Am. J. Nephrol.* 2001; **21**: 449–54.
113. Ansquer JC, Foucher C, Rattier S *et al.* Fenofibrate reduces progression to microalbuminuria over 3 years in a placebo-controlled study in type 2 diabetes: Results from the Diabetes Atherosclerosis Intervention Study (DAIS). *Am. J. Kidney. Dis.* 2005; **45**: 485–93.
114. Keech A, Simes RJ, Barter P *et al.* Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): Randomised controlled trial. *Lancet.* 2005; **366**: 1849–61.
115. Radermecker RP, Scheen AJ. Field, a randomized clinical trial of cardiovascular prevention with fenofibrate in type 2 diabetes. *Revue. Medicale. Liege.* 2005; **60**: 957–61.
116. Nagai T, Tomizawa T, Nakajima K *et al.* Effect of bezafibrate or pravastatin on serum lipid levels and albuminuria in NIDDM patients. *J. Atherosclerosis. Thrombosis.* 2000; **7**: 91–6.
117. Endo K, Miyashita Y, Sasaki H *et al.* Probucol delays progression of diabetic nephropathy. *Diabetes. Res. Clin. Prac.* 2006; **71**: 156–63.
118. Cardenas C, Bordiu E, Bagazgoitia J *et al.* Polyunsaturated fatty acid consumption may play a role in the onset and regression of

microalbuminuria in well-controlled type 1 and type 2 diabetic people: A 7-year, prospective, population-based, observational multicenter study. *Diabetes. Care*. 2004; **27**: 1454–57.

119. Shemesh O, Golbetz H, Kriss JP *et al*. Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney. Int*. 1985; **28**: 830–38.
120. Robertson L, Waugh N, Robertson A. Protein restriction for diabetic renal disease. *Cochrane. Database. Syst. Rev*. 2007; **4**.
121. Dussol B, Iovanna C, Raccah D *et al*. A randomized trial of low-protein diet in type 1 and in type 2 diabetes mellitus patients with incipient and overt nephropathy. *J. Renal. Nutr*. 2005; **15**: 398–406.
122. Suckling RJ, He FJ, MacGregor GA. Altered dietary salt intake for preventing and treating diabetic kidney disease. *Cochrane. Database. Syst. Rev. Protoc*. 2007; **4**: CD006763.
123. Muhlhauser I. Cigarette smoking and diabetes: An update. *Diabetic. Med*. 1994; **11**: 336–43.
124. Yudkin JS. How can we best prolong life? Benefits of coronary risk factor reduction in non-diabetic and diabetic subjects. *BMJ*. 1993; **306**: 1313–18.
125. Forsblom CM, Sane T, Groop PH *et al*. Risk factors for mortality in Type II (non-insulin-dependent) diabetes: Evidence of a role for neuropathy and a protective effect of HLA-DR4. *Diabetologia*. 1998; **41**: 1253–62.
126. Gambaro G, Bax G, Fusaro M *et al*. Cigarette smoking is a risk factor for nephropathy and its progression in type 2 diabetes mellitus. *Diabetes. Nutr. Metabol. Clin. Exp*. 2001; **14**: 337–42.
127. Smulders YM, Rakic M, Stehouwer CD *et al*. Determinants of progression of microalbuminuria in patients with NIDDM. A prospective study. *Diabetes. Care*. 1997; **6**: 999–1005.
128. Chuahirun T, Wesson DE. Cigarette smoking predicts faster progression of type 2 established diabetic nephropathy despite ACE inhibition. *Am. J. Kidney. Dis*. 2002; **39**: 376–82.
129. Chuahirun T, Simoni J, Hudson C *et al*. Cigarette smoking exacerbates and its cessation ameliorates renal injury in type 2 diabetes. *Am. J. Med. Sci*. 2004; **327**: 57–67.
130. Chuahirun T, Khanna A, Kimball K *et al*. Cigarette smoking and increased urine albumin excretion are interrelated predictors of nephropathy progression in type 2 diabetes. *Am. J. Kidney. Dis*. 2003; **4**: 3–21.
131. Cederholm J, Eliasson B, Nilsson PM *et al*. Microalbuminuria and risk factors in type 1 and type 2 diabetic patients. *Diabetes. Res. Clin. Prac*. 2005; **67**: 258–66.
132. Biarnes J, Masana L, Morales C *et al*. Factors influencing incipient diabetic nephropathy: ESODIAH study. *Medicina. Clinica*. 2005; **125**: 401–04.
133. Braatvedt GD, Rosie B, Bagg W *et al*. Current and former smoking increases mortality in patients on peritoneal dialysis. *NZ. Med. J*. 2006; **119**.
134. Nakamura T, Ushiyama C, Osada S *et al*. Combination therapy of trandolapril and candesartan cilexetil reduces microalbuminuria and urinary endothelin-1 excretion in patients with type 2 diabetes. *Clin. Exp. Nephrol*. 2002; **6**: 135–39.
135. Nishimura M, Sasaki T, Ohishi A *et al*. Angiotensin-converting enzyme inhibitors and probucol suppress the time-dependent increase in urinary Type IV collagen excretion of Type II diabetes mellitus patients with early diabetic nephropathy. *Clin. Nephrol*. 2001; **56**: 96–103.
136. Barnard ND, Cohen J, Jenkins DJ *et al*. A low-fat vegan diet improves glycemic control and cardiovascular risk factors in a randomized clinical trial in individuals with type 2 diabetes. *Diabetes. Care*. 2006; **29**: 1777–83.
137. Nicholson AS, Sklar M, Barnard ND *et al*. Toward improved management of NIDDM: A randomized, controlled, pilot intervention using a lowfat, vegetarian diet. *Prev. Med*. 1994; **29**: 87–91.
138. Nielsen S, Hermansen K, Rasmussen OW *et al*. Urinary albumin excretion rate and 24-h ambulatory blood pressure in NIDDM with microalbuminuria: Effects of a monounsaturated-enriched diet. *Diabetologia*. 1995; **38**: 1069–75.
139. Shimizu H, Ohtani K, Tanaka Y *et al*. Long-term effect of eicosapentaenoic acid ethyl (EPA-E) on albuminuria of non-insulin dependent diabetic patients. *Diabetes. Res. Clin. Prac*. 1995; **28**: 35–40.
140. Barsotti G, Cupisti A, Barsotti M *et al*. Dietary treatment of diabetic nephropathy with chronic renal failure. *Nephrol. Dial. Transplant*. 1998; **13** (Suppl 8): 49–52.
141. de mello VD, Zelmanovitz T, Perassolo MS *et al*. Withdrawal of red meat from the usual diet reduces albuminuria and improves serum fatty acid profile in type 2 diabetes patients with macroalbuminuria. *Am. J. Clin. Nutr*. 2006; **83**: 1032–38.
142. Gross JL, Zelmanovitz T, Moulin CC *et al*. Effect of a chicken-based diet on renal function and lipid profile in patients with type 2 diabetes: A randomized crossover trial. *Diabetes. Care*. 2002; **25**: 645–51.
143. Meloni C, Tatangelo P, Cipriani S *et al*. Adequate protein dietary restriction in diabetic and nondiabetic patients with chronic renal failure. *J. Renal. Nutr*. 2004; **14**: 208–13.
144. Pijls LT, de Vries H, Donker AJ *et al*. The effect of protein restriction on albuminuria in patients with type 2 diabetes mellitus: A randomized trial. *Nephrol. Dial. Transplant*. 1999; **14**: 1445–53.
145. Pijls LT, de Vries H, van Eijk JT *et al*. Protein restriction, glomerular filtration rate and albuminuria in patients with type 2 diabetes mellitus: A randomized trial. *Euro. J. Clin. Nutr*. 2002; **56**: 1200–07.
146. Pomerleau J, Verdy M, Garrel DR *et al*. Effect of protein intake on glycaemic control and renal function in type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia*. 1993; **36**: 829–34.
147. Teixeira SR, Tappenden KA, Carson L *et al*. Isolated soy protein consumption reduces urinary albumin excretion and improves the serum lipid profile in men with type 2 diabetes mellitus and nephropathy. *J. Nutrition*. 2004; **134**: 1874–80.
148. Wheeler ML, Fineberg SE, Fineberg NS *et al*. Animal versus plant protein meals in individuals with type 2 diabetes and microalbuminuria: Effects on renal, glycemic, and lipid parameters. *Diabetes. Care*. 2002; **25**: 1277–82.
149. Houlihan C, Allen T, Hovey A *et al*. A low salt diet in patients with type II diabetes significantly amplifies the effects of angiotensin II receptor blockade with losartan. *Nephrology*. 2000; **5**.
150. Houlihan CA, Akdeniz A, Tsalamandris C *et al*. Urinary transforming growth factor-beta excretion in patients with hypertension, type 2 diabetes, and elevated albumin excretion rate: Effects of angiotensin receptor blockade and sodium restriction. *Diabetes. Care*. 2002; **25**: 1072–77.
151. Houlihan CA, Allen TJ, Baxter AL *et al*. A low-sodium diet potentiates the effects of losartan in type 2 diabetes. *Diabetes. Care*. 2002; **25**: 663–71.
152. Imanishi M, Yoshioka K, Okumura M *et al*. Sodium sensitivity related to albuminuria appearing before hypertension in type 2 diabetic patients. *Diabetes. Care*. 2001; **24**: 111–16.
153. Vedovato M, Lepore G, Coracina A *et al*. Effect of sodium intake on blood pressure and albuminuria in Type 2 diabetic patients: The role of insulin resistance. *Diabetologia*. 2004; **47**: 300–03.
154. Yoshioka K, Imanishi M, Konishi Y *et al*. Glomerular charge and size selectivity assessed by changes in salt intake in type 2 diabetic patients. *Diabetes. Care*. 1998; **21**: 482–86.
155. Anan F, Masaki T, Takahashi N *et al*. Smoking is associated with urinary albumin excretion: An evaluation of premenopausal

patients with type 2 diabetes mellitus. *Metab. Clin. Exp.* 2007; **56**: 179–84.
156. Baggio B, Budakovic A, Dalla VM *et al.* Effects of cigarette smoking on glomerular structure and function in type 2 diabetic patients. *J. Am. Soc. Nephrol.* 2002; **13**: 2730–36.
157. Corradi L, Zoppi A, Tettamanti F *et al.* Association between smoking and micro-albuminuria in hypertensive patients with type 2 diabetes mellitus. *J. Hypertension.* 1993; **11**: S190–S91.
158. Dean JD, Matthews SB, Dolben J *et al.* Cholesterol rich apo B containing lipoproteins and smoking are independently associated with macrovascular disease in normotensive NIDDM patients. *Diabetic. Medicine.* 1994; **11**: 740–47.
159. Gatling W, Mullee MA, Knight C *et al.* Microalbuminuria in diabetes: Relationships between urinary albumin excretion and diabetes-related variables. *Diabetic. Medicine.* 1988; **5**: 348–51.
160. Ikeda Y, Suehiro T, Takamatsu K *et al.* Effect of smoking on the prevalence of albuminuria in Japanese men with non-insulin-dependent diabetes mellitus. *Diabetes. Res. Clin. Prac.* 1997; **36**: 57–61.
161. Nilsson PM, Gudbjornsdottir S, Eliasson B *et al.* Smoking is associated with increased HbA1c values and microalbuminuria in patients with diabetes – Data from the National Diabetes Register in Sweden. *Diab. &. Metab.* 2004; **30** (3): 261–68.
162. Pijls LT, de Vries H, Kriegsman DM *et al.* Determinants of albuminuria in people with Type 2 diabetes mellitus. *Diabetes. Res. Clin. Prac.* 2001; **52**: 133–43.
163. Savage S, Nagel NJ, Estacio RO *et al.* Clinical factors associated with urinary albumin excretion in type II diabetes. *Am. J. Kidney. Dis.* 1995; **25**: 836–44.
164. Thomas GN, Tomlinson B, McGhee SM *et al.* Association of smoking with increasing vascular involvement in type 2 diabetic Chinese patients. *Exp. Clin. Endocrinol. Diab.* 2006; **114**: 301–05.

APPENDIX

Table A1 Definition of NHMRC grades of recommendation

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice.
B	Body of evidence can be trusted to guide practice in most situations.
C	Body of evidence provides some support for recommendations(s) but care should be taken in its application.
D	Body of evidence is weak and recommendation must be applied with caution

Table A2 Summary of studies relevant to the assessment of the role of glucose control in CKD in individuals with type 2 diabetes

Study ID	Study description	Intervention	Outcome (relevant to CKD)	Follow up (months)	Comments/conclusions
ADVANCE (2008)[58]	RCT Multicentre (215 across 20 countries) Type 2 diabetes diagnosed at 30 years or older. Age ≥55 years at the start of the study. History of major vascular or microvascular disease or at least one other risk factor for vascular disease. *n* = 11 000	Intensive blood glucose control (target <6.5% HbAc1). Achieved using glicazide and other drugs as required *vs* Standard blood glucose control.	Worsening nephropathy i.e. development of macroalbuminuria, doubling of serum creatinine, need for renal replacement therapy or death due to kidney disease	60 (median)	Overall the main benefit identified by the ADVANCE study was a one fifth reduction in kidney complications in particular the development of macroalbuminuria. 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 systolic blood pressure was on average 1.6 mm Hg lower than the standard group. Intensive 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 macroalbuminuria and new onset microalbuminuria (0.91 CI 0.85 – 0.98). A trend towards a reduction in the need for renal replacement therapy.
Amador-Licona *et al*. (2000)[56]	RCT Type 2 diabetes, incipient nephropathy, <65, normotensive *n* = 51	Metformin *vs* GLB	GFR, HbA1c, renal plasma flow, UAE	3	Metformin significantly. reduced UAE with none of the expected changes in renal haemodynamics.
Bakris *et al*. (2003)[54]	RCT, open label, cardiac safety Multicentre, US Type 2 diabetes 40 to 80 years, no ACEi ARB beta-blockers or CCB *n* = 203	RSG *vs* GLB	ACR	12	RSG reduced ACR from baseline. Strongly correlated with changes in amb. SBP, DBP and little relation to changes in FPG or HbA1c. Given similar levels of glucose control, the mean reduction in ACR was greater for RSG than GLB and a greater proportion of participants in the RSG treatment group with baseline microalbuminuria achieved normalization of the ACR by the 12 months. The differences in ACR between the groups were not statistically significant – ACR was a secondary prospective endpoint and study design was of low power for ACR. Suggests a potential benefit of RSG.
Davidson *et al*. (2007)[59]	RCT, double blind, placebo controlled US Multicentre (38), US Hispanic and African American Type 2 diabetes, FPG ≥ 140 mg/dL and HbA(1c) ≥ 7.5%, monotherapy with sulfonyl urea for a minimum of 2 months *n* = 245.	Glyburide + Rosiglitazone *vs* Glyburide + Placebo	ACR (secondary and as a CVD risk marker)	6	ACR reduced by 26.7% in treatment group (GLY + RSG) compared with control group (GLY + placebo). Improved insulin sensitivity and β-cell function with thiazolidinedione treatments.
De Jager *et al*. (2005) HOME[57]	RCT Netherlands – 3 centres Type 2 diabetes *n* = 345	Metformin plus insulin *vs* Placebo plus insulin	UAE	4	Metformin treatment was associated with a 21% increase in UAE compared with the placebo. However considered a short anomaly as UAE shown to be associated with HbAc1.
Gaede *et al*. (2003) Steno2[63]	RCT Type 2 diabetes, microalbuminuria *n* = 160	Multifactorial intensive treatment *vs* Standard treatment	UAE	94 (mean)	Target driven long term intensified treatment aimed at multiple risk factors reduced nephropathy by about 50%.

Gambaro *et al.* (2002)[62]	RCT, double blind, placebo Multicentre Type 1 diabetes and type 2 diabetes, micro or macroalbuminuric $n = 223$	Suloexide *vs* Placebo	UAE	4	Significantly reduced albuminuria in people with both type 1 and type 2 diabetes.
Hanefeld *et al.* (2004)[49]	RCT, double blind Multicentre Type 2 diabetes, inadequately managed $n = 649$	Pioglitazone plus SU *vs* Metformin plus SU	ACR	12	Clinically equivalent improvements in glycaemic control. Pioglitazone plus SU resulted in a reduction of ACR. Overall differences from baseline ACR small (i.e. <15%).
Johnston *et al.* (1998)[60]	RCT Type 2 diabetes, Hispanic $n = 385$	Miglitol *vs* Placebo	ACR.	12	Miglitol had 'just non-significant' reduction of ACR.
Johnston *et al.* (1998)[61]	RCT Type 2 diabetes, African-American $n = 345$	Miglitol *vs* Placebo	ACR	12	Minor reduction in ACR with miglitol.
Lebovitz *et al.* (2001)[53]	RCT Multicentre (42), US, mixed race. Type 2 diabetes, 36–81 years, FPG (7.8–16.7 mmol/L), BMI between 22–38 kg/m^2, no renal impairment or DN. $n = 493$	Rosiglatzone (2 or 4 mg/day) *vs* Placebo	UAE, ACR	7	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 glycaemic control or a different effect of RSG.
Levin *et al.* (2000)[46]	RCT Type 2 diabetes (mean age 60, mean duration of diabetes 8 years) $n = 153$	Intensive (HbA1c goal 7.1%) *vs* Standard (HbA1c goal 9.1%)	UAE, ACR	24	Intensive glycaemic control retarded microalbuminuria, but may not lessen the progressive deterioration of glomerular function.
Matthews *et al.* (2005)[50]	RCT, double blind Type 2 diabetes, poorly managed $n = 630$	Metformin plus pioglitazone *vs* Metformin plus gliclazide	ACR	12	Mean ACR reduced by 10% in met plus piog group. Potential benefits are indicated.
Ohkubo *et al.* (1995)[7]	RCT Japan Type 2 diabetes, divided into primary prevention and secondary intervention cohorts on the basis of albuminuria and retinopathy. $n = 110$	Multiple Insulin Treatment (MIT) *vs* Conventional Insulin Treatment (CIT)	UAE	60	Intensive glycaemic control can delay the onset and progression of nephropathy. The cumulative percentages of the development and the 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 ($P = 0.032$).
Schernthaner *et al.* (2004)[51]	RCT, double-blind Multicentre, 167 centres across 12 European countries Type 2 diabetes inadequately treated by diet alone (HbA between 7.5% and 11%), 35–75 years $n = 1199$	Pioglitazone *vs* Metformin	ACR	12	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.
Shichiri *et al.* (2000)[47] Kunamoto Study	RCT $n = 110$	MIT *vs* CIT	Albuminuria	96	Intensive glycaemic control (MIT) – cumulative percentages of worsening in nephropathy were significantly lower.

Table A3 Summary of studies relevant to the assessment of the role of blood pressure control and antihypertensive agents in CKD and individuals with type 2 diabetes.

Study ID	Study description	Intervention	Outcome relevant to CKD	Follow up (months)	Comments
ADVANCE (2007)[67] and de Galan (2009)[68]	RCT Multicentre (215 across 20 countries) Type 2 diabetes diagnosed at 30 years or older. Age ≥55 years at the start of the study. History of major vascular or microvascular disease or at least one other risk factor for vascular disease. *n* = 11 000	Perindopril plus indapamide *vs* placebo	Worsening nephropathy i.e. development of macroalbuminuria, doubling of serum creatinine, need for renal replacement therapy or death due to kidney disease.	52 (median)	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).
Agardh *et al.* (1996)[74]	RCT, double blind Multicentre, multinational Type 2 diabetes, microalbuminuria, early diabetic neuropathy, hypertensive 239 males 96 females	Lisinopril *vs* Nifedipine	UAE, creatinine clearance	12	Significantly more beneficial effect on UAE, however creatinine clearance did not change significantly with either treatment.
Ahmad *et al.* (1997)[25]	RCT single blind India Type 2 diabetes Normotensive *n* = 103	ACEi *vs* Placebo	AER	60	After 5 years ACEi treated patients experienced significantly less progression of microalbuminuria to clinical albuminuria.
Baba & MIND Study Group (2001)[82]	RCT – intent to treat analysis Multicentre Japan Type 2 diabetes Normoalbuminuria Microalbuminuria *n* = 486	ACEi *vs* CCB	UAE	24	CCB and ACEi had a similar effect on nephropathy in hypertensive people with type 2 diabetes without overt proteinuria.
Bakris *et al.* (2005)[95]	RCT Type 2 diabetes, hypertension, ACEi or ARB as part of the treatment regime prior to commencement of the study. *n* = 1235	Metoprolol (maintain ACEi/ARB) *vs* Carvedilol (maintain ACEi/ARB)	Albuminuria (spot ACR)	5 after reaching target BP	Pre specified and post hoc analyses of the GEMINI trial. Greater reduction in microalbuminuria was observed for carvedilol. Those with normoalbuminuria fewer progressed to micro on carvedilol. 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.
Barnett *et al.* (2004)[96]	RCT, double blind. Multicentre (39), 6 European countries Type 2 diabetes, mild to moderate hypertension, all had to have been treated by an ACEi to eliminate intolerance, GFR >70 mL/min per 1.73 m^2, mostly white and male. *n* = 250	ARB (telisartan – 40 mg/day up to 80 mg/day for BP control) ACEi (enalapril – 10 mg/day up to 20 mg/day for BP control) (Additional hypertensive allowed as required)	GFR (calculated from serum creatinine), UAE	60	The difference in GFR between the ARB and the ACEi was –3.1 mL/min per 1.73 m^2 and was insignificant. The mean annual declines in GFR were 3.7 mL/min per 1.73 m^2 for the ARB and 3.3 mL/min per 1.73 m^2 for the ACEi. These 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 m^2. Telmisartan is not inferior to enalapril in providing long-term renoprotection. Does 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.

Chan *et al.* (2000)[76]	RCT Type 2 diabetes Hypertensive *n* = 102	ACEi *vs* CCB	UAE, CCr	Initially 12 then 54 (mean)	Treatment with ACEi associated with greater reduction in albuminuria than with CCB in the entire patient group and especially in those with microalbuminuria. In macroalbuminuria, rate of deterioration in renal function was also attenuated with ACEi.
Estacio (2006)[85]	RCT type 2 diabetes normotensive *n* = 129	Intensive BP control (valsartan + other as required) *vs* Moderate BP control (placebo plus others as required)	UAE, serum creatinine, creatinine clearance	23 (median)	Int BP – 118 ± 10.9/75 ± 5.7 Mod BP – 124 ± 109/80 ± 6.5 UAE – significant treatment difference at 2 years.
ABCD Estacio *et al.* (2000)[73] Estacio & Schrier (1998)[12] Schrier *et al.* (2002)[70]	RCT prospective Type 2 diabetes Normotensive (DBP between 80 and 89 mm/Hg, not receiving antihypertensives) *n* = 470	ACEi, enalpril *vs* CCB nisoldipine *vs* Placebo	Creatinine clearance, UAE	64	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 incipient 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.
Fogari *et al.* (2000)[83]	RCT Type 2 diabetes (well controlled), 60 to 75 years, hypertensive *n* = 147	ACEi *vs* CCB	UAE, creatinine clearance	24	At 24 months UAE significantly decreased in both treatments. Creatinine clearance unaffected by ACEi, but increased by CCB
Galle *et al.* (2008)[86]	RCT Multicentric Type 2 diabetes with hypertension, proteinuria and serum creatinine ≤3.0 mg/dL) *n* = 885	Telmisartan *vs* valsartan. (additional non-ACEi/ARB antihypertensives permitted as necessary)	24 h proteinuria, eGFR	12	Mean reduction in proteinuria 33% (same for both treatments). Greater renoprotection seen among patients with better blood pressure control.
Hollenberg *et al.* (2007)[87]	RCT Multicentric Type 2 diabetes with hypertension and albuminuria (AER 20–700 µg/min) *n* = 391	valsartan 160 mg/day *vs* 320 mg/day *vs* 640 mg/day (add on medications for BP control as required)	AER, serum creatinine	7.5	High dose valsartan above 160 mg/day – greater reduction from baseline AER with greater number (12%) regressing to normoalbuminuria.
Jerums *et al.* (2004)[80]	RCT prospective open, blinded endpoint Type 2 diabetes *n* = 77	ACEi CCB *vs* Placebo	GFR, albuminuria	66 (median)	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.
Lacourciere *et al.* (1993)[75]	RCT double blind Caucasian (45 to 75 years) Type 2 diabetes Mild to moderate hypertension *n* = 109	ACEi *vs* conventional therapy	UAE	36	Treatment with captopril decreased albuminuria and reduced the development of macroalbuminuria in those with persistent microalbuminuria.

Table A3 *Continued*

Study ID	Study description	Intervention	Outcome relevant to CKD	Follow up (months)	Comments
Lacourciere *et al.* (2000)[84]	RCT prospective Multicentre Canada Type 2 diabetes Hypertensive Early nephropathy *n* = 92	ACEi *vs* ARB	Renal bioindicators	12	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.
Lebovitz *et al.* (1994)[71]	RCT, double blind Type 2 diabetes Hypertensive *n* = 121	ACEi *vs* Placebo	UAE, protein, urea, nitrogen, creatinine, GFR	36	ACEi preserved GFR better in patients with sub-clinical proteinuria at baseline better than other antihypertensives without ACEi. Smaller percentage proceeded to clinical albuminuria.
Marre *et al.* (2004)[81]	RCT double blind, parallel group Multicentre, primary care, 16 European and North African Type 2 diabetes >50 years Persistent microalbuminuria or proteinuria *n* = 4912	ACEi (on top of usual treatment) *vs* Placebo	ESKD Secondary – UAE, urinary protein	72 (median)	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.
Muirhead *et al.* (1999)[100]	RCT, double blind, placebo Multicentre, Caucasian Type 2 diabetes, normotensive, microalbuminuria *n* = 122	ACEi ARB *vs* Placebo	UAE	12	The ARB slowed progressive rise of UAE compared with the ACEi.
Nakamura *et al.* (2002)[134]	RCT, Type 2 diabetes, normotensive, microalbuminuria *n* = 60	ACEi ARB ACEi + ARB *vs* Placebo	UAE	18	Data suggest the combination of ARB/ACEi has an additive effect. On the reduction of microalbuminuria.
ONTARGET (2008)[97] and Mann *et al.* (2008)[98]	RCT Heart disease, included 38% with diabetes (type 1 and type 2) and 13% with microalbuminuria *n* = 25 000	ACEi (Ramipril) *vs* ARB (Telmisartan) *vs* Combination	eGFR, UAE Secondary- Renal impairment (based on clinical investigators report) Renal failure requiring dialysis.	56 (median)	No subgroup analysis has been presented including diabetes and microalbuminuria. Therefore not generaliseable 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 greeter rate of decline in eGFR.
Parving *et al.* (2001)[72] and Brenner *et al.* (2001)[19]	RCT, double blind Multicentre, multinational Type 2 diabetes *n* = 1513	ARB 150 mg/day ARB 300 mg/day *vs* Placebo (and conventional hypertensive treatment)	Serum creatinine doubling, ESKD, death, proteinuria, progression of kidney disease	40 (mean)	Losartan conferred significant renal benefits in type 2 diabetes with neuropathy and was generally well tolerated.
Parving *et al.* (2008)[99]	RCT, double blind, placebo controlled Multicentric, multinational Type 2 diabetes, nephropathy. Excluded – known non-diabetic nephropathy, ACR >3500 mg/g, eGFR <30 mL/min, chronic UTI, severe hypertension, cardiovascular disease within the previous 6 months. *n* = 599	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).	Urinary ACR, eGFR.	6	After adjustment for changes from base line in systolic BP, 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 reduction was greater than 50% (24.7% *vs* 12.5%). The benefit of aliskiren appeared to be independent of differences (small) in blood pressure.

Ravid *et al.* (1993)[14]	RCT – double blind fist phase and open second phase Israel, Multicentre Type 2 diabetes Normotensive Microalbuminuria *n* = 94	ACEi *vs* Placebo	AER	60 – on treatment 24 – choice for treatment	ACEi offers long term protection against the development of nephropathy in normotensive with microalbuminuria, and it stabilizes renal function in previously untreated patients with impaired renal function. Discontinuation of treatment results in renewed progression of nephropathy.
Ravid *et al.* (1998)[66]	RCT double blind Multicentre Type 2 diabetes Normotensive Normoalbuminuria *n* = 156	ACEi *vs* Placebo	UAE, creatinine clearance	70	ACEi attenuated the decline in renal function and reduced the extent of albuminuria in normotensive, normoalbuminuric people with type 2 diabetes.
Rosei *et al.* (2005)[94]	RCT Multicentre Type 2 diabetes Mild hypertension, either previously untreated for hypertension or unsuccessfully treated. *n* = 129	ACEi – enalapril (20 mg/day) *vs* ARB – candesartan (16 mg/day) (HCT used for additional treatment as required.)	UAE	6	Candestartan and enalapril showed similar effects on BP and circulating adhesion molecules. UAE was reduced significantly more by candestartan. However, the majority of patients had normal protein excretion and therefore difficult to extrapolate the results obtained.
Ruggenenti *et al.* (1998)[91] also Remuzzi *et al.* (2006)[92] BENEDICT	RCT Multi centre Type 2 diabetes Hypertension Normoalbuminuria *n* = 1204	– Verapamil – 240 mg/day – Tradolapril – 2 mg/day – Verapamil plus trandolapril *vs* Placebo	UAE	43.2	Additional agents permitted to achieve BP control. Trandolapril plus verapamil and trandolapril alone decreased incidence of microalbuminuria to similar extent. Verapamil alone no different to placebo.
Sano *et al.* (1996)[69]	RCT prospective Japan Type 2 diabetes Normotensive Microalbuminuria *n* = 62	ACEi *vs* No treatment	UAE, creatinine clearance	48	UAE in treated group decreased and increased slowly in untreated group.
Schram *et al.* (2005)[93]	RCT, double blind, double dummy Multi-centre, The Netherlands, Caucasian. Type 2 diabetes, Hypertensive, mean age in treatments 60 to 63, UAE <100 mg/d (normo and microalbuminuric) *n* = 70	HCT – 12.5 mg/d ACEi – 10 mg/d ARB – 8 mg/d *vs* Dummy placebos used to maintain double blind.	UAE (secondary outcome)	1 run in 4 to 6 titration period 12 study	There was no significant difference in the UAE between the treatment groups, which may be a consequence of the small sample size. Aggressive antihypertensive therapy can improve UAE in hypertensive people with type 2 diabetes regardless of the type of therapy used.
SMART Group (2007)[88]	RCT Type 2 diabetes with microalbuminuria *n* = 341	Valsartan *vs* mlodipine	ACR	3	Valsartan – ACR 68% of baseline Amlodipine – ACR 118% of baseline Remission – 23 *vs* 11% Regression – 34 *vs* 16%
Tan *et al.* (2002)[89]	RCT double blind Type 2 diabetes Microalbuminuria *n* = 80	ARB *vs* Placebo	UAE	6	People with type 2 diabetes and microalbuminuria have impaired endothelium-dependent and –independent vasodilatation. Treatment with low dose losartan is sufficient to reduce microalbuminuria without alteration in endothelial function and systemic blood pressure.

Table A3 *Continued*

Study ID	Study description	Intervention	Outcome relevant to CKD	Follow up (months)	Comments
The HOPE Study Group (2000)[18]	RCT Multicentre CVD or diabetes plus high CVD risk. (98% type 2 diabetes) *n* = 3577	Ramipril *vs* Placebo	Albuminuria (secondary outcome)	54	Significant reduction in risk of overt nephropathy in ramipril treatment group. No difference in risk of new microalbuminuria.
Trevisan & Tiengo (1995)[103]	RCT double blind Italy – multicentre Type 2 diabetes Microalbuminuria Normal or mild hypertension *n* = 122	ACEi *vs* Placebo	AER	6	Low dose ACEi can arrest the progressive rise in albuminuria in type 2 diabetes with persistent microalbuminuria.
UKPDS (1998)[65]	RCT Multicentre UK 20 hospital clinics Type 2 diabetes Hypertensive *n* = 1148	ACEi *vs* Beta blocker	UAE	100 (median)	BP lowering with captopril was similarly effective in reducing the incidence of diabetic complications.
UKPDS (1998)[8]	RCT Multicentre UK 20 hospital clinics Type 2 diabetes Hypertensive *n* = 1148	ACEi *vs* Beta blocker	Diabetes related deaths and all cause mortality. UAE	100 (median)	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
Viberti (2002)[90]	RCT Type 2 diabetes with microalbuminuria *n* = 332	Valsartan *vs* amlodipine (additional agents used to meet BP target of 135/80 mm/Hg)	AER	6	More patients reverted to normoalbuminuria with losartan 29.9% *vs* 14.5%). BP reductions were similar.
Yasuda *et al*. (2005)[79]	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	ARB – losartan 25 up to 100 mg/d CCB – amlodipine 2.5 up to 10 mg/d	UAE, ACR	6	ARB – UAE reduced from 810 mg/day to 570 mg/day ($P < 0.001$). CCB no drop. Similar for ACR significant drop for ARB ns 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.

Table A4 Summary of studies relevant to the role of blood lipid profiles in CKD in individuals with type 2 diabetes

Study ID	Study description	Intervention	Outcome (relevant to CKD)	Follow up (months)	Comments/conclusions
Ansquer *et al.* (2005)[113]	RCT 11 Centres located in Canada, Finland, France and Sweden Type 2 diabetes (40 to 65 years), normo or microalbuminuria, adequate glucose control, mild to moderate lipid abnormalities. $n = 314$	Fenofibrate *vs* Placebo	UAE (secondary to main study)	38 (average)	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.
Endo *et al.* (2006)[117]	RCT, open study, Single centre, Japan Type 2 diabetes, clinical albuminuria (UAE >300 mg/g Cr). 102 defined as advanced patients on the basis of serum Cr >2.0 mg/dL. $n = 102$	Probucol (500 mg/day). Protein restriction diet. Blood glucose control to HbA1c (<6.5%). Blood pressure control with CCB or α-blocker. *vs* No treatment Protein restriction diet. Blood glucose control to HbA1c (<6.5%). Blood pressure control with CCB or α-blocker.	UAE	36 (max) 28.5 (mean all) 18.6 (mean for advanced cases)	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 propucol may suppress the progression of diabetic nephropathy.
Gaede *et al.* (2003)[63]	RCT Type 2 diabetes, microalbuminuria $n = 160$	Multifactorial intensive treatment *vs* Standard treatment	UAE	94 (mean)	Target driven long-term intensified treatment aimed at multiple risk factors reduced nephropathy by about 50%.
Keech *et al.* (2005)[114] Radermecker & Scheen (2005)[115]	RCT Multicentre, multi country Type 2 diabetes, not taking statin therapy. $n = 9\,795$	Fenofibrate *vs* Placebo	UAE	60 (average)	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%).
Nagai *et al.* (2000)[116]	RCT Type 2 diabetes $n = 71$	Benzafibrate *vs* Pravastatin	UAE	48	UAE – no significant change over the 48 months with either drug. Conclude useful in preventative treatment of albuminuria and lipid lowering.
Nakamura *et al.* (2001)[112]	RCT, double blind Type 2 diabetes, microalbuminuria, dyslipidaemia $n = 60$	Cerivastatin *vs* Placebo	UAE	6	BP, HbAc1 not significantly affected. Total chl and LDL chl reduced and concomitant decrease in UAE.
Nishimura *et al.* (2001)[135]	RCT Multicentre, Japan Type 2 diabetes, normo and microalbuminuric $n = 168$	ACEi Probucol *vs* Placebo	UAE	24	ACEi has a beneficial effect and probucol may have a beneficial effect in preventing the progression of early diabetic nephropathy.
Sorof *et al.* (2006)[111]	RCT, double blind, parallel group Multicentre, Sweden Type 2 diabetes, dyslipidaemia (fasting LDL-C >3.3 mmol/L) >18 years (actual 65 years average), exclusions included – nephrotic syndrome, severe renal dysfunction, uncontrolled hypertension. $n = 344$	Rosuvastatin – 10 mg with titration up to 40 mg *vs* Atorvastatin – 10 mg with possible titration to 80 mg	UAE, GFR	6 weeks run in 4 month treatment.	No change from baseline UAE for either treatment group, no significant change in GFR for either treatment group.
The Heart Protection Study (2003)[108]	RCT Multicentre, UK Type 1 diabetes (10%) and type 2 diabetes (90%) 5963 – Diabetes 11307 – No diabetes	Simvastatin (40 mg/day) *vs* Placebo	Plasma creatinine, eGFR (retrospectively)	60	Allocation to simvastatin was associated with a significantly smaller fall in eGFR over the trial period (5.9 mL/min *vs* 6.7 mL/min) and was slightly larger among those with diabetes.

Table A5 Summary of studies relevant to the assessment of the role of dietary fat

Study ID	Study description	Intervention	Outcome (relevant to CKD)	Follow up (months)	Comments/conclusions
Barnard *et al.* (2006)[136]	RCT Type 2 diabetes *n* = 99	Low Fat Vegan *vs* ADA diet	UAE	5	UAE greater reduction in vegan diet. Also improved glycaemic and lipid control.
Cardenas *et al.* (2004)[118]	Prospective cohort Population based, multicentre Type 1 diabetes, type 2 diabetes *n* = 192		ACR	84	Normoalbuminuria 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.
Nicholson *et al.* (1999)[137]	RCT Type 2 diabetes *n* = 11	Low fat vegan *vs* Conventional low fat	UAE	3	No significant effect on UAE.
Nielsen *et al.* (1995)[138]	Before and after cross over. Pseudo randomized trial. Type 2 diabetes, persistent microalbuminuria *n* = 10	Diet rich in MUF *vs* Recommended high carbohydrate diet	UAE	3 weeks	No effect on UAE. However a potential beneficial effect on LDL/HDL ratio was detected.
Shimizu *et al.* (1995)[139]	Before and after non-randomized trial. Comparative study using patients grouped according to albuminuric status. Type 2 diabetes *n* = 115	Eicosapentaenoic acid ethyl (EPA-E) (present in cod liver oil)	ACR	12	Improved increased albumin excretion in type 2 diabetes with nephropathy and the effects were sustained at least 12 months after the start of treatment.

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

Study ID	Study design	Intervention	Outcome (relevant to CKD)	Follow up (months)	Comments/conclusions
Barsotti *et al.* (1998)[140]	RCT Type 1 diabetes, type 2 diabetes with chronic renal failure $n = 32$	Low protein diet *vs* Free	Residual renal function	62.4 (median)	Study confirms the protective effect of low protein diets on nephropathy in the absence of any sign of protein malnutrition.
de Mello *et al.* (2006)[141]	Before and after – random order of diet Crossover Type 2 diabetes, macroalbuminuric $n = 17$	Chicken (CD) Lactovegetarian Low Protein (LPD) *vs* Usual (UD)	GFR, UAE	4 wk for each diet	Withdrawing red meat from diet reduces UAE rate.
Dussol *et al.* (2005)[121]	RCT (unblinded) Single centre Type 1 diabetes and type 2 diabetes Incipient or overt nephropathy and mild renal failure, Strict BP control using ACEi or ARB $n = 63$	Low protein *vs* Usual protein (provided not greater than 1.2 g/kg per day)	GFR, UAE	24	The low protein diet did not alter the course of GFR or UAE. The impact of a low protein diet in preventing the progression of diabetic nephropathy, if any, is small.
Gross *et al.* (2002)[142]	RCT, cross over Type 2 diabetes, normo or microalbuminuric $n = 28$	Low protein Chicken (no red meat) *vs* Usual diet	GFR, UAE	1/1 with 1 washout between	Normoalbuminuric – both LP and chicken reduced UAE compared with normal diet. Microalbuminuric – only chicken reduced UAE compared with normal diet.
Meloni *et al.* (2004)[143]	RCT, prospective Nephrology out patients, 80 with DKD (24 type 1 diabetes, 56 type 2 diabetes) $n = 169$	Low protein diet *vs* Free protein diet	Renal function	12	Significant slowing of the progression of kidney damage was only observed in non-diabetics.
Pijls *et al.* (1999)[144]	RCT Type 2 diabetes, microalbuminuria $n = 121$	Counselling on protein restriction *vs* Usual advice	UAE	6 and 12	At 6 months experimental group had significantly. Lower protein intake and significantly. Lower UAE. At 12 months differences between groups had decreased.
Pijls *et al.* (2002)[145]	RCT Type 2 diabetes, microalbuminuria $n = 131$	Dietary counselling – protein restriction *vs* Usual dietary advice	GFR, UAE	28 ± 7	Protein intake between groups at follow at 6 months differed by only 0.08 g/kg per day. No differences 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 non-significantly difference in GFR. Conclude that protein restriction is neither feasible or efficacious.
Pomerleau *et al.* (1993)[146]	RCT, cross over Type 2 diabetes, normotensive $n = 12$	3 week moderate protein *vs* 3 week high protein	UAE, GFR, creatinine clearance	3 week/3 weeks	Moderate diet reduced the UAE, GFR, proteinuria and creatinine clearance without adversely affecting glycaemic control. High protein diet induced small changes in renal function.
Teixeira *et al.* (2004)[147]	Before and after cross over. Random order of interventions Type 2 diabetes $n = 14$	Isolated soy protein *vs* Casein	UAE	2/2 with 1 lead in and wash out	UAE significantly reduced in ISP compared with casein.
Wheeler *et al.* (2002)[148]	RCT, cross over Type 2 diabetes, microalbuminuric $n = 17$	Plant based protein *vs* Animal based protein	GFR, UAE	1.5/1.5	No significant difference between GFR and UAE.

Table A7 Summary of studies relevant to the assessment of the role of restricted salt intake

Study ID	Study design	Intervention	Outcome (relevant to CKD)	Follow up (months)	Comments/conclusions
Houlihan *et al*. (2000)[149]	RCT – w.r.t losartan and placebo Type 2 diabetes, hypertensive, microalbuminuric *n* = 17	Low sodium *vs* Normal sodium	UAE	1/1	Low salt amplified both anti-hypertensive and anti-proteinuric effects of losartan and no significant effect in the placebo.
Houlihan *et al*. (2002)[150]	RCT Type 2 diabetes, UAE 10–200 µg/day, hypertension *n* = 21	Losartan + low and high salt *vs* Placebo + low and high salt	TGF-beta (urine), UAE	1/1	The ARB not sodium restriction reduced urinary TGF-beta.
Houlihan *et al*. (2002)[151]	RCT Type 2 diabetes, UAE 10–200 µg/day *n* = 20	Losartan + low and high salt *vs* Placebo + low and high salt	ACR	1/1	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.
Imanishi *et al*. (2001)[152]	Before and after cross over Type 2 diabetes – normo to macroalbuminuria, normal levels of serum creatinine *n* = 32	Sodium restricted diet *vs* Normal sodium diet.	UAE	1 week/1 week	Sodium sensitivity of blood pressure appears before hypertension and is related to albuminuria.
Vedovato *et al*. (2004)[153]	Before and after Type 2 diabetes Case – microalbuminuria Control – normoalbuminuria *n* = 42	Reduced salt *vs* High salt	UAE	1 week	High salt increased BP and UAE.
Yoshioka *et al*. (1998)[154]	Cross over randomization is limited to the order of diet Type 2 diabetes, normo to macroalbuminuria. *n* = 19	Sodium restricted diet *vs* Normal sodium diet.	Calculated IgG and albumin fractional clearances.	1 week/1 week	Charge selectivity is lost before size selectivity as diabetic nephropathy progresses.

Table A8 Summary tables of studies of smoking as risk factor for the development and progression of CKD in people with type 2 diabetes

Study ID	Study design	Outcome (relevant to CKD)	Follow up (months)	Comments/conclusions
Anan *et al.* (2007)[155]	Cross sectional. Type 2 diabetes premenopausal women, $n = 20/35$ (Smokers/non-smokers)	UAE		UAE was independently associated with current smoking suggesting smoking as a risk factor for development of increased UAE.
Baggio *et al.* (2002)[156]	Cross sectional Type 2 diabetes with abnormal AER $n = 96$	UAE, GFR, GBM width		Smoking affects glomerular structure and function in type 2 diabetes and may be an important factor for the onset and progression of diabetic nephropathy.
Biarnes *et al.* (2005)[132]	Prospective cohort Type 2 diabetes, high cholesterol $n = 930$	Albuminuria	24	OR for smoker and development of microalbuminuria 3.19 (1.02–9.96).
Bruno *et al.* (1996)[26]	Cross sectional Type 2 diabetes $n = 1574$	UAE		Smoking habits are independently related to both micro and macroalbuminuria.
Cederholm *et al.* (2005)[131]	Prospective cohort Type 2 diabetes and type 1 diabetes 4097 (type 1 diabetes) 6513 (type 2 diabetes)	Albuminuria	60	Smoking identified as an independent risk factor for established microalbuminuria and for the development of microalbuminuria.
Chuahirun *et al.* (2003)[130]	Prospective cohort Type 2 diabetes undergoing BP control $n = 84$	Plasma creatinine, UAE	64	Smoking and increased UAE are interrelated predictors of nephropathy progression and smoking increases UAE in patients despite improved BP control and ACE inhibition.
Chuahirun *et al.* (2004)[129]	Prospective cohort Type 2 diabetes with and without macroalbuminuria. Smoking cessation in type 2 diabetes microalbuminuria $n = 237$	Urine excretion of TGFbetaV, UAE	6	Cigarette smoking exacerbates renal injury despite BP control and ACEi – cessation by those with microalbuminuria ameliorates the progressive renal injury caused by continual smoking.
Corradi *et al.* (1993)[157]	Cross sectional Type 2 diabetes, hypertensive, males $n = 90$	UAE		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.
Dean *et al.* (1994)[158]	Cross sectional Type 2 diabetes, normotensive $n = 87$	UAE		Relationship if any between smoking and UAE not stated in abstract

Table A8 *Continued*

Study ID	Study design	Outcome (relevant to CKD)	Follow up (months)	Comments/conclusions
Forsblom *et al.* (1998)[125]	Retrospective cohort Type 2 diabetes $n = 134$	UAE	108	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.
Gambaro *et al.* (2001)[126]	Retrospective cohort Italy Type 2 diabetes $n = 273$	AER, serum creatinine.	36	Logistic regression – smoking was the most important risk factor for progression of nephropathy. Quitting smoking should be part of the prevention therapy.
Gatling *et al.* (1988)[159]	Cross sectional Type 2 diabetes $n = 842$	UAE, ACR		Significant association found between UAE and smoking category.
Ikeda *et al.* (1997)[160]	Cross sectional Type 2 diabetes – men $n = 148$	ACR		OR for the prevalence of micro/macroalbuminuria was significantly higher for smokers than ex smokers.
Nilsson *et al.* (2004)[161]	Cross sectional Type 1 diabetes and type 2 diabetes Hospitals, primary health care $n \geq 17\,000$ type 2 diabetes	Albuminuria		Smoking was associated with poor glycaemic control and microalbuminuria.
Pijls *et al.* (2001)[162]	Cross sectional Type 2 diabetes – primary care patients $n = 335$	ACR		Smoking independently associated with ACR.
Savage *et al.* (1995)[163]	Cross sectional Type 2 diabetes with appropriate BP control $n = 933$	UAE		The most significant predictors of micro and macroalbuminuria were systolic hypertension, BMI, HDL, insulin use and smoking pack years.
Smulders *et al.* (1997)[127]	Prospective cohort Type 2 diabetes with microalbuminuria $n = 58$	ACR	24	Smoking was not a significant predictor of the progress of albuminuria.
Thomas *et al.* (2006)[164]	Cross section Type 2 diabetes Chinese males $n = 496$	ACR		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, $P = 0.040$)