National Evidence Based Guideline for Diagnosis, Prevention and Management of Chronic Kidney Disease in Type 2 Diabetes

Prepared by:
CARI Guidelines
Centre for Kidney Research &
NHMRC Centre of Clinical Research Excellence
The Children's Hospital at Westmead

In collaboration with:
The Diabetes Unit
Menzies Centre for Health Policy
The University of Sydney

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Diabetes Australia Guideline Development Consortium

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Diabetes Australia Guideline Development Consortium

The Diabetes Australia Guideline Development Consortium comprises Diabetes Australia; Australian Diabetes Society; the Australian Diabetes Educators' Association; the Royal Australian College of General Practitioners; and The Diabetes Unit, Menzies Centre for Health Policy, The University of Sydney.

A link to the guideline can be found on the Diabetes Australia website:
www.diabetesaustralia.com.au/For-Health-Professionals/Diabetes-National-Guidelines/

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Disclaimer

This document is a general guide to appropriate practice, to be followed subject to the clinician's judgement and the patient's preference in each individual case. The guidelines are designed to provide information to assist decision-making and are based on the beset evidence available at the time of development.

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Table of Contents

List of Tables:

Glossary of Acronyms

ACR	Albumin creatinine ratio
ACE	Angiotensin-converting enzyme
ACEi	Angiotensin-converting enzyme inhibitor
AER	Albumin excretion rate
ARB	Angiotensin receptor blocker
BMI	Body Mass Index
BP	Blood pressure
CCB	Calcium channel blocker
CG	Cockcroft-Gault
CHD	Chronic Heart Disease
CI	Confidence interval
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DKD	Diabetic kidney disease
ESKD	End stage kidney disease
ESRD	End stage renal disease
ESRF	End stage renal failure
GFR	Glomerular filtration rate
eGFR	Estimated glomerular filtration rate
GLY	Glyburide
HbA1c	Glycated haemoglobin
HDL	High density lipoprotein
IT	Immunoturbidimetry
KDOQI	Kidney Disease Outcomes Quality Initiative
LDL	Low density lipoprotein
MDRD	Modified Diet in Renal Disease
NEPH	Nephelometry
NHMRC	National Health and Medical Research Council
OR	Odds ratio
QALY	Quality adjusted life year
RBG	Random blood glucose
RCT	Randomised controlled trial
RIA	Radioimmunoassay
RID	Radial immunodiffusion
RSG	Rosiglitazone
SBP	Systolic blood pressure
UAC	Urinary albumin concentration
UAE	Urinary albumin excretion
UKPDS	UK Prospective Diabetes Study
WHO	World Health Organisation

Kidney Disease Expert Advisory Group

Co-Chairs	Professor Jonathan Craig Department of Nephrology The Children's Hospital at Westmead SYDNEY NSW
	Professor Steve Chadban Royal Prince Alfred Hospital Department of Renal Medicine Transplantation, CAMPERDOWN NSW
Australian Diabetes Society	A/Professor Stephen Twigg Endocrinology, Discipline of Medicine Central Clinical School, University of Sydney SYDNEY NSW
ADEA	Ms Marjory Ross Clinical Nurse / Credentialed Diabetes Educator The Queen Elizabeth Hospital ADELAIDE SA
Dieticians Association of Australia	Ms Annabelle Stack Lifestyle Disease's Stream Logan Hospital BRISBANE QLD
Content Experts	A/Professor Merlin Thomas Danielle Alberti Memorial Centre for Diabetic Complications Baker Medical Research Institute MELBOURNE VIC
	A/Professor Mark Thomas Renal Unit Royal Perth Hospital PERTH WA
	Dr Alan Cass Director Renal and Metabolic Division George Institute for International Health SYDNEY NSW
	Professor George Jerums Director of Endocrinology Austin Health Heidelberg Repatriation Hospital WEST HEIDELBERG VIC
	Dr Kathy Nicholls Dept of Nephrology Royal Melbourne Hospital PARKVILLE VIC
	A/Professor George Mangos Department of Medicine St George Hospital KOGARAH NSW

	Dr Richard McIsaac Endocrine Centre of Excellence Austin Health & University of Melbourne Heidelberg Repatriation Hospital HEIDELBERG WEST VIC
Consumer	Ms Kathy Green NORTH RYDE NSW 2113
Guideline Assessment Review Consultant	Dr Janet Salisbury Biotext YARRALUMLA ACT
Medical Advisor	Professor Stephen Colagiuri Institute of Obesity, Nutrition and Exercise Faculty of Medicine The University of Sydney
Project & Research Manager	Dr Seham Girgis The Diabetes Unit Australian Health Policy Institute The University of Sydney
Research Officers	Dr Martin Howell Research Officer CARI Guidelines Centre for Kidney Research & NHMRC Centre of Clinical Research Excellence Children's Hospital at Westmead WESTMEAD NSW
	Allison Tong Research Officer CARI Guidelines Centre for Kidney Research & NHMRC Centre of Clinical Research Excellence Children's Hospital at Westmead WESTMEAD NSW

Guideline for Prevention and Management of Chronic Kidney Disease in Type 2 Diabetes

Aim of the guideline

This guideline covers issues related to the prevention of chronic kidney disease (CKD) in individuals with established type 2 diabetes. The aim is to inform and guide the management of individuals with type 2 diabetes with evidence based information on what interventions prevent the development and/or progression of CKD. The target audience of this guideline is health practitioners, principally general practitioners.

These guidelines do not address the care of diabetic individuals with end-stage kidney disease or those who have a functional renal transplant. Such recommendations can be found elsewhere (www.kidney.org.au). 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, each of the recommendations for the prevention of CKD made in these guidelines must be balanced against the overall management needs of each individual patient.

Methods

The methods used to identify and critically appraise the evidence to formulate the guideline recommendations are described in detail in the Overview of Guideline Development Process and Methods (Apendix 5).

Guideline Format

Questions identified by the Expert Advisory Group (EAG) for the diagnosis, prevention and management of CKD in type 2 diabetes are shown on the next page.

Each of these questions is addressed in a separate section in a format presenting:

- ***Recommendation(s)***
- ***Practice Point (s) –*** including experts' consensus in absence of gradable evidence
- ***Evidence Statements –*** supporting the recommendations
- ***Background –*** to issues for the guideline
- ***Evidence –*** detailing and interpreting the key findings
- ***Evidence tables –*** summarising the evidence ratings for the articles reviewed

For all questions combined, supporting material appears at the end of the guideline topic and includes:

- ***References***
- ***Search Strategy and Yield Tables*** documenting the identification of the evidence sources

Questions for Chronic Kidney Disease

The following questions have been addressed in the preparation of the guidelines

1. How should kidney function be assessed and how often in people with type 2 diabetes?

2. How should chronic kidney disease be prevented and/or managed in people with type 2 diabetes?

    i. What is the role of blood glucose control?
    ii. What is the role of blood pressure control?
    iii. What is the role of blood lipid modification?
    iv. What is the role of diet modification?
    v. What is the role of smoking cessation?

3. Is the prevention and management of chronic kidney disease in people with type 2 diabetes cost effective and what are the socioeconomic implications?

Summary of Recommendations and Practice Points

Recommendations

1. Kidney status in people with type 2 diabetes should be assessed by: (GRADE B)*

   a. Annual screening for albuminuria by:

   Albumin Excretion Rate (AER) – timed urine collection.

   Microalbuminuria is indicated by:
   AER 30-300 mg/24 hrs or
   AER 20-200 µg/min in timed collection

   Macroalbuminuria is indicated by:
   AER >300 mg/24 hrs or
   AER >200 µg/min in timed collection

   OR

   Albumin: Creatinine Ratio (ACR) – spot urine sample.

   Microalbuminuria is indicated by:
   ACR 2.5 - 25 mg/mmol in males
   ACR 3.5 - 35 mg/mmol in females

   Macroalbuminuria is indicated by:
   ACR >25 mg/mmol in males
   ACR >35 mg/mmol in females

   If AER or ACR screening is positive for microalbuminuria:

   Perform additional ACR or AER measurements 1 to 2 times within 3 months. Microalbuminuria is confirmed if at least 2 of 3 tests (including the screening test) are positive.

   If AER or ACR screening is positive for macroalbuminuria:

   Perform a 24 hour urine collection for quantitation of protein excretion.

   AND

   b. Annual estimation of the Glomerular Filtration Rate (eGFR).

   eGFR <60 ml/min/1.73m^2 indicates at least moderate kidney dysfunction (Stage 3-5 CKD).

   eGFR 60-90 ml/min/1.73m^2 may indicate mild kidney dysfunction (Stage 2 CKD if albuminuria also present).

   c. Continue annual screening for albuminuria and eGFR in the event of negative screening tests.

* A single grade has been provided, however the recommendation has been based on evidence relating to both prognosis and diagnostic accuracy (refer to text).

2. Blood glucose control should be optimised aiming for a general HbA1c target ≤ 7%. (GRADE A).

3. In people with type 2 diabetes and microalbuminuria or macroalbuminuria, ARB or ACEi antihypertensive should be used to protect against progression of kidney disease. (GRADE A)

4. The blood pressure 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)

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

Practice Points

- Screening for microalbuminuria and Glomerular Filtration Rate (GFR) should be preformed on an annual basis from the time of diagnosis of type 2 diabetes.

- Albumin: Creatinine Ratio (ACR) should be measured using a morning urine sample, however random urine samples can be used.

- Measurement of urinary albumin can be influenced by a number of factors including:
  - urinary tract infection
  - high dietary protein intake
  - congestive heart failure
  - acute febrile illness
  - menstruation or vaginal discharge
  - water loading
  - drugs (NSAIDS, ACEi)

- Tests such as albumin concentration > 20 µg/litre or a dipstick test for albuminuria are semi-quantitative and should be confirmed by ACR or AER measurements.

- GFR is most commonly estimated using the MDRD equation which is based on serum creatinine, age and sex. The MDRD formula tends to underestimate GFR at levels greater than 60 ml/min but is more accurate at lower levels.

- GFR can be estimated using the Cockcroft-Gault formula which is based on serum creatinine, age, sex and body weight. The Cockcroft-Gault formula tends to underestimate GFR at levels less than 60 ml/min but is more accurate at higher levels.

- Interpretation of eGFR should refer to Kidney Health Australia report, "The Management of chronic kidney disease (CKD) in General Practice" (www.kidney.org.au), in brief:

  - eGFR < 30 ml/min/1.73 m^2 indicates severe CKD (Stage 4-5) and if persistent should prompt referral to a nephrologist.

  - eGFR 30 to 59 ml/min/1.73 m^2 indicates moderate kidney dysfunction (Stage 3 CKD). Referral to a nephrologist or endocrinologist interested in kidney disease should be considered.

  - eGFR 60-89 ml/min/1.73 m^2 may indicate mild kidney dysfunction. A detailed clinical assessment of glycaemic control, blood pressure and lipid profile is recommended in such cases.

- The HbA1c target may need to be individualised taking in to account history of hypoglycaemia and co-morbidities. refer to "Blood Glucose Control in Type 2 Diabetes" guidelines)

- 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.

- Due to potential renoprotective effects, the use of ACEi or ARB should be considered for the small subgroup of people with normal blood pressure who have type 2 diabetes and microalbuminuria.

- 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 diseases.

- Based on favourable cost studies, screening for microalbuminuria and treatment with antihypertensive medications should be routinely performed for the prevention and management of kidney disease in people with type 2 diabetes.

- Socio-economic factors should be considered when developing programs for prevention, and management of CKD in people with type 2 diabetes.

Overview of Chronic Kidney Disease in Type 2 Diabetes

Introduction

Diabetes is the leading cause of Chronic Kidney Disease (CKD) in developed countries (Zimmet et al, 2001). The AusDiab study found 27.6% of people with diabetes had CKD and the prevalence of CKD was three times higher in those with diabetes compared to those without (AIHW 2005; Chadban et al, 2003).

Chronic kidney disease has been defined by the Kidney Disease Outcomes Quality Initiative (KDOQI 2002) as: Glomerular filtration rate (GFR) <60ml/min/1.73 m^2 that is present for 3 months or more; or evidence of kidney damage for 3 months or more with or without decreased GFR as evidenced by any of the following: microalbuminuria; macroalbuminuria/proteinuria; glomerular haematuria; pathological abnormalities; anatomical abnormalities.

For the purpose of this guideline, CKD is defined as:

A level of kidney function associated with an increased risk of adverse clinical outcomes. For example, diabetic individuals with increased amounts of albumin in their urine or those with a reduced glomerular filtration rate (GFR) have an increased risk of morbidity and mortality. This risk is continuous with respect to these parameters, such that lowering albuminuria or preventing decline in GFR in an individual with type 2 diabetes is more important in preventing adverse outcomes than preventing transit over thresholds for which limited evidence is available to support biological relevance.

The stages of CKD are classified on the basis of the GFR as summarised in Table 1 below.

Table 1: Classification of chronic kidney disease GFR

Stage of Chronic Kidney Disease	GFR (ml/min per 1.73 m^2 body surface area)
1. Kidney damage (albuminuria, haematuria or abnormal kidney imaging) with normal eGFR.	≥90
2. Kidney damage with mild kidney dysfunction	60-89
3. Moderate kidney dysfunction	30-59
4. Severe kidney dysfunction	15-29
5. End Stage Kidney Disease (ESKD)	<15

The stages of diabetic kidney disease are not as clearly defined in type 2 diabetes as they are in type 1 diabetes and include microalbuminuria (incipient nephropathy), overt nephropathy (proteinuria/ macroalbuminuria, with or without renal insufficiency), renal insufficiency without albuminuria and ESKD. Microalbuminuria represents a mildly increased urinary albumin excretion commonly defined by an albumin excretion rate (AER) between 20-200 µg/min (30-300 mg/24 hours). At this stage of CKD dipstick tests for proteinuria are typically negative. Although hyperfiltration has been recognised in these early stages in people with

type 2 diabetes, renal and glomerular enlargement are not well documented. Proteinuria (macroalbuminuria) represents overt kidney disease and is defined by an AER persistently exceeding 200 μg/min (300 mg/24 hours). In addition it is associated with declining GFR and rising blood pressure. This stage usually follows several years of microalbuminuria (Mogensen 2003).

Prevalence of CKD in People with Type 2 Diabetes:

In people with type 2 diabetes, estimates of the prevalence of CKD are in the order of 5-30% with a cumulative incidence of approximately 10-40%. The lowest incidence is seen in elderly Caucasians and the highest in Pima Indians, Nauruans, Australian Aborigines, Maoris and African Americans. In early studies of elderly Caucasian people with type 2 diabetes, the risk of progression from microalbuminuria to proteinuria was reported as only 22% (Mogensen 1984) compared with 80% in people with type 1 diabetes and microalbuminuria with a similar follow up of 9 years (Mogensen & Christensen 1984). However, other studies in non-Caucasian people with type 2 diabetes have found a higher predictive value of microalbuminuria for overt nephropathy, similar to that in type 1 diabetes. For instance, in the Pima Indians, the four-year cumulative incidence of overt nephropathy was 37% (Nelson et al, 1996) and in young Jewish people with type 2 diabetes and microalbuminuria, the five year incidence of overt nephropathy was 42% (Ravid et al, 1993).

Approximately 1 in 6 people with type 2 diabetes develop overt nephropathy (macroalbuminuria) compared with 1 in 3 people with type 1 diabetes (Tung & Levin 1988). Once macroalbuminuria is present, the interval to the onset of ESKD varies from 4 to 18 years but can be delayed by intensive antihypertensive intervention based on inhibitors of the renin angiotensin system (Fabre et al, 1982; Parving 1998) [Refer to Section 2 of these guidelines].

In Australia, CKD associated with diabetes accounts for over 30% of new people entering ESKD treatment programs and has contributed to a large part of the increase in the incidence rate of ESKD (Australian and New Zealand Dialysis and Transplant Registry 2007). This is likely to continue to increase as the AusDiab study indicates that 7.4% of adult Australians now have diabetes, representing a 2-fold increase over the last 20 years (Barr et al, 2006; Dunstan et al, 2002). The ANZDATA Registry (Australian and New Zealand Dialysis and Transplant Registry 2007) shows a trend to an increasing proportion of new ESKD patients with type 2 diabetes from 28% in 2000 to 40% in 2006. In the AusDiab study the prevalence (adjusted for age and sex) for microalbuminuria and macroalbuminuria was 10.6% and 2.0% respectively in people with newly diagnosed diabetes and 23.2% and 5.8% respectively for those with known diabetes (Tapp et al, 2004). Furthermore, the prevalence of albuminuria increased with increasing glycaemia. People with diabetes and impaired glucose tolerance had an increased risk for albuminuria compared to those with normal glucose tolerance, independent of other known risk factors for albuminuria (including age and sex).

Despite survival bias, whereby many people with kidney disease and type 2 diabetes do not reach ESKD because of the increased cardiovascular mortality, CKD in people with type 2 diabetes is still the single most common cause of ESKD in Europe (Ritz & Orth 1999) and in the United States where it accounts for approximately 50% of all people enrolled in ESKD programs (US Renal Data System 2007). The review by Stewart and colleagues concluded that the increasing trend in the incidence of type 2 diabetes was a prime cause of the increasing incidence of ESKD in Australia (Stewart et al, 2004).

Natural History of Chronic Kidney Disease in people with Type 2 Diabetes

The natural history of CKD in people with type 2 diabetes has been characterised by changes in AER which may progress through three phases namely: normoalbuminuria (AER <20 μg/min), microalbuminuria (AER 20-200 μg/min) and proteinuria (macroalbuminuria) (AER >200 μg/min) [Table 2]. The proportion of people with type 2 diabetes who develop microalbuminuria is in the order of 25% after 10 years (Mogensen 2003). The stage of proteinuria, also called overt nephropathy, is typically characterised by the onset of a decline in GFR, and subsequently a rise in serum creatinine. Increased serum creatinine above the normal range occurs relatively late and indicates a loss of at least 50% of total kidney function. It should be noted that kidney disease remains asymptomatic until about 75% of kidney function has been lost (Bakris et al, 2000). However, up to 30% of people with type 2 diabetes who have a GFR < 60 ml/min/1.73 m^2 (i.e. Stage 3 CKD) may remain normoalbuminuric (Bash et al, 2008; Kramer & Molitch 2005). For this group the natural history of kidney disease has yet to be defined.

The GFR in people with type 2 diabetes typically begins to decline in the late microalbuminuric stage and, without intervention declines at an average rate of 8-12 ml/min/1.73 m^2/year (Biesenbach et al, 1994). However, it is important to note, that up to 30% of people with type 2 diabetes may be normoalbuminuric and have a GFR <60 ml/min/1.73 m^2 indicating CKD Stage 3 to 4 (Bash et al, 2008; Kramer & Molitch 2005). ESKD follows after 5-10 years dependent on the level of intervention [refer to Section 2 of these guidelines] (Morioka et al, 2001).

In observational studies, overt nephropathy has been shown to develop in approximately 20-50% of microalbuminuric people with type 2 diabetes over ten years. The risk of a major cardiovascular event in subjects with overt kidney disease and type 2 diabetes is 30% over ten years (Wang et al, 1996).

Persistent microalbuminuria usually indicates early (incipient) nephropathy in people with type 2 diabetes which may progress to overt nephropathy in about 50% of subjects over 10 years. However, microalbuminuria is also an indicator and predictor of generalised vascular disease, especially in the elderly, and is less specific for diabetic nephropathy in type 2 diabetes than in type 1 diabetes.

Although albuminuria is most accurately measured by albumin excretion in timed urine samples, measurement of ACR represents a convenient alternative especially for screening or follow-up once kidney status has been established (refer to Section 2 of these guidelines).

A summary of the relationship between urinary albumin and the progression of CKD in people with type 2 diabetes is presented in Table 2.

Table 2 : Natural history of kidney disease in type 2 diabetes where declining GFR is accompanied by increasing albuminuria

Stage	Urinary albumin		Dipstick	GFR* (ml/min per 1.73 m^2)	Serum Creatinine	BP	Prevalence (%)	Incidence (%)
	AER	ACR						
Normal	< 20 µg/min < 30 mg/24h	< 2.5 mg/mmol male < 3.5 mg/mmol female	Negative	Normal or increased ≥90	Normal	Normal or increased	45	-
Incipient kidney disease (Microalbuminuria)	20-200 µg/min 30-300 mg/24h	2.5-25 mg/mmol male 3.5-35 mg/mmol female	Negative	Normal or onset of decreased 60-89	Normal	Normal or increased	30	2-3
Overt nephropathy (Proteinuria / Macroalbuminuria)	≥ 200 µg/min > 300 mg/24h	≥ 25 mg/mmol male ≥ 35 mg/mmol female	Positive	Decreased 30-59	Normal	Increased	15	1-2
Renal insufficiency	As above	As above	Positive	Decreased 15-29	Increased	Increased	3-5	1
ESKD	As above	As above	Positive	Decreases <15	Increased	Increased	1-2	0.5

* GFR may decline below 60 ml/min per 1.73 m^2 in the absence of albuminuria. The prognosis for these individuals has yet to be defined.

Studies in Caucasian populations have shown a similar rate of progression from proteinuria (overt nephropathy) to ESKD in people with type 1 or type 2 diabetes (Ritz & Stefanski 1996). Apparent differences in the natural history of diabetic kidney disease in various studies may reflect variations in the prevalence of coronary heart disease (CHD) (leading to survival bias) and differences at the stage of detection of the nephropathic process (microalbuminuria vs. macroalbuminuria). The natural history of diabetic kidney disease is difficult to define because it will change over time and with changes in treatment for elevated blood pressure and diabetes. In type 2 diabetes, the predictive value of microalbuminuria for the development of macroalbuminuria is approximately 20% over 10 years in Caucasian populations (Mogensen 1984), but occurs at a rate of up to 5% per year (50% over 10 years) in non-Caucasian populations (Nelson et al, 1996; Ravid et al, 1993).

There are important similarities in the course of kidney disease in type 1 and type 2 diabetes. For instance, risk factors for the development of kidney disease include poor glycaemic control and increasing blood pressure in both types of diabetes. Also, once proteinuria develops its course is similar in type 1 and type 2 diabetes. Important differences in the natural history of kidney disease in type 1 and type 2 diabetes are that elevated blood pressure is commonly seen much earlier in the course of kidney disease in type 2 diabetes and a decline in GFR in the absence of albuminuria is more common in type 2 diabetes (Mogensen 1999).

Other causes of kidney disease resulting in increased albumin excretion may be present in a minority of people with type 2 diabetes. These so-called 'non-diabetic kidney diseases' include glomerulonephritis, polycystic kidney disease and immunoglobulin-A (IgA) diabetic kidney disease. Renal pathology may also be the result of primary hypertension, analgesic abuse or obstructive uropathy (Ritz & Stefanski 1996). Non-diabetic kidney disease influences kidney function and may determine the rate of progression to kidney failure and the response of proteinuria to therapy.

In contrast to the situation in type 1 diabetes, where proteinuria is almost always associated with typical diabetic kidney disease on biopsy, in type 2 diabetes the onset of proteinuria may

reflect different patterns of renal ultrastructural change including typical lesions, nephrosclerosis or forms of glomerular disease of non-diabetic type (Gambaro et al, 1993; Parving et al, 1992). Biopsy studies in people with type 2 diabetes have found non-diabetic lesions were present in about 10% to 30% of people with type 2 diabetes who had overt kidney disease but did not have retinopathy (Goldstein & Massry 1978; Olsen & Mogensen 1996; Schwartz et al, 1998). In approximately 25% of biopsies from people with diabetes and macroalbuminuria, coexistent non-diabetic kidney disease has been found (Parving et al, 1992; Taft et al, 1990). In a study of 53 randomly selected people with type 2 diabetes and microalbuminuria, no cases of definable non-diabetic kidney disease were found (Fioretto et al, 1998; Goldstein & Massry 1978). Furthermore, the rate of kidney disease progression may not be clearly related to the type of underlying glomerular ultrastructural lesions but rather to the level of urinary protein excretion (Ruggenenti et al, 1998). Thus, kidney biopsy is generally not warranted to establish a diagnosis of diabetic nephropathy.

Type 2 Diabetes, Chronic Kidney Disease and End Stage Kidney Disease

A worldwide increase in type 2 diabetes is contributing to an epidemic of diabetic related ESKD. Kidney disease in people with type 2 diabetes has been the most common cause of ESKD in Australia since 2004 (Table 3) (Australian and New Zealand Dialysis and Transplant Registry 2007). People from disadvantaged and transitional populations are disproportionately affected. Factors contributing to the high incidence rates of ESKD in these groups include a complex interplay between genetic susceptibility, age of onset of diabetes, glycaemic control, elevated blood pressure, obesity, smoking, socio-economic factors and access to health care [refer to Section 3 of these guidelines].

Table 3: Causes of primary kidney failure in new patients presenting to ESKD Centres in Australia

Cause of ESKD	% ESKD Patients			
	2003	2004	2005	2006
Diabetic Nephropathy	26	30	31	32
Glomerulonephritis	27	25	24	23
Hypertension	15	13	15	15
Polycystic Kidney Disease	5	7	7	6
Analgesic Nephropathy	4	2	3	2
Reflux Nephropathy	4	3	3	4
Miscellaneous	12	13	11	13
Uncertain Diagnosis	7	7	6	5

Source: ANZDATA Registry Report 2007

Chronic kidney disease affects approximately 5-30% of people with type 2 diabetes. At the time of diagnosis, an average of 15% of people with type 2 diabetes across all ethnic groups have elevated urinary albumin excretion. Progression to ESKD occurs in only 5-10% of elderly Caucasian people with type 2 diabetes, however this figure may be much higher in other populations (DeFronzo & Goodman 1995). ESKD is increasing in Australia in part related to the increase in type 2 diabetes in younger people (Dunstan et al, 2002). In Australia during 2006, diabetes was the primary cause of kidney disease in 32% of new patients presenting to ESKD centres followed by glomerulonephritis (23%) (Australian and New Zealand Dialysis and Transplant Registry 2007). The multinational review of End Stage

Renal Disease (ESRD) registries by the (ESRD Incidence Study Group et al, 2006) indicates an overall reduction in non diabetic causes of ESRD which the group consider to be consistent with the success of secondary prevention measures. However the study group have estimated that diabetic ESRD (which is predominantly type 2 diabetes) has "*continued to increase by over 3% per year in persons aged 45-64 years in the Europid populations in the study*." The estimate was made after accounting for changes in access to renal replacement therapy with time.

Diabetes is the leading cause of ESKD in Indigenous Australians accounting for approximately 48% of cases compared to approximately 23% in non Indigenous Australians over the period 2003 to 2006 (Appendix II of the ANZDATA Registry Report 2007). Studies over the last ten years have documented that in Aboriginal Australians, renal deaths have increased from 18 to 30-fold and the incidence of ESKD approaches 1000/million (Spencer et al, 1998). In the Northern Territory of Australia, all cause ESKD is 21 times higher in Aboriginal and Torres Strait Islanders communities compared with non-Aboriginal Australians. In addition, the incidence of ESKD is doubling every 3-4 years, in part because of better detection but also in real terms. In the Northern Territory, 96% of people on dialysis are Aboriginal and Torres Strait Islanders although they represent only 28% of the population (Spencer et al, 1998). Even within the Aboriginal population there is much heterogeneity, with the incidence of ESKD being 5-fold greater in the Tiwi Community than in the East Arnhem Community. Although multiple factors have been implicated, including post-streptococcal glomerulonephritis, an increased prevalence of diabetes is an important contributing factor. More recently Preston-Thomas et al (2007) confirmed the high rates of ESKD amongst Indigenous Australians, with the highest rates (17 times higher than the total Australian population) occurring in the most remote regions. The rate of increase in ESKD may be slowing which in turn may be consistent with a slowing in the rise in mortality rates in some chronic diseases in Indigenous Australians, however, not enough is known about the extent of early CKD (a predictor of CVD mortality and ESKD) in Indigenous Australians (Preston-Thomas et al, 2007).

In people with type 2 diabetes, progression of microalbuminuria to proteinuria varies with ethnicity and age, but once proteinuria is present the course of kidney disease is similar. Microalbuminuria affects an average of 25 to 30% of people with type 2 diabetes (Klein et al, 1993; Mattock et al, 1992). Although the prevalence of microalbuminuria is similar in type 1 and type 2 diabetes (Gall et al, 1991), the cumulative risk of ESKD is less in people with type 2 diabetes compared with type 1 diabetes, with one early study showing a cumulative risk of ESKD of 11% (Humphrey et al, 1989). The main reason for this disparity is that most Caucasian people with type 2 diabetes die from CVD before developing overt diabetic kidney disease (Schmitz & Vaeth 1988) resulting in survivor bias in published studies.

Cardiovascular Disease and Chronic Kidney Disease

Microalbuminuria is an independent risk factor for cardiovascular diseases (CVD) (Beilin et al, 1996; Dinneen & Gerstein 1997; Gerstein et al, 2001; Mogensen 2003). The presence of microalbuminuria in people with type 2 diabetes and elevated blood pressure indicates a 2-4 fold increase in cardiovascular risk when compared with those who are normoalbuminuric matched for age, sex and duration of diabetes (Mattock et al, 1992; Mogensen 1984; Schmitz & Vaeth 1988). This link between AER and CVD risk is considered by some to extend into what is currently defined as the normoalbuminuric range (Ritz 2006). However, it is still uncertain whether an increase in AER into the microalbuminuric range is itself contributing to the pathogenesis of vascular disease (Mogensen 1999). This is because microalbuminuria is usually associated with known cardiovascular risk factors, including raised blood pressure, quantitative and qualitative changes in the lipid profile, and procoagulant changes in the coagulation sequence. Ritz (2006) notes that there is growing evidence for a link between the

progression of albuminuria and development of insulin resistance in type 2 diabetes and that kidney disease may need to be considered as a key component rather than a consequence of the metabolic syndrome. However, there is insufficient evidence to test the hypothesis that minor derangements of kidney function directly cause endothelium dysfunction and thus directly contribute to CVD (Ritz 2006).

Risk factors shared by people with type 2 diabetes and CVD account for the excessive morbidity and mortality caused by macrovascular disease (Laakso 1998). Increased urinary albumin is more closely associated with CVD than ESKD in people with type 2 diabetes (Deckert et al, 1992; Mogensen 1984).

Microalbuminuria is a strong predictor of total and CVD mortality and morbidity in people with type 2 diabetes (Dinneen & Gerstein 1997). Kidney disease significantly increases cardiovascular morbidity and mortality in people with type 2 diabetes, being 2-4 fold higher in the presence of microalbuminuria and 4-8 fold higher with overt kidney disease (Gerstein et al, 2001). In the United Kingdom Prospective Diabetes Study (UKPDS) study, the death rate of individuals with type 2 diabetes with macroalbuminuria was greater than the rate of progression of ESKD (Adler et al, 2003). Microalbuminuria has also been associated with a three fold increase in the risk of hospitalisation for heart failure (Schocken et al, 2008).

Apart from its links with diabetic kidney disease, microalbuminuria also reflects widespread vascular disease (Deckert et al, 1992). Microalbuminuria independently predicts total and cardiovascular mortality in people with type 2 diabetes (Beilin et al, 1996; Jarrett et al, 1984; Mattock et al, 1992; Mogensen 1984) as well as in non-diabetic subjects (Damsgaard et al, 1990; Yudkin et al, 1988). In some but not all of these studies microalbuminuria predicted mortality independently of other conventional cardiovascular risk factors such as dyslipidaemia, elevated blood pressure and smoking.

People with type 2 diabetes and microalbuminuria have an annual total mortality of 8% and a cardiovascular mortality of 4% which is up to 4-fold higher than in people with type 2 diabetes without microalbuminuria (Mattock et al, 1992; Mogensen 1984; Schmitz & Vaeth 1988). Several longitudinal studies in Caucasian people with type 2 diabetes have confirmed that microalbuminuria is a better predictor of cardiovascular events than of microvascular disease (Gall et al, 1991; Mattock et al, 1992; Schmitz & Vaeth 1988). In elderly people with type 2 diabetes, the 10 year mortality is approximately 2-4 times higher in microalbuminuric compared with normoalbuminuric people (Mogensen 1984).

The exact molecular mechanisms linking an increase in urinary albumin to CVD are not known. However, increased AER is associated with generalised endothelial dysfunction (Deckert et al, 1992) which results in increased capillary permeability, a shift towards a procoagulant state and reversal of the normal vasodilatory response to acetylcholine. To what degree this increase in vascular risk is mediated by conventional risk factors such as elevated blood pressure, dyslipidaemia and glycaemic control as opposed to a specific effect of increased AER remains unclear.

Many factors may contribute to the increase in cardiovascular events associated with microalbuminuria. These include poor metabolic control which is also a risk factor for the progression of microalbuminuria in type 2 diabetes (Fioretto et al, 1996; Schmitz & Vaeth 1988) and high blood pressure (Tanaka et al, 1998). Other macrovascular risk factors include dyslipidaemia and hyperinsulinaemia (Niskanen et al, 1990; Uusitupa et al, 1993), indices of endothelial dysfunction including increased levels of Von Willebrand factor (Stehouwer et al, 1992), increased platelet adhesiveness and increased PAI-I and fibrinogen levels (Deckert et al, 1992; Nagi et al, 1996). Microalbuminuria in type 2 diabetes is also associated with

dyslipidaemia which has worsened in parallel with progression of proteinuria (Jerums et al, 1993).

Whilst there is uncertainty with respect to the relationship between CKD and the pathogenesis of CVD, it is clear that the prevention and management of CKD in people with type 2 diabetes is key to reducing their risk of CVD.

Individual Susceptibility to Type 2 Diabetes and Chronic Kidney Disease

There are racial, social, dietary and physical differences in susceptibility to type 2 diabetes and in rates of progression to its complications. In the United States, diabetic microvascular disease is substantially more common in minority populations. In people with type 2 diabetes proteinuria is twice as common in Mexican Americans than in non-Hispanic whites (Haffner et al, 1989). The rate of ESKD is up to 4 times higher in African Americans (Cowie et al, 1989), and more than 10 times higher in native Americans (Stahn et al, 1993) than in whites. The observational study by Karter et al (2002) of in excess of 62,000 people with diabetes with comparable health insurance coverage in the US indicate ethnic disparities for a range of complications despite similar access to medical services. The age and sex adjusted incidence of ESKD was highest for African-Americans at 6.8 per 1000 person years and lowest for Caucasians at 3.2 per 1000 person years. The ethnic differences were not consistent across the five health outcomes assessed with incidence rates for myocardial infarction, stroke, congestive heart failure and lower extremity amputation being similar.

Studies from a number of countries have shown that the prevalence of kidney disease in people with type 2 diabetes is high in certain ethnic groups. Diabetic nephropathy is a common primary cause of ESKD in New Zealand Maoris and in Pacific Islanders accounting for 61% and 49% of cases, respectively (Ritz & Orth 1999). These higher rates of ESKD also apply to Mexican Americans, African Americans and Indian Subcontinent (Burden et al, 1992; Held et al, 1991; Pugh et al, 1995). On the other hand data from the U.S. Renal Data System show that African Americans survive longer than Caucasians on dialysis (Held et al, 1991).

The prevalence of microalbuminuria and proteinuria is higher in Asians, Indians, African Americans and Hispanics compared with Caucasians. In many of these studies, these differences persist after correction for blood pressure, duration of diabetes and metabolic control (Allawi et al, 1988; Garza et al, 1997; McGill et al, 1996; Savage et al, 1995; Weijers et al, 1997).

An Australian study compared differences in the prevalence of microalbuminuria and proteinuria and elevated blood pressure among 1845 consecutive people with type 2 diabetes attending a Diabetes Centre for complications assessment (McGill et al, 1996). The seven ethnic groups in the study were Anglo-Celtic (n=896), Italian (n=246), Greek (n=209), Arabic (n=147), Chinese (n=131), Indian (n=115) and Aboriginal (n=101). After correction for age, duration of diabetes and glycaemic control, the Odds Ratio for microalbuminuria [based on 1 timed AER of 50-200 µg/min] relative to Anglo-Celts were higher in all groups and reached statistical significance for Arabic (OR 2.1; $p<0.05$) and Chinese (OR 1.9; $p<0.05$) people. Similar findings were observed for proteinuria (AER > 200µg/min) which reached statistical significance for Arabic (OR 3.0, $p<0.0005$), Aboriginal (OR 3.1, $p<0.0004$) and Italian (OR 1.8, $p=0.05$) people. This above study failed to show that Indian people in Australia had a higher prevalence of albuminuria than Caucasians which contrasts with the UK experience (Burden et al, 1992).

The persistence of ethnic differences in prevalence of diabetes related kidney disease after correction for confounding factors suggests that the presence of intrinsic differences in

susceptibility to CKD. Another possibility is that the rate of progression of diabetic kidney disease differs between ethnic groups, however, there are conflicting data on this issue (Garza et al, 1997; Koppiker et al, 1998; Varughese & Lip 2005). The review by Lindner et al (2003) concludes that overall the available studies indicate that diabetic nephropathy has a strong dependence on ethnicity with Caucasians of European origin having the lowest prevalence compared to North American Indigenous groups and African Americans.

Differences in the expression of kidney disease in different populations are related in part to marked differences in the age of onset of type 2 diabetes. There is a higher prevalence and more rapid progression of kidney disease in younger, non-Caucasian people with type 2 diabetes than in older Caucasian people with type 2 diabetes. The exact reasons for this are unknown. In Caucasian populations the onset of type 2 diabetes is usually between the sixth and ninth decades and kidney disease is confounded by the co-existence of elevated blood pressure and renal atherosclerosis. By contrast, in populations such as the Pima Indians and Aboriginal Australians, the onset of type 2 diabetes is generally between the third and sixth decades (Nelson et al, 1993; O'Dea 1991). The ANZDATA 2007 annual report (Australian and New Zealand Dialysis and Transplant Registry 2007) shows a disparity occurring in the relative incidence of ESKD between Aboriginal and non-Aboriginal Australians (peak incidence ratio approximately 15) in the 40 to 59 age group. Ethnic differences in the natural history of CKD in type 2 diabetes likely reflects a complex interplay between genetic predisposition to kidney disease and associations with vascular risk factors such as elevated blood pressure, dyslipidaemia and smoking (e.g. Satko et al, 2007). In addition, socioeconomic deprivation, with its attendant effects on access and attitudes to medical care, may play a role [refer to Section 3 of these guidelines]. The effects of the ageing process on kidney function may also play a part in differentiating kidney disease in type 2 diabetes from that in type 1 diabetes.

In Aboriginal Australians with type 2 diabetes, the nature of kidney disease is more complex than in other populations and it is not clear what proportion of kidney disease is attributable to diabetes. The presence of skin infections, post-streptococcal glomerulonephritis, alcoholism, multiparity in women and a family history of kidney disease, as well as features of the metabolic syndrome, are all associated with an increase in urinary albumin (Hoy 2000).

A population-based cross-sectional study in south-eastern Australia (Guest et al, 1993) highlighted the increased prevalence of albuminuria in Aboriginal Australians compared with Europids (Australians of European descent) (Table 4).

Table 4: Urine Albumin and Albumin Creatinine Ratios in Australian Aborigines and Europids

	Aboriginal men n=31	**Europid men n=148**		**Aboriginal women n=62**	**Europid women n=154**	
Albumin concentration >0.03 g/L	36%	14%	p<0.01	39%	18%	P<0.01
Albumin:creatinine ratio ≥ 1.30 mg/mmol	61%	12%	p<0.01	56%	23%	P<0.01

Source: Guest et al (1993)

Albuminuria is more common at every age in Aboriginal people with diabetes compared to those without diabetes (Hoy et al, 1998). The study by McGill et al (1996) reported a

significantly higher prevalence of macroalbuminuria (1 measurement: >200 μg/min) in Aboriginal people compared with Anglo-Celtic people (OR 3.1; p<0.0005). The study by Hoy et al (2007) reported a significantly higher rate of proteinuria (from 2.5 to 5.3 times) amongst adult volunteers from three remote communities in the Northern Territory, compared with the AusDiab study rates for non Indigenous Australians. Elevated rates of high blood pressure and diabetes were also recorded with an increased risk of having two or more conditions compared to non Indigenous Australians.

Familial clustering of diabetic kidney disease in type 1 diabetes has suggested that genetic factors may influence susceptibility to kidney disease (Seaquist et al, 1989). In type 2 diabetes, familial clustering of albuminuria (Pettitt et al, 1990), elevated blood pressure and cardiovascular complications has been recognised (Satko et al, 2007). These results are consistent with a genetic component that predisposes an individual with diabetes to develop kidney disease. However, the occurrence of kidney disease within families is not definite proof of genetic factors, since similar exposure to a common environment is not excluded (Ritz & Stefanski 1996). Although some associations have been found between certain genetic polymorphisms and kidney disease in type 2 diabetes, known genetic factors at present cannot explain the development of kidney disease in most people with type 2 diabetes. Any genetic susceptibility to kidney disease is most likely polygenic (Adler et al, 2000). Mogensen (2003) argue that it is probable that the genetic component of diabetic kidney disease is weak and may be more related to the presence of major phenotypic risk factors such as hyperglycaemia and elevated blood pressure.

In contrast to people with type 1 diabetes, most people with type 2 diabetes and diabetic kidney disease do not have living parents, therefore family studies are limited. Population studies suggest a genetic predisposition to diabetic kidney disease (Cowie et al, 1989; McGill et al, 1996; Nelson et al, 1993). However, phenotypic and genetic studies of diabetic nephropathy have shown very little progress despite the likely importance of genetic predispositions for both nephropathy and diabetes (Satko et al, 2007). Nonetheless, it has been shown that kidney disease clusters in families with type 2 diabetes. In Pima Indians, proteinuria occurred in 14% of diabetic offspring if neither parent with diabetes had proteinuria, 23% if one parent with diabetes had proteinuria and 46% if both parents had diabetes and proteinuria (Pettitt et al, 1990). These family data are compatible with a major gene effect being responsible for susceptibility to diabetic kidney disease in Pima Indians with type 2 diabetes (Imperatore et al, 1998).

The ACE gene, has been proposed as a candidate gene for a range of chronic diseases, including kidney disease, on the basis of several observations (Chowdhury et al, 1995):

1. Elevated blood pressure frequently accompanies kidney disease in people with diabetes.
2. ACE inhibitors may have a specific beneficial effect on progression of kidney disease in people with diabetes.
3. Serum ACE levels may be elevated in people with increased albuminuria.
4. Familial clustering of CVD has been noted to occur in diabetic kidney disease

Some of the candidate genes conferring susceptibility to chronic kidney disease in people with type 2 diabetes, apart from ACE, include angiotensinogen, apolipoprotein E, hepatocyte nuclear factor 1, interleukin-1 receptor antagonist, plasma kallikrein and matrix metalloproteinase genes (Adler et al, 2000).

Summary – Characteristics of Chronic Kidney Disease in Type 2 diabetes

- CKD in people with type 2 diabetes is the most common cause of ESKD in Australia. This largely reflects the increasing prevalence of type 2 diabetes in the Australian population.

- CKD in people with type 2 diabetes is a major risk factor for cardiovascular and all cause mortality.

- The majority but not all of CKD in type 2 diabetes is caused by diabetic kidney disease, and a definitive diagnosis (e.g. by biopsy) is likely to be of little value in overall patient management compared to assessment of albuminuria and rate of decline in GFR. Stages of CKD and subsequent recommendations for management have been defined on this basis.

- CKD in people with type 2 diabetes classically falls into two stages: incipient nephropathy (microalbuminuria with normal or elevated GFR) and overt nephropathy (macroalbuminuria, proteinuria and declining GFR) with the natural history of progression being from normal to incipient to overt nephropathy to ESKD. However, in people with type 2 diabetes who develop GFRs of < 60 ml/min/1.73m2 up to 30% have no significant albuminuria and for this group the natural history is yet to be defined.

- There is a strong association between CKD and CVD in people with type 2 diabetes.

- Familial clustering and ethnic differences in the prevalence of CKD in type 2 diabetes as well as genetic studies indicate a heritable component. However, this is likely to involve a complex interaction between environment and genetic susceptibility to factors associated with the natural history of CKD in type 2 diabetes, such as elevated blood pressure and hyperglycaemia as well as genetic factors related to renal outcomes.

Section 1: Assessment of Kidney Function

Question

How should kidney function be assessed and how often in people with type 2 diabetes?

Recommendations

Kidney status in people with type 2 diabetes should be assessed by: (GRADE B)*

a. Annual screening for albuminuria by:
Albumin Excretion Rate (AER) – timed urine collection.

Microalbuminuria is indicated by:
AER 30-300 mg/24 hrs or
AER 20-200 µg/min in timed collection

Macroalbuminuria is indicated by:
AER >300 mg/24 hrs or
AER >200 µg/min in timed collection

OR

Albumin: Creatinine Ratio (ACR) – spot urine sample.

Microalbuminuria is indicated by:
ACR 2.5 - 25 mg/mmol in males
ACR 3.5 - 35 mg/mmol in females

Macroalbuminuria is indicated by:
ACR >25 mg/mmol in males
ACR >35 mg/mmol in females

If AER or ACR screening is positive for microalbuminuria:
Perform additional ACR or AER measurements 1 to 2 times within 3 months. Microalbuminuria is confirmed if at least 2 of 3 tests (including the screening test) are positive.

If AER or ACR screening is positive for macroalbuminuria:
Perform a 24 hour urine collection for quantitation of protein excretion.

AND

b. Annual estimation of the Glomerular Filtration Rate (eGFR).

eGFR <60 ml/min/1.73m^2 indicates at least moderate kidney dysfunction (Stage 3-5 CKD).

eGFR 60-90 ml/min/1.73m^2 may indicate mild kidney dysfunction (Stage 2 CKD if albuminuria also present).

c. Continue annual screening for albuminuria and eGFR in the event of negative screening tests.

* A single grade has been provided, however the recommendation has been based on evidence relating to both prognosis and diagnostic accuracy (refer to text).

Practice Points

- Screening for microalbuminuria and Glomerular Filtration Rate (GFR) should be preformed on an annual basis from the time of diagnosis of type 2 diabetes.

- Albumin: Creatinine Ratio (ACR) should be measured using a morning urine sample, however random urine samples can be used.

- Measurement of urinary albumin can be influenced by a number of factors including:
    - urinary tract infection
    - high dietary protein intake
    - congestive heart failure
    - acute febrile illness
    - menstruation or vaginal discharge
    - water loading
    - drugs (NSAIDS, ACEi)

- Tests such as albumin concentration > 20 µg/litre or a dipstick test for albuminuria are semi-quantitative and should be confirmed by ACR or AER measurements.

- GFR is most commonly estimated using the MDRD equation which is based on serum creatinine, age and sex. The MDRD formula tends to underestimate GFR at levels greater than 60 ml/min but is more accurate at lower levels.

- GFR can be estimated using the Cockcroft-Gault formula which is based on serum creatinine, age, sex and body weight. The Cockcroft-Gault formula tends to underestimate GFR at levels less than 60 ml/min but is more accurate at higher levels.

- Interpretation of eGFR should refer to Kidney Health Australia report, "The Management of chronic kidney disease (CKD) in General Practice" (www.kidney.org.au), in brief:

    - eGFR < 30 ml/min/1.73 m^2 indicates severe CKD (Stage 4-5) and if persistent should prompt referral to a nephrologist.

    - eGFR 30 to 59 ml/min/1.73 m^2 indicates moderate kidney dysfunction (Stage 3 CKD). Referral to a nephrologist or endocrinologist interested in kidney disease should be considered.

    - eGFR 60-89 ml/min/1.73 m^2 may indicate mild kidney dysfunction. A detailed clinical assessment of glycaemic control, blood pressure and lipid profile is recommended in such cases.

Evidence Statements

- Microalbuminuria is a key predictor for the development of CKD in people with type 2 diabetes, however CKD may develop in the absence of abnormalities in albumin excretion
  Evidence Level II - Prognosis

- AER and ACR are the most common and reliable methods to assess albuminuria based on sensitivity and specificity, however both methods are subject to high intra-individual variability so that repeat tests are needed to confirm the diagnosis
  Evidence Level III - Diagnostic Accuracy

- Estimation of GFR (eGFR) based on serum creatinine is a pragmatic, clinically relevant approach to assessing kidney function in people with type 2 diabetes
  Evidence Level III - Diagnostic Accuracy

Background – Assessment of Kidney Function in Type 2 Diabetes

Introduction

It is important to recognise that CKD in individuals with type 2 diabetes is a multifactorial disorder, to which diabetes, elevated blood pressure, atherosclerosis, endothelial dysfunction and many other factors potentially contribute. In routine clinical practice and in most clinical trials it is not possible to determine the aetiology of CKD in individuals with type 2 diabetes. For example, the prevention of microalbuminuria in a type 2 diabetes trial may be due to effects on diabetic kidney disease, hypertensive kidney disease, or endothelial function. However, this question is irrelevant in diabetes care, as the presence of CKD is associated with adverse outcomes irrespective of the aetiology.

The introductory section of these guidelines provides a overview of the characteristics and progression of kidney disease in people with type 2 diabetes that form the basis for consideration of the assessment of kidney function. Screening for CKD aims to identify abnormal urine albumin excretion and declining GFR, so that interventions can be given to slow progression of kidney disease, to prevent ESKD and to reduce the risk of a CVD. Assessment of kidney function in people with type 2 diabetes includes measurement of urinary albumin excretion and estimation of GFR for the following purposes:

- Screening
- Diagnosis
- Monitoring response to management

In a significant proportion of people with type 2 diabetes, CKD may progress (i.e. declining GFR) in the absence of increasing albuminuria. Thus both GFR and albuminuria are important in screening, diagnosis and monitoring. Albuminuria may be assessed by measurement of the Albumin Excretion Rate (AER) or the Albumin Creatinine Ratio (ACR) with AER being regarded as the gold standard. The GFR is most commonly estimated rather than measured.

Albumin excretion typically increases in a continuous manner over several years, rather than showing an abrupt transition from normal to abnormal values. The average increase in AER ranges from 10-30% per year until overt nephropathy develops. However, in some people, the rate of increase in AER slows after the stage of microalbuminuria (Mogensen 2003). Regression from microalbuminuria to normoalbuminuria may occur in people with newly diagnosed type 2 diabetes due to interventions or for unknown reasons (KDOQI 2007; McIntosh et al, 2002), whilst in others regression does not occur (Niskanen et al, 1993). Regular monitoring of albuminuria in people with type 2 diabetes is warranted on the basis of the rate of progression of albuminuria in type 2 diabetes and ESKD associated with increasing albuminuria and the increased risk of CVD (Adler et al, 2003).

There is a high intra-individual variability in 24h albumin excretion with a coefficient of variation of 40-50%, therefore a diagnosis of persistent microalbuminuria should be based on repeated measurements, especially if long-term treatment of normotensive individuals are being considered.

Whilst increasing albuminuria is a risk factor for both CVD and ESKD, cross sectional studies have also shown a higher degree of heterogeneity in people with type 2 diabetes compared to type 1 diabetes with respect to CKD. As such a significant proportion of people with type 2 diabetes may have CKD and be normoalbuminuric (Kramer & Molitch 2005;

McIntosh et al, 2002; Tapp et al, 2004). In the recently reported ARIC study [a population based prospective biracial long term observational study of 2,187 individuals with predominantly type 2 diabetes], 30% of incident CKD (defined as eGFR < 60 ml/min/1.73m^2 or kidney disease at hospitalisation) did not have albuminuria (ACR ≥ 30 mg/g) (Bash et al, 2008).

In people who do not have diabetes, the expected rate of decline in GFR with ageing is approximately 1 ml/min per year (Kesteloot & Joossens 1996). A proportion of people with type 2 diabetes show a more rapid decline in GFR, in the absence of microalbuminuria or macroalbuminuria (Tsalamandris et al, 1994). In people with type 2 diabetes and established nephropathy, longitudinal studies have documented a decline in GFR without intervention of about 10 ml/min/year (Biesenbach et al, 1994). In people with type 1 diabetes, and overt kidney disease, the extent of early reduction in AER by ACEi predicts the degree of protection from subsequent decline in GFR) (Rossing et al, 1994). Whether this occurs in people with type 2 diabetes is not yet known.

Cross-sectional studies in people with type 2 diabetes and microalbuminuria have generally shown that GFR is normal, however, increased GFR (hyperfiltration) have been observed in cross sectional studies. For example the cross-sectional study of 158 microalbuminuric Danish patients where the GFR was increased (139 ± 29 ml/min) compared with 39 patients with normoalbuminuria (115 ± 19 ml/min) and 20 control subjects without diabetes (111 ± 23 ml/min) (Vedel et al, 1996). However, the cross-sectional study by Premaratne et al (2005) of 662 Australian people with type 2 diabetes showed no significant difference in AER and prevalence of microalbuminuria between hyperfilters and normofilters.

In people with type 2 diabetes and microalbuminuria some but not all longitudinal studies have documented a decline in GFR without intervention of about 3-6 ml/min/year. Lack of uniformity in results is in part due to study design, since most studies have focussed on albuminuria and have been too short to document clinically significant changes in GFR. In a Japanese study over 48 months, no change in GFR was demonstrated in 48 patients who were either untreated or treated with nifedipine, enalapril or both drugs (Sano et al, 1994). In another study of 103 normotensive Indians over 5 years, there was no change in GFR during treatment with placebo or enalapril (Ahmad et al, 1997).

By contrast, two studies have shown a significant decline in GFR in at least one study arm. In a 5 year study of 94 middle aged normotensive Israelis, GFR remained stable in those treated with enalapril but declined in those treated with placebo (Ravid et al, 1993). This study used the inverse of the serum creatinine level as an index of GFR. In a 3 year study of 18 hypertensive Italians, the GFR (measured isotopicaly) decreased in those treated with cilazapril or amlodipine (Velussi et al, 1996). In three other long term studies of microalbuminuric patients kidney function there was no change in serum creatinine over 5 years in a study of 102 hypertensive patients from Hong Kong (Chan et al, 2000) in a 3 year study of 10 hypertensive Italian patients (Gambardella et al, 1991) and in a 3 year study of normotensive and hypertensive French patients (Lacourciere et al, 1993).

Although not recognised as a stage of CKD, hyperfiltration (GFR > 130 ml/min/1.73 m2) represents an early phase of kidney dysfunction in diabetes. However, its clinical significance remains controversial. By definition, this phase can only be detected by measurement of GFR.

Laboratory Methods

The methods which can be used to assess urinary albumin and protein excretion include:

- Dipstick
- Measurement of AER on timed urine samples
- Measurement of ACR on spot urine

Timed urine collection, either 24h or overnight (usually 8h) is considered the gold standard for the measurement of albuminuria e.g (Polkinghorne, 2006). Shorter timed collection periods can be used (e.g. 4h) but these are time consuming for both patients and staff. AER and ACR on early morning urine are preferred as these tests are not subject to concentration bias.

Considerations in choosing a particular test for assessment of albuminuria include:

- The purpose for which the test is being done
- The performance of the assay
- The convenience and practicalities of specimen collection

Screening will result in identification of individuals who have an increased risk of kidney and cardiovascular morbidity and mortality. Screening should not be reserved for known high risk populations (e.g. age >40 years, Australian Aborigines, positive family history of kidney disease) but should be offered to all people with type 2 diabetes. In people with microalbuminuria, a reduction in AER has been documented with improved glycaemic control, blood pressure control, lipid profile optimization and specific renoprotective therapy with ACEi, or ARB (Mogensen 2003).

The evidence for how kidney function should be assessed consists mainly of cross sectional studies assessing various diagnostic tests against a reference method. In various clinical situations, ACR has been proposed as both a screening and diagnostic test for kidney disease (Connell et al, 1994). However many have recommended the use of ACR only in screening (Bennett et al, 1995; Jerums et al, 1994; Mogensen 1995; Viberti et al, 1994), as the test has a high false positive rate and low specificity. Albumin-to-creatinine ratio is also considered to have a useful monitoring role in diabetes with respect to detecting kidney disease progression and the evaluation of treatment effects (Warram et al, 1996).

All of the original assessments of microalbuminuria were based on AER measurements in timed urine collections. AER measurements performed in this way are still regarded as the gold standard for assessment of microalbuminuria. This presumes that the assay technique is sufficiently sensitive, the interassay coefficient of variation is less than 15% and at least 2 of 3 urine samples are in the appropriate range before a diagnosis of microalbuminuria is made (Sacks et al, 2002).

Albuminuria is commonly measured in the clinical laboratory by one of the following methods: radioimmunoassay (RIA), nephelometry (NEPH), immunoturbidimetry (IT) or radial immunodiffusion (RID). All of these methods are available as commercial kits. RIA is considered as the reference method for albumin measurement as it is the longest established assay. In an evaluation of RID, IT, NEPH against RIA the intra and interassay coefficient of variation (CV) of the methods were not found to be significantly different (Tiu et al, 1993). A second study has also found similar degrees of precision and accuracy between the RIA, RID, and IT methods. The IT method was found to be consistently lower than the RIA method (the difference was greatest for albumin concentrations > 30mg/L) although the difference was considered to be not clinically important (Watts et al, 1986). Comparison of albumin

concentrations measured by the different methods has however shown greater variability (Tiu et al, 1993; Watts et al, 1986).

Size-exclusion High-Performance Liquid Chromatography (HPLC) has been shown to give consistently higher urinary albumin concentrations particularly in people with diabetes when compared to the routine immunoassay techniques (Comper, 2004; Comper, 2005; Osicka, 2004; Russo, 2007).. The difference has been attributed to the presence of immunochemically nonreactive albumin which if measured has been postulated to allow for earlier prediction of microalbuminuria in people with type 1 and type 2 diabetes (Osicka, 2004). However, whether HPLC detects a form of albumin not detected by immunoassay (i.e. non-immunoreactive) or other molecules of approximately the same size as albumin, remains unresolved (Miller, 2009). An analysis of the AusDiab cohort, identified both HPLC-detected albumin and albumin detected by immunonephelometry as risk factors for mortality, however HPLC detected albumin identifies some people at increased risk of mortality that are not detected by immunonephelometry (Magliano, 2007). The clinical significance of HPLC versus immunoassay detected urinary protein has not been established (Polkinghorne, 2006).

The choice of method to be used by a particular laboratory depends on factors such as equipment availability, the number of samples to be processed and the required turnover time for results. There are advantages and disadvantages for each of the methods and these are discussed below.

1. Radioimmunoassay (RIA)
   Advantages: established reliability.
   Disadvantages: assay time of 2hrs; rapid deterioration of reagents; handling precautions; needs a gamma counter; expensive; not suitable for a few samples a day; time consuming.
2. Radial immunodiffusion (RID)
   Advantages: no sophisticated equipment required; convenient for a small number of samples.
   Disadvantages: assay time of 2 hrs.
3. Nephelometry (NEPH)
   Advantages: wide range; assay time of ½ hr; simple calibration.
   Disadvantages: expensive equipment required.
4. Immunoturbidimetry (IT)
   Advantages: assay time of 1 hr; wide range; least expensive.
   Disadvantages: requires multiple samples for standard curves with each assay.

In summary, any of the 4 methods are suitable for routine use. Variation between methods however may influence comparison of results between laboratories or by different methods within the one laboratory.

A number of groups have demonstrated that storage of frozen urine samples (for 2 weeks to 6 months) at -20^{o}C results in lower measurements of microalbuminuria compared with freshly analysed samples (Elving et al, 1989; Osberg et al, 1990). However one group has reported that adequate mixing (3-4 hand inversions) after thawing of frozen aliquots resulted in the same albumin values as unfrozen aliquots measured by nephelometry (Innanen et al, 1997). This same group found however, that a small number of samples (2 to 9), despite mixing, gave falsely low urinary albumin results by up to 50%. It is postulated that freezing may distort the target albumin antigen in such a way that antibodies may not detect all of the albumin present.

Studies of unfrozen urine samples stored at 4^{o}C for up to 8 weeks have shown no significant effect on urinary albumin (Osberg et al, 1990). It has also been reported that albumin in urine is stable when stored at room temperature for one week (Hara et al, 1994). In view of these findings, it is considered that urinary albumin measurement should either be analysed as fresh

specimens or stored unfrozen at 4^{o}C and assayed within 8 weeks. Timed urine collection (either overnight or 24h) or a single void early morning urine sample should be obtained.

Confounding factors in assessment of albuminuria

Urinary albumin results can be affected by several confounding factors and the interpretation of albuminuria should take these into consideration. The following factors may affect urinary albumin results (Mogensen 1995; Mogensen et al, 1995).

- Urinary tract infection
- High dietary protein intake
- Congestive heart failure
- Acute febrile illness
- Menstruation or vaginal discharge
- Water loading
- Drugs (NSAIDS, ACE inhibitors)

In addition it is advisable to avoid assessing AER within 24 hours of high-level exercise or fever.

Glomerular Filtration Rate

An accurate measure of GFR can be undertaken using low molecular weight markers of kidney function such as inulin, iohexol or technetium (labelled DTPA), however the methods are time consuming, expensive and generally not available (Mathew & Australasian Creatinine Consensus Working Group 2005). In addition to direct measurement of GFR by isotopic methods there are several methods for estimating GFR. The measurement of 24h creatinine clearance tends to underestimate hyperfiltration and overestimate low GFR levels and is subject to errors in urine collection unless great care is taken. The regular measurement of serum creatinine levels is easy to perform and is currently the most common method. However because creatinine is invariably reabsorbed by the renal tubules, serum creatinine and creatinine clearance measurements tend to underestimate the GFR in the context of hyperfiltration and over estimate the GFR in the context of hypofiltration (Shemesh et al, 1985).

In addition, for optimal approximation of GFR from serum creatinine measurements allowances need to be made for age, gender, height and weight of the individual. If the variables are taken into account, as in the Cockcroft-Gault (CG) and Modified Diet in Renal Disease (MDRD) equations, a satisfactory index of GFR can be achieved. This is particularly important in thin elderly female people whose baseline serum creatinine levels may be as low as 40-50 μM. In these people delay in referral until the serum creatinine rises above 110 μM would imply that more than 50% of kidney function had been lost (Levey et al, 1999).

The 6 variable and 4 variable MDRD equations used for the estimation of GFR were developed from general populations (i.e. not specifically people with type 2 diabetes). The 6 variable equation , which is the most commonly used equation for the estimation of GFR, was derived from the Modified Diet in Renal Disease study and includes the variables: creatinine, age, gender, race, serum urea nitrogen and serum albumin as follows (KDOQI 2002):

- eGFR = 170 x serum creatinine (mg/dl)-0.999 x age (yr)-0.176 x 0.762 (if female) x 1.18 (if male) x serum urea nitrogen (mg/dl)-0.17 x albumin (g/l)+0.318

The 6 variable MDRD equation correlated well with directly measured GFR (R^2=90.3%).

The modified 4 variable MDRD , again developed from general populations and not specific to people with type 2 diabetes is as follows (Levey et al, 1999):

- eGFR = 186 x serum creatinine-1.154 x age -0.203 x 1.212 (if black) x 0.742 (if female)

The 4 variable MDRD equation also correlated well with directly measured GFR (R^2=89.2%). By contrast, 24h creatinine clearance or the Cockcroft-Gault equation overestimated subnormal GFR levels by 19% and 16% respectively (Levey et al, 1999; Manjunath et al, 2001).

The position statement of the Australasian Creatinine Consensus Working Group recommend that an eGFR be automatically calculated and reported for every request for serum creatinine measurement in people of 18 years and over using the abbreviated MDRD equation (Mathew & Australasian Creatinine Consensus Working Group 2005). On the basis of survey and anecdotal information, the group considered that the vast majority of laboratory reports in Australia and New Zealand comply with this recommendation (Mathew et al, 2007). Some key aspects of the recommendations from the Australasian Creatinine Consensus Working Group are summarised below:

- Pathology laboratories should automatically report eGFR calculated using the "175" MDRD formula, with every request for serum creatinine.
- eGFR values over 90 mL/min/1.73 m2 should only be reported as > 90 mL/min/1.73 m2.
- Pending further studies laboratories also should report eGFR for Australian Aboriginal and Torres Strait Islander peoples and other ethnic groups (previously no recommendation had been made).

Measurement of serum cystatin C can be also used to estimate GFR. This may be more accurate than creatinine based eGFR methods particularly at normal levels (90-120 ml/min) or above normal levels (> 120 ml/min) but the assay is more expensive and is not yet generally available. Serial measurements of cystatin C levels have been shown to estimate progressive decline of GFR more accurately than creatinine based methods in both type 1 and type 2 diabetes. As with serum creatinine, the cystatin C is affected by factors other than the GFR and as with creatinine, knowledge of these factors is required in both estimating the GFR and interpretation of eGFR in particular populations. Currently the non GFR factors associated with cystatin C are poorly defined which limits the routine application of serum cystatin C in the estimation of GFR both in people with and without type 2 diabetes (e.g. Knight, 2004; Sjostrom, 2009; Stevens, 2008). The recent review by Stevens (2008) indicated many factors other than GFR to be associated with serum cystatin-C, including diabetes, measures of body size, higher C-reactive protein, higher white blood cell and lower serum albumin. The impact of these non GFR factors on serum cystatin C appear to be less than the non GFR influences on serum creatinine, however they remain poorly defined and may introduce significant variability within select sub populations. The recent study by Tidman et al (2008) concluded that the use of cystatin C only as "*a determinator of eGFR does not yield improved accuracy"* over estimation using the MDRD formula alone, however a formula that combines both serum creatinine and cystatin C may provide greater accuracy, consistent with the conclusions made by (Stevens, 2008).

Evidence – Assessment of Kidney Function in Type 2 Diabetes

Microalbuminuria and CKD

- **Microalbuminuria is a key predictor for the development of CKD in people with type 2 diabetes, however CKD may develop in the absence of abnormalities in albumin excretion *(Level II - Prognosis)*.**

Two retrospective studies in the early 1980s demonstrated that small increases in urinary AER predicted the development of overt nephropathy in people with type 1 diabetes (Mogensen & Christensen 1984; Viberti et al, 1982). This increase in AER was termed microalbuminuria and by consensus, referred to levels of AER of 20-200 μg/min in at lease 2 of 3 samples. By comparison, in healthy subjects, AER ranges from 3-11 μg/min (Viberti et al, 1982) and routine dipstick tests do not become positive until AER exceeds 200μg/min (equivalent to total proteinuria of 0.5g/24h). Subsequent studies showed that microalbuminuria also predicts the development of clinical overt diabetic nephropathy in type 2 diabetes (Mogensen 1984; Nelson et al, 1996) although it is not as strong a predictor as it is in type 1 diabetes. Persistent microalbuminuria confers an approximately 5 fold increase in the risk of overt nephropathy over 10 years in Caucasian persons with type 2 diabetes (approximately 20% cumulative incidence), compared with a 20 fold increase in risk of nephropathy in type 1 diabetes (approximately 80% cumulative incidence). However, in certain ethnic populations with a high prevalence of type 2 diabetes and diabetic nephropathy, including Pima Indians, Mexican Americans, African Americans, Maoris and Australian Aborigines, microalbuminuria is as strong a predictor of nephropathy as in type 1 diabetes (Hoy et al, 2001; Nelson et al, 1996; Pugh et al, 1995).

The prospective cohort type study of 599 normoalbuminuric people with type 2 diabetes (Rachmani et al, 2000), found the baseline AER as a significant predictor of a subsequent decline in renal function as well as the risk of mortality and CVD (median follow up of 8 years).

The usefulness of microalbuminuria as a predictor of overt nephropathy in people with type 2 diabetes is shown in the accompanying Table 5 adapted from Parving et al (2002). The studies selected in the are RCT trials of varying size and duration that the measured the progression of albuminuria as a primary outcome. Parving et al, (2002) concluded that the studies collectively show the value of microalbuminuria as a predictor of overt nephropathy based on the rate of development of overt nephropathy amongst the placebo groups.

Table 5: Progression of microalbuminuria to overt nephropathy in people with type 2 diabetes.

Study ID	N	Observation period (yrs)	Individuals developing overt nephropathy (%/yr)
Mogensen (1984)	59	9	2.4
Nelson et al (1996)	50	4	9.3
Ravid et al (1996)	49	5	8.4
Gaede et al (1999)	80	4	5.8
Ahmad et al (1997)	51	5	4.8
Estacio et al (2000)	150	5	4.0
The HOPE Study Group (2000)	1140	4.5	4.5
Parving et al (2001)	201	2	7.5
Parving (2001)	86	5	7.0
Bruno et al (2003)	1253 (765 normoalbuminuria, 488 microalbuminuria)	7	3.7

Adapted from Parving et al (2002)

Other prospective studies where the rate of decline in GFR was found to be enhanced in people with microalbuminuria are:

- Murussi et al (2006) (n=65) –normoalbuminuric people with type 2 diabetes showed a similar rate of decline in GFR over a 10 year period (<2 ml/min/1.73m2 per year) as people without type 2 diabetes. In contrast in people with type 2 diabetes and microalbuminuria a GFR decline of 4.7 ml/min/1.73m2 per year was recorded.

- Murussi et al (2007) (n=193) – the urinary albumin excretion (UAE) rate (even within the normal limits) was a significant baseline predictor of mortality (rate of 19%) over an 8 year follow up period whilst eGFR was not significant. Baseline UAE was also a predictor of micro- and macroalbuminuria which had a cumulative incidence of 26%.

Whilst microalbuminuria in people with type 2 diabetes is an important risk factor for CKD and CVD, it is important to recognise that kidney disease in type 2 diabetes is more heterogeneous than in type 1 diabetes and that a significant number of people will develop CKD (i.e. declining GFR) without development of persistent microalbuminuria (refer to Overview Section) of these guidelines.

In a US population cross sectional study reported by Kramer et al (2003) 13% of adults with type 2 diabetes had CKD as defined by an eGFR <60 ml/min per 1.73 m^2. Of these 30 % had neither abnormal albuminuria or retinopathy taking into account the use of ACE inhibitors. Similarly, Tsalamandris et al (1994) report that in 40 adults with worsening kidney disease and both type 1 diabetes (n=18) and type 2 diabetes (n=22), 8 of the 22 people (36%) with type 2 diabetes had normal albumin excretion over the 8 to 14 year follow up period, while the creatinine clearance declined at a rate of 4/ml/min/year.

In a small prospective cohort study (n=13) of type 2 diabetes outpatients who were normotensive to borderline hypertensive, in the absence of hypertensive agents, a median rate of GFR decline of 4.5 (0.4 to 12) ml/min/yr with a rise in albuminuria of 494 (301-1868) to 908 (108-2169) mg/24hr (P=0.25) was observed, however there was no significant correlation between change in albuminuria and decline in eGFR (Christensen et al, 1999).

In a retrospective cross sectional study of 301 adults with type 2 diabetes attending an outpatients clinic in Melbourne, the majority with reduced measured GFR (<60 ml/min/1.73 m^2) were found to have microalbuminuria or macroalbuminuria, however, 39 % (23 % after exclusion of individuals using ACEi or ARB antihypertensives) were found to be normoalbuminuric. The rate of decline in measured GFR in this group was 4.6 ml/min/1.73 m^2 per year and was not significantly different to people with microalbuminuria and macroalbuminuria (MacIsaac et al, 2004).

A prospective cohort study of 108 people with type 2 diabetes with microalbuminuria or macroalbuminuria found the course of kidney function to be heterogeneous (Nosadini et al, 2000). A greater number who progressed from microalbuminuria to macroalbuminuria were classified as progressors as defined by an elevated rate of decline of GFR, and a greater number who regressed from microalbuminuria to normoalbuminuria were identified as non-progressors as defined by the rate of decline in GFR. However, the level of AER both at baseline and during the 4 year follow up was a poor predictor of the loss of kidney function among microalbuminuric patients. The authors conclude that the heterogeneity of the course of kidney function meant that abnormalities in AER have a *"different renal prognostic value"* amongst subgroups of people with type 2 diabetes.

These studies demonstrate that a significant decline in GFR may occur in adults with type 2 diabetes in the absence of increased urine albumin excretion. Thus screening of people with type 2 diabetes needs also to include GFR in order to identify individuals at increased risk of ESKD.

Measurement of Albuminuria

- **AER and ACR are the most common and reliable methods to assess albuminuria based on sensitivity and specificity, however both methods are subject to high intra-individual variability so that repeat tests are needed to confirm the diagnosis *(Level III - Diagnostic Accuracy).***

A systematic review of the effectiveness of screening methods for microalbuminuria in the prevention of nephropathy in people with both type 1 diabetes and type 2 diabetes has been undertaken by Scheid et al (2001). Key findings of the review were:

- No controlled trials of microalbuminuria screening were identified.
- Quantitative tests (AER and ACR) have reported sensitivities of 56% to 100% and specificities of 81% to 98%. Test performance was similar for all types of urine samples.
- Semiquantitative tests (e.g. Micral) have reported sensitivities of 51% to 100 % and specificities of 21% to 100%. The sensitivity has been reported to vary with the level of experience of the operators being lowest for general practitioners and highest for laboratory technicians. Thus accuracy may not be reliable in all settings.

Assessment of proteinuria by spot protein:creatinine ratio is appropriate for macroalbuminuria (100% sensitivity, 92% specificity) (Zelmanovitz et al, 1998). However this is not sufficiently sensitive for assessment of microalbuminuria. Previous studies have shown the inherent variability in 24h AER to be in the range of 40-50% (Feldt-Rasmussen et al, 1985). This variability is thought to be related to such factors as posture, activity level, diet and glycaemic control. The variability of overnight AER has been shown to be similar to 24h collections however the AER in overnight urine samples is 25% lower compared with 24h urine samples, and has a lower intra-individual variability (Eshoj et al, 1987).

Screening tests are designed to maximise true positive results (i.e. high sensitivity) at the expense of performing a greater number of confirmatory tests. Several studies have examined the relationship between AER and ACR performed on the same timed urine sample (Bakker 1999; Connell et al, 1994; Hutchison et al, 1988; Shield et al, 1995; Wiegmann et al, 1990), however only 2 of these took gender into account (Bakker 1999; Connell et al, 1994). A number of studies have also compared ACR on a spot urine or early morning sample with a timed AER (Eshoj et al, 1987; Marshall & Alberti 1986; Nathan et al, 1987; Wiegmann et al, 1990; Zelmanovitz et al, 1997) however none of these studies were stratified by gender. In these studies timed urine collections were used as the gold standard for comparison. Using the recommended cut-off values, the sensitivities of spot ACR in these studies were ≥ 88%. However different definitions for microalbuminuria on the timed collections (15-30μg/min) as well as varying definitions for a "positive" ACR level (2.0-4.5 mg/mmol) were used.

Because of high intra-individual variability, transient elevations of AER into the microalbuminuric range occur frequently. The 95%CI for a sample with AER of 20 μg/min, assuming a coefficient of variation of 20%, are 12-28 μg/min (1 measurement), 14-26 μg/min (2 measurements) and 15-25 μg/min (3 measurements) (Tsalamandris et al, 1998). Therefore, clinical assessment should be based on at least 2 measurements taken over 3-6 months.

Another option for assessment of albuminuria is the ACR which is usually performed on an early morning urine but can also be performed on a random sample. The use of ACR for assessment of microalbuminuria is easier and less time-consuming for the patient than measurement of AER. ACR measurements are particularly useful for screening purposes and for assessing the effects of treatment. For instance, measurements at every visit can be used to evaluate the albuminuric response separately from the blood pressure response during titration of antihypertensive therapy. Comparisons of ACR to the gold standard AER have been made in several studies. All the studies show satisfactory sensitivity (80-100%) and specificity (81-100%) (refer to Table 6 for summary). Table 6 includes a summary of the key components of the cross sectional studies in relation to the assessment of the applicability of ACR.

Table 6: ACR – sensitivity and specificity for microalbuminuria screening

Study ID	Reference method for AER	Reference level for AER	ACR urine sample	ACR result	Sensitivity (%)	Specificity (%)
Bakker (1999)	Immunoturbidimetry (overnight sample)	20 µg/min	Overnight	2.5 mg/mmol (female) 1.8 mg/mmol (male)	94 (female) 94 (male)	92 (female) 93 (male)
Gatling et al (1985)	Micro-ELISA (overnight sample)	AER 30 µg/min	Early morning	>3.5 mg/mmol	86	97
Hutchison et al (1988)	Radioimmunoassay (overnight sample)	AER 30 µg/min	Early morning	>3.0 mg/mmol	97	94
Nathan et al (1987)	Radioimmunoassay (24 hr sample)	44 mg/24hr	24 hr	3.4 mg/mmol	100	100
Parsons et al (1999)	Immunoturbidimetry (24 hr sample)	20mg/l	24 hr	2.65 mg/mmol	95	79
Poulsen & Mogensen (1998)	Immunoturbidimetry (overnight sample)	ACR 3.5 mg/mmol (female), 2.5 mg/mmol (male)	Not stated	>3.5 mg/mmol (female) >2.5 mg/mmol (male)	91	98

A large study of people with type 2 diabetes from the United States showed that ACR, measured on a random urine sample, in the range 3.0 – 37.8 mg/mmol was over 88% sensitive and specific for the presence of microalbuminuria (Zelmanovitz et al, 1997). However it is important to note that the microalbuminuria range for ACR is influenced by both gender and age. There were approximately 30% false positives for ACR in people aged >65 years in a more recent study by Houlihan et al (2002c). For these reasons ACR has limitations as a diagnostic test but remains an excellent screening test for microalbuminuria.

ACR performed on overnight urine samples has been reported in a number of studies as the least variable parameter (lowest co-efficient of variation) for measuring microalbuminuria. The coefficient of variation for the day to day variability or urinary creatinine excretion is in the range of 8-13% (Smulders et al, 1998) and 40-50% for AER (Feldt-Rasmussen et al, 1985). As discussed by others, the reasons for this variability include changes in blood pressure, activity and fluid intake for albumin excretion, and changes in dietary protein intake for creatinine excretion (e.g Mogensen 1995 and Flynn et al, 1992). Previous studies have shown the intra-individual coefficient of variation for ACR to be 49% in first morning urine samples (McHardy et al, 1991) compared with 27% in timed overnight urine collections. ACR on overnight urine collections has been found to be the least variable parameter for the measurement of microalbuminuria (Harvey et al, 1999; Smulders et al, 1998).

ACR is influenced by gender such that for a similar degree of albuminuria the ACR will be lower in males. Ageing has not been widely recognized as an important predictor of ACR and current guidelines only take gender into account as indicated in the review article by Mogensen et al (1995). In one study examining the inter-individual variability of urinary creatinine excretion and influence on ACR in people with diabetes, only gender and body

mass index, but not age, were found to be significant determinants (Connell et al, 1994). In that study however, the individuals age range was relatively narrow at 36-68 years. In a more recent study in a clinic population with a wide age range (18-84 years) (Houlihan et al, 2002c) and in one recent large study age was shown to have a significant effect on urinary creatinine excretion and on the relationship between ACR and AER (Bakker 1999).

The gender specific microalbuminuria cut-off values for ACR of ≥2.5 mg/mmol and ≥3.5 mg/mmol in males and females respectively are equivalent to an AER of 20 µg/min. These cut-off values have been supported in a study comparing timed overnight AER and ACR on the same sample in which the values of ACR corresponding to AER of 20µg/min were 2.4 (95%CI: 2.2-2.7) in males and 4.0 (95%CI: 3.5-4.7) in females (Harvey et al, 1999). In the study of 314 patients, using regression analysis, a 24h AER of 20 µg/min yielded 24 hr ACR values of 2.5 (95%CI: 2.3-2.6) mg/mmol for males and 3.6 (95%CI: 3.4-3.7) mg/mmol for females. Spot ACR data, however produce higher ACR values at 20µg/min, and had wider confidence limits (Houlihan et al, 2002c).

Age influences ACR such that for the same degree of albuminuria, ACR will increase with age. By definition, the ACR is dependent on albumin and creatinine excretion rates. The influence of age and sex on 24hr urinary creatinine is well established. For example, one large population-based Belgian study of over 4000 people (26-60 yrs) demonstrated significantly lower creatinine excretion in females and significant negative correlation of 24 hr urinary creatinine excretion with age (Kesteloot & Joossens 1996). Therefore, increases in ACR with age can be explained in part by the age related changes in AER and 24 hr urinary creatinine excretion observed in both males and females. Normal ageing is characterised by a progressive decline in skeletal muscle mass and increase in body fat composition. Other age related factors that may influence ACR include the decline in skeletal muscle mass between the 20 – 80 years of age, which has been estimated to range from 22% up to 40% (Fleg & Lakatta 1988; Walser 1987), a decrease in the proportion of muscle in lean body mass (Walser 1987) and a lower meat intake in older subjects (Flynn et al, 1992).

Bakker (1999) has proposed the use of age-specific cut off values for ACR to help restrict the number of people selected for follow up with timed urine collections. In this large study (n>2,300) an increase in the ACR cut-off for each decade, from age group <50 to >70 years, was required to maintain equivalent sensitivities and specificities in each age subgroup. However, the use of both gender and age-specific cut off values for ACR may be confusing and impractical.

The clinical importance of an age-related increase in ACR is an increased false positive rate in older patients (e.g. decreased specificity). Using the recommended cut off values, the age-related increase in false positive rates for spot ACR was approximately 30% for patients of either sex over 65 years (Houlihan et al, 2002c).

Table 7 presents a summary of studies (including those discussed above) that provide evidence in relation to the use of AER and ACR for the screening and diagnosis of albuminuria. Included in the table is a summary of the key components of the cross sectional studies relevant to assessment of diagnostic accuracy. Where reported the sensitivity and specificity is shown along with the key conclusions made by the authors. It should be noted that only a few of the studies provided PPV and NPV values.

Table 7: Summary of studies relevant to evidence for use of AER and ACR screening

Study ID	Study design and Setting	Test	Reference method(s)	Ref level	Urine sample	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Corr.	Comments
Ahn et al (1999)	Cross sectional Korea n=105	UAC, ACR	AER, Immunonephelometry, 24 hr		RUS	77, 77 (mic.) 84, 88 (mac)	82, 92 (mic.) 90, 90 (mac)			0.81, 0.75	Albumin measurements (UAC, UACR) in a RUS were considered as a valid test for screening diabetic nephropathy
Bakker (1988)	Cross sectional Netherlands n= 159	ACR overnight, ALB albumin conc.	AER Immunoturbidimetry, overnight	20 µg/min	Overnight	(F/M) 94, 94 89, 90	(F/M) 92, 93 90, 89				ACR performs better than ALD in screening for microalbuminuria, however the ACR needs sex- and age-specific discriminator values
Cortes-Sanabria et al (2006)	Cross sectional Mexico n=245	Micraltest II – morning	AER Nephelometry, 24hr		Morning	83	96	95	88	0.81, P<0.001	Micraltest II is a rapid, valid and reliable method for albuminuria screening
Gatling et al (1988)	Cross sectional UK n=842	ACR-random, ACR-overnight	AER MicroELISA overnight	30 µg/ml	RUS	96 (overnight) 80 (random)	99.7 (overnight) 81 (random)				An overnight ACR > 2 mg/mmol was the optimal screening test.
Houlihan et al (2002c)	Cross sectional Australia n=314	ACR	AER, immunoturbidimetry 24 hr	20 ug/ml	morning	(F/M) 93.35, 95.7					The increase in spot ACR relative to 24 hr AER with age supports the use of sex- and age-adjusted cut off values for ACR. The clinical significance of the lack of age-adjusted cut off values for ACR is an increased false positive rate in older subjects (31.8% in men >65 years and 28.2% in women greater than 65 years).

Study ID	Study design and Setting	Test	Reference method(s)	Ref level	Urine sample	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Corr.	Comments
Hutchison et al (1988)	Cross sectional Scotland n=276	Albumin conc., ACR	AER Radioimmunoassay	30 µg/min	First morning	9.8 96.8	90.7 93.9	58.8 68.2		0.904 0.921	Either method was concluded to be acceptable as an initial screening procedure.
Incerti et al (2005)	Cross sectional Brazil n=278	Micraltest II	Immunoturbidimetry, 24hr		RUS	90	46				Measurement of UAC in a random urine specimen was the best choice for the diagnosis or screening of microalbuminuria.
Jermendy et al (2001)	Cross sectional n=192	UAC, ACR	UAE immunoturbidimetry		First void	79.3 (UAC) 74.6 (ACR)	69.5 (UAC) 68.8 (ACR)				Besides the standard measurement of UAE in timed urine samples, the use of convenient morning urinary spot collection could provide useful results.
Mogensen et al (1997)	Cross sectional Europe/UK n=2228	Micraltest II for microalbuminuria	Albumin concentration in urine. Immunoturbidimetry, nephelometer, nephelometry	20 mg/l	Spot, first, second morning sample	96.7	71.0	0.78	0.95		Micral Test II permits an immediate and reliable semi quantitative determination of low albumin conc. In urine samples with an almost user-independent colour interpretation
Mosca et al (2003)	Cross sectional Italy n=87	ACR	AER Immunoturbidometry, timed overnight								ACR is more suitable for monitoring albumin excretion in longitudinal studies than the AER.
Mundet(X et al (2001)	Cross sectional n=214	ACR-first void	AER 24 hr							0.93 P< 0.01	ACR is a useful method for diagnosis DN, depends on gender

Study ID	Study design and Setting	Test	Reference method(s)	Ref level	Urine sample	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Corr.	Comments
Nathan et al (1987)	Cross sectional US n= 25	Single void	AER Radioimmunoassay, 24 hr	20 µg/ml		94	96			0.82 P< 0.001	Single-void specimens adjusted for creatinine discriminate between normal and abnormal levels of microalbuminuria as determined in 24-h collection with high sensitivity and specificity.
Parikh et al (2004) ABCD	RCT US n= 326	Micratest strips + urine specific gravity determination (dipstick)	AER immunoturbidimetry, timed collections	≥ 30 mg/d		88	80	69	92		While the use of test strips provides a rapid approach to detecting microalbuminuria , the method has limitations.
Zelmanovitz et al (1998)	Cross sectional Brazil n= 167, 217 urine samples	Timed 24h urinary protein (UP), UPC, UPCR	24h UAER I Immunoturbidometry, timed collections	20 µg/mmol			95.7, 92.9, 76.2			0.95, 0.77, 0.72	Protein measurement in spot urine is a reliable and simple method for screening and diagnosis of overt diabetic nephropathy

Estimation of GFR

- **Estimation of GFR (eGFR) based on serum creatinine is a pragmatic, clinically relevant approach to assessing kidney function in people with type 2 diabetes *(Level III - Diagnostic Accuracy).***

The Cockcroft-Gault and the MDRD formulas for the estimation of GFR were developed predominantly in individuals without diabetes. Studies involving people with type 2 diabetes, are summarised in Table 8 and are generally consistent with the findings for the large number of studies in non diabetes populations (KDOQI 2002). Nonetheless, the study by Rossing et al (2006) questioned the acceptability of the CG and MDRD equations for monitoring kidney function in individuals with type 2 diab etes.

Table 8: GFR estimation studies with people with type 2 diabetes

Study ID	Study Type	Findings	
Fontsere et al (2006)	Prospective cohort n = 87	The best prediction equation compared to the isotopic method proved to be MDRD with a slope of GFR of -1.4/- 1.3 ml/min/yr compared with the CG formula -1.0 +/- 0.9 ml/min/yr. Creatinine clearance presented the greatest variability in estimation P<0.001.	
Poggio et al (2005)	Cross sectional n = 249	MDRD equation performed better than the Cockcroft-Gault equation with respect to bias. (1% vs. 22%, P<0.05) and accuracy within 30% (63% vs. 53%, P<0.05) and within 50% (87% vs. 70%, P<0.05	
Rossing et al (2006)	Prospective cohort n = 383	Particularly in microalbuminuric (hyperfiltering) patients, GFR is significantly underestimated with wide limits of agreement by the MDRD equation as well as by the CG formula. The rate of decline in GFR is also significantly underestimated with both equations.	

Summary – Assessment of Kidney Function in Type 2 diabetes?

- Regular monitoring of kidney function in people with type 2 diabetes is indicated by the high risk of development of CKD and the increased risk of CVD and mortality associated with increasing albuminuria and/or GFR <60 ml/min/1.73m2.

- The screening, diagnosis and monitoring of treatment is undertaken by measurement of albuminuria and estimation of the GFR (eGFR). AER and ACR are the most common and reliable methods to assess albuminuria, ACR values are affected by gender and thus different values are needed for males and females.

- As a significant proportion of people with type 2 diabetes may have or develop CKD in the absence of albuminuria, estimation of GFR is required in addition to screening for albuminuria.

- There are a range of factors that can influence the values of both ACR and AER in individuals with type 2 diabetes.

- The MDRD equation is the most common method used for the estimation of GFR in Caucasian populations and the most appropriate method for the Caucasian population of Australia.

Evidence Tables: Section 1

Assessment of Kidney Function

a) Microalbuminuria and CKD

Author (year)	Evidence (Prognosis)				
	Level of Evidence		Quality Rating	Magnitude of the effect Rating	Relevance Rating
	Level	*Study Type*			
Ahmad et al (1997)	III-2	RCT	High	High	Medium
Bruno et al (2003)	II	Prospective cohort	Medium	Medium	Medium
Christensen et al (1999)	II	Prospective cohort	Low	Medium	Medium
Estacio et al (2000)	III-2	RCT	Medium	High	High
Gaede et al (1999)	IV	RCT	Medium	Medium	High
Hoy et al (2001)	II	Prospective cohort	Medium	High	High
Kramer et al (2003)	IV	Cross-sectional	Medium	Medium	High
MacIsaac et al (2004)	IV	Cross sectional	Medium	High	High
Murussi et al (2006)	II	Prospective cohort	Low	Medium	Medium
Murussi et al (2007)	II	Prospective cohort	Medium	Medium	Medium
Mogensen & Christensen (1984)	II	Prospective cohort	Medium	High	Low
Mogensen (1984)	IV	Case series	Medium	High	High
Nelson et al (1996)	II	Prospective cohort	Medium	Medium	Medium
Nosadini et al (2000)	II	Prospective cohort	Low	Medium	Medium
Parving (2001)	IV	RCT	Low	Low	Medium
Parving et al (2001)	III-2	RCT	High	High	High
Pugh et al (1995)	II	Prospective cohort	Medium	Medium	Low
Rachmani et al (2000)	II	Prospective cohort	High	High	Medium
Ravid et al (1996)	III-2	RCT Phase 1 Open Phase 2	High	High	High
Tsalamandris et al (1994)	II	Prospective cohort	Medium	Medium	Medium
The HOPE Study Group (2000)	IV	RCT	High	High	High
Viberti et al (1982)	II	Prospective cohort	Medium	High	Low

b) AER and ACR

Author (year)	Evidence (Diagnostic Accuracy)				
	Level of Evidence		Quality Rating	Magnitude of the effect Rating	Relevance Rating
	Level	*Study Type*			
Ahn et al (1999)	III-2	Cross sectional	Low	Medium	Medium
Bakker (1988)	III-3	Diagnostic case control	Medium	Low	Medium
Bakker (1999)	III-2	Cross sectional	Medium	High	Medium
Connell et al (1994)	III-3	Diagnostic case control	Medium	High	High
Cortes-Sanabria et al (2006)	III-2	Cross sectional	Low	Medium	Medium
Eshoj et al (1987)	IV	Correlation study	Medium	Medium	Medium
Feldt-Rasmussen et al (1985)	IV	Correlation study	Low	Low	Medium
Gatling et al (1985)	III-2	Cross sectional	Low	High	Medium
Gatling et al (1988)	III-2	Cross sectional	Low	Low	Medium
Harvey et al (1999)	IV	Test method variability	Medium	Medium	Medium
Houlihan et al (2002c)	III-3	Cross sectional	Low	Medium	High
Hutchison et al (1988)	III-2	Cross sectional	Low	Medium	Medium
Incerti et al (2005)	III-2	Cross sectional	High	High	Medium
Jermendy et al (2001)	III-2	Cross sectional	Low	Medium	Medium
Kesteloot & Joossens (1996)	III-2	Cross sectional	Medium	Medium	Medium
McHardy et al (1991)	IV	Test method reproducibility	Medium	Medium	High
Marshall & Alberti (1986)		Cross sectional	Low	Medium	Medium
Mogensen et al (1997)	III-2	Cross sectional	Medium	Medium	Medium
Mosca et al (2003)	III-2	Cross sectional	Low	Medium	High
Mundet, X et al (2001)	III-2	Cross sectional	Low	Medium	Medium
Nathan et al (1987)	III-2	Cross sectional	Low	Low	Medium
Parsons et al (1999)	III-2	Cross sectional	Medium	High	High
Parikh et al (2004) (ABCD)	III-2	Cross sectional	High	Medium	High
Poulsen & Mogensen (1998)	III-2	Cross sectional	Low	High	High
Shield et al (1995)	III-2	Cross sectional	Low	Medium	Medium
Scheid et al (2001)	III	Systematic Review (of Level III studies)	Medium	Medium	High
Smulders et al (1998)	IV	Test variability	Medium	Medium	High
Tsalamandris et al (1998)	III-2	Cross sectional	Medium	High	Medium
Wiegmann et al (1990)	III-2	Cross sectional	Low	Medium	Medium
Zelmanovitz et al (1998)	III-2	Cross sectional	Medium	Medium	High
Zelmanovitz et al (1997)	III-2	Cross sectional	Medium	Medium	High

c) Estimation of GFR

Author (year)	Evidence (Diagnostic Accuracy)				
	Level of Evidence		Quality Rating	Magnitude of the effect Rating	Relevance Rating
	Level	*Study Type*			
Fontsere et al (2006)	III-2	Prospective cohort	High	Medium	High
Poggio et al (2005)	III-2	Cross sectional	Medium	Medium	High
Rossing et al (2006)	III-2	Prospective cohort	High	Low	High

Section 2: Prevention and/or Management of Chronic Kidney Disease

Question

How should chronic kidney disease be prevented and/or managed in people with type 2 diabetes?

i. What is the role of blood glucose control?
ii. What is the role of blood pressure control?
iii. What is the role of blood lipid modification?
iv. What is the role of diet modification?
v. What is the role of smoking cessation?

Recommendations

Blood glucose control should be optimised aiming for a general HbA1c target ≤ 7%. (GRADE A).

In people with type 2 diabetes and microalbuminuria or macroalbuminuria, ARB or ACEi antihypertensives should be used to protect against progression of kidney disease. (GRADE A)

The blood pressure 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 (GRADE B)

Practice Points

- The HbA1c target may need to be individualised taking in to account history of hypoglycaemia and co-morbidities. refer to "Blood Glucose Control in Type 2 Diabetes" guidelines)
- 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.
- Due to potential renoprotective effects, the use of ACEi or ARB should be considered for the small subgroup of people with normal blood pressure who have type 2 diabetes and microalbuminuria.
- 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 CVD.

Evidence Statements

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

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

- 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

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

- 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

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

Background – Prevention and Management of Chronic Kidney Disease 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 (www.diabetesaustralia.com.au). The present guidelines specifically target the management of individuals with established type 2 diabetes.

The onset of type 2 diabetes is characterised by slow progressive increases in plasma glucose levels and is frequently associated with other risk factors for CVD such as elevated blood pressure, elevated AER's, dyslipidaemia and smoking.

A risk factor analysis for kidney dysfunction in type 2 diabetes following 15 years of follow up from the UKPDS study (Retnakaran et al, 2006), 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 type 2 diabetes hospital patients (Hanai et al, 2008) used logistic regression to identify large waste circumference and elevated blood pressure as risk factors for microalbuminuria while dyslipidaemia was identified as a risk factor for decreased 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 (Mogensen et al, 1983). Blood pressure control modulates the progression not only of microangiopathy (diabetic kidney disease and retinopathy) but also of macroangiopathy (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 (Newman et al, 2005). The large observational WESDR study (Klein et al, 1996) 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, including the onset of microalbuminuria, which was reduced by 25% (UKPDS 1998c). These findings are supported by a study of intensified glycaemic control in non-obese Japanese subjects with type 2 diabetes (Ohkubo et al, 1995). In the UKPDS, there was no significant reduction in the risk of progression from microalbuminuria to proteinuria with intensive blood glucose control (UKPDS 1998d).

The AusDiab study collected information on albuminuria, measured as a spot ACR (mg/mmol) with microalbuminuria being between 3.4 – 34 mg/mmol and macroalbuminuria at >34 mg/mol (Tapp et al, 2004). The prevalence of albuminuria increased with increasing glycaemia. People with diabetes and impaired glucose tolerance had an increased risk for albuminuria compared to 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 (UKPDS 1998c) and from normo- or microalbuminuria to overt kidney disease (Ohkubo et al, 1995). 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 ESKD (Morioka et al, 2001).

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 (Skyler et al, 2009). The AHA review is focused on cardiovascular events, however, 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 than the general goal of <7% 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 (Skyler et al, 2009).

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 (Estacio & Schrier 1998; Tatti et al, 1998). 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 (Estacio & Schrier 1998; Ravid et al, 1993; Ravid et al, 1996). 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 blood pressure as opposed to an intrarenal effect of the ACEi.

Antihypertensive therapy, especially with ARB's and ACEi, has been clearly shown to reduce AER (Strippoli et al, 2005; Strippoli et al, 2006). There are trials indicating that ACEi exert cardioprotective effects in addition to lowering of blood pressure, even in normotensive people (The HOPE Study Group 2000). Renoprotection has been demonstrated for ARB's in two large studies (Brenner et al, 2001; Lewis et al, 2001). The existence of a specific renoprotective effect of ACE inhibition in people with type 2 diabetes was not confirmed in the UKPDS (UKPDS 1998d) although it is possible that both captopril and atenolol exerted an equal renal protective effect, over and above lowering of systemic blood pressure .

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 to a control group treated with other antihypertensive agents in equihypotensive doses

However, that inclusion of proteinuria is a weaker basis for identifying renoprotective treatments than a reduction in the rate of decline of GFR (Mogensen 1999).

Several studies have documented the efficacy of antihypertensive therapy in lowering AER in both hypertensive (Chan et al, 1992; Ferder et al, 1992; Slataper et al, 1993) and people with type 2 diabetes and microalbuminuria who are normotensive (Ahmad et al, 1997).

People with type 2 diabetes and kidney disease show a broad range of lipid abnormalities, characterised 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 (Bruno et al, 1996; Mattock et al, 1992; Nielsen et al, 1993). The high triglyceride levels are associated with an increased proportion of atherogenic small dense LDL cholesterol particles (Lahdenpera et al, 1996). The implication is that serum triglycerides should be as low as possible to prevent atherogenic changes in LDL-cholesterol particles (Groop et al, 1993). HDL cholesterol levels in people with type 2 diabetes have been reported to be normal in association with overt diabetic kidney disease (Nielsen et al, 1993) whereas decreased HDL-cholesterol levels have been reported in association with microalbuminuria (Mattock et al, 1992). 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 (Jenkins et al, 1992). Apolipoprotein (a) levels have been related to the rates of progression of albuminuria (Jerums et al, 1993), however, others have not confirmed these findings in people with diabetes and CKD (Nielsen et al, 1993).

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 (Keane et al, 1988).

Primary or secondary intervention with statins in hypercholesterolaemic people has shown similar cardioprotective effects in diabetic and non-diabetic subjects (Pyorala et al, 1997; Sacks et al, 1996; Shepherd et al, 1995). 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 (Pyorala et al, 1997).

Observational studies have shown that dyslipidaemia interacts with other risk factors to increase cardiovascular risk (Kannel 1996; Stamler et al, 1993). Microalbuminuria is a risk factor for CVD as well as overt kidney disease in people with type 2 diabetes (Mogensen 1984; Schmitz & Vaeth 1988), and dyslipidaemia is more common in microalbuminuric than normoalbuminuric people with type 2 diabetes (Mattock et al, 1992). 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 (Parving 1998; Smulders et al, 1997b). 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 (National Heart Foundation of

Australia 2001). 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 (Kannel 1996; Mattock et al, 1992; Stamler et al, 1993) (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 (Costa et al, 2006). The absolute risk benefit of lipid lowering is much larger reflecting the increased absolute risk of adverse cardiovascular outcomes.

Evidence – Prevention and Management of Chronic Kidney Disease in Type 2 Diabetes

i) 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 9 with key studies discussed in the text below. Whilst 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 (2005) 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, 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 (Levin et al, 2000) 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 (Shichiri et al, 2000), UKPDS (UKPDS 1998c) and the VA Cooperative study (Levin et al, 2000). 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 (2006) 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 (2004), Matthews et al (2005) and Schernthaner et al (2004). The Hanefeld et al (2004) 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 to a 2% increase in the metformin group with both treatments giving clinically equivalent glycaemic control. The Matthews et al (2005) 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 to a 6% increase in the glicazide group with no significant difference in HbA1c.

The Schernthaner et al (2004) study of 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 12 European countries. Pioglitazone treatment resulted in a 19% decrease in ACR compared to 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 (2007) assessed the effects of rosiglitazone in the treatment of type 2 diabetes. The study by Lebovitz et al (2001) 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 to 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 (2003) comparing rosiglitazone with glyburide in a randomised 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 normalisation 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 (2005) 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 (Amador-Licona et al, 2000), 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 (2005), the HOME trial (De Jager et al 2005) examnined the efficacy of metformin in 345 people with type 2 diabetes over a four month period. Metformin was associated with a 21 % increase in the UAE compared to 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 (ADVANCE 2008) 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, 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 to 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 systolic blood pressure was on average 1.6 mm Hg lower than the standard group.

A significant reduction (hazard ratio 0.86 CI 0.77 to 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 (ADVANCE 2008).

A significantly higher number of severe hypoglycaemic episodes was recorded in the intensive group compared to 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 to 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 (ADVANCE 2008).

A US study of Hispanic and African Americans assessed the efficacy of rosiglitazone in a high risk (based on ethnicity) type 2 diabetes group (Davidson et al, 2007). 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 to control group (GLY+ placebo). Improved insulin sensitivity and β-cell function with thiazolidinedione treatments was also noted.

US studies on the long term effectiveness of miglitol have been conducted by Johnston and colleagues for 385 Hispanic Americans with type 2 diabetes and 345 African Americans with type 2 diabetes (Johnston et al (1998a) and Johnston et al (1998b) respectively). 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 Gambaro et al (2002), 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 (Gaede et al 2003b) 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. Whilst a 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.

Table 9 presents a summary of studies that provide evidence in relation to the role of blood glucose control. The summaries are provided as an overview of the evidence.

Table 9: 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 (mths)	Comments/Conclusions
ADVANCE (2008)	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)	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)	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 normalisation of the ACR by the 12 months. The differences in ACR between the groups was not statistically significant – ACR was a secondary prospective endpoint and study design was of low power for ACR. Suggests a potential benefit of RSG.

Study ID	Study Description	Intervention	Outcome (relevant to CKD)	Follow up (mths)	Comments/Conclusions
Davidson et al, (2007)	RCT, double blind, placebo controlled US Multicentre (38), US Hispanic and African American Type 2 diabetes, FPG > or = 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 to control group (GLY+ placebo). Improved insulin sensitivity and β-cell function with thiazolidinedione treatments.
De Jager et al (2005) HOME	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 to the placebo. However considered a short anomaly as UAE shown to be associated with HbAc1
Gaede et al (2003b) Steno2	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)	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)	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 (1998a)	RCT Type 2 diabetes, Hispanic n=385	Miglitol vs. Placebo	ACR.	12	Miglitol had “just non significant” reduction of ACR.
Johnston et al (1998b)	RCT Type 2 diabetes, African-American n=345	Miglitol vs. Placebo	ACR	12	Minor reduction in ACR with miglitol..

Study ID	Study Description	Intervention	Outcome (relevant to CKD)	Follow up (mths)	Comments/Conclusions
Lebovitz et al (2001)	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)	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)	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)	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)	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 to 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) Kunamoto Study	RCT n=110	MIT vs. CIT	Albuminuria	96	Intensive glycaemic control (MIT) – cumulative percentages of worsening in nephropathy were significantly lower.

ii) Role of Blood Pressure Control

a) Blood Pressure 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 blood pressure lowers the risk of microvascular disease, CVD and mortality in type 2 diabetes (refer to systematic reviews of Kaiser et al (2003), Newman et al (2005), Strippoli et al (2005) and Strippoli et al (2006).

The UKPDS has been the largest long-term study to compare the effects of intensive vs. less intensive blood pressure control in hypertensive people with type 2 diabetes. In this 9-year study of 1148 people, allocated to tight blood pressure control (n=758) or less tight control (n=390), mean blood pressure was significantly reduced in the tight control group (144/82 mmHg), compared with the group assigned to less tight control (154/87 mmHg) ($p<0.0001$). 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 ($p<0.01$) (UKPDS 1998d). 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 (UKPDS 1998b).

Elevated blood pressure 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 Ravid et al (1998b). Those with elevated blood pressure (>95 mm Hg) had an almost 10 fold increased risk of developing microalbuminuria compared to those with lower blood pressure over the average 8 year follow-up period.

Recent analysis of the blood pressure arm data of the ADVANCE Trial (ADVANCE 2007) by Galan et al (2008) 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 mmHg.

The 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 Newman et al (2005) considered that a 72% drop in clinical proteinuria noted in relevant trials was unlikely to be caused by the small difference in the blood pressures between treatment groups and is consistent with renoprotective effects of ACEi.

b) Blood Pressure 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 10 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 (2005) examined three areas relevant to consideration of the use of antihypertensive therapy that are summarised 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 to 2.21) with similar results for death from kidney failure (UKPDS 1998d).
- The HOPE Study demonstrated that there was a non significant relative risk reduction for the requirement for renal dialysis amongst people treated with ramipril (The HOPE Study Group 2000).

As a consequence he above two trials, Newman et al (2005) 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 namely Ahmad et al (1997), Ravid et al (1993) and Sano et al (1996). Newman et al (2005) conclude that the data are inconclusive. No appropriate trials comparing different antihypertensive agents and intensive versus moderate blood pressure control were identified. However, later analysis of the ABCD trial (Schrier et al, 2002) 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 namely Lebovitz et al (1994) and Parving et al (2001). Newman et al (2005) conclude that the limited evidence indicates kidney function to remain stable in hypertensive people with type 2 diabetes with microalbuminuria treated with ACEi compared to a decline in the placebo group (36 month follow up). The Parving et al (2001) study also indicated a significant reduction in the rate of progression to clinical proteinuria with ARB treatment however this was not associated with significant decline in creatinine clearance.

Two trials were identified that compared intensive and moderate blood pressure control in hypertensive people with type 2 diabetes with microalbuminuria, namely ABCD (Estacio et al, 2000) and UKPDS (UKPDS 1998d). 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 namely Agardh et al (1996), Estacio et al (2000) and Lacourciere et al (1993). 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 randomised placebo-controlled trials in normotensive people with type 2 diabetes with microalbuminuria were identified namely, Ahmad et al (1997), Ravid et al (1993) and Sano et al (1996). 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 to 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 blood pressure between treatment and placebo were small and as such Newman et al (2005) consider that a 72% drop in clinical proteinuria was unlikely to be caused by such a small difference and more likely that ACEi have a specific renoprotective effect.

No appropriate trials were identified comparing antihypertensive agents and intensive versus moderate blood pressure control with the exception of 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 or the CCB (Estacio et al, 2000).

Only one available placebo controlled study was identified for hypertensive people with type 2 diabetes with microalbuminuria (Parving et al, 2001). The treatment involved two dose levels of the ARB antagonist irbesartan for two years. A combined relative risk for clinical proteinuria for the ARB treatments was 0.50 (95% CI 0.0.31 to 0.81). This reduction in the rate of progression to clinical proteinuria was independent of blood pressure.

Only the ABCD trial (Estacio et al, 2000) was identified as being relevant for comparing intensive versus moderate blood pressure control in hypertensive people with type 2 diabetes with microalbuminuria. Individuals were randomised 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 (2005) noted that the results supported the observations from the UKPDS of progression to clinical proteinuria amongst microalbuminuric and normoalbuminuric people with type 2 diabetes was not affected by the level of blood pressure 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 namely Agardh et al (1996), Chan et al (2000), Estacio & Schrier (1998) and Lacourciere et al (1993). The trials all included an ACEi treatment compared with either a CCB antagonist or β blocker. The overall relative risk of

development of clinical proteinuria for ACEi versus other hypertensive therapy was 0.74 (95% CI 0.44 to 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 by Strippoli et al (2005) and Strippoli et al (2006) addressed the use of antihypertensive agents in people with diabetes with respect to renal outcomes. The objectives of the review by Strippoli et al (2005) were to evaluate the effects of antihypertensive agents in people with diabetes and normoalbuminuria. While the objectives of the review by Strippoli et al (2006) 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 in the case of Strippoli et al (2006) people with either microalbuminuria or macroalbuminuria. Whilst 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 summarised 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 blood pressure and, kidney function and type of diabetes. However, there is insufficient data to be confident that these factors are not important effects modifiers (Strippoli et al, 2005).
- There is randomised trial evidence that ACEi versus placebo/no treatment used at their 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 (Strippoli et al, 2006).

In relation to type 2 diabetes the following outcomes are of note from the reviews by Strippoli et al (2005) and Strippoli et al (2006):

- All-cause mortality:
  - non significant effect of ACEi. vs. 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 vs. placebo/no treatment – no significant effect.
  - at the maximum tolerable dose for ACEi vs. 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 vs. 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 vs. placebo.
  - comparison of ACEi and CCB – no available suitable studies where relative risk was able to be estimated.
  - for ACEi vs. placebo/no treatment – overall effect of marginal significance in favour of ACEi.
  - for ARB vs. placebo/no treatment – the two studies selected both included people with type 2 diabetes with an overall significant reduction for ARB compared to placebo/ no treatment.

- Progression to ESKD
  - non significant effect of ACEi vs. placebo in the one mixed type 1/type 2 diabetes study only (The HOPE Study Group 2000).
  - comparison between ACEi and CCB - no available suitable studies where relative risk was able to be estimated.
  - for ACEi vs. placebo/no treatment – non significant relative risk in the two studies that included people with type 2 diabetes.
  - for ARB vs. 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 to placebo/ no treatment.
- Progression from normoalbuminuria to microalbuminuria or macroalbuminuria
  - overall significant effect of ACEi vs. placebo in reducing the rate of progression.
  - ACEi compared to other hypertensive agents – limited to the UKPDS study which showed no significant effect of ACEi in reducing the rate of progression.
  - normotensive patients - ACEi vs. placebo – no trials identified with people with type 2 diabetes.
  - hypertensive patients - ACEi vs. placebo - evidence for significant reduction in rate of progression with ACEi treatment.
  - ACEi compared to CCB – significant effect of ACEi in reducing the rate of progression.
- Progression of microalbuminuria to macroalbuminuria:
  - ACEi vs. 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 of the studies with type 2 diabetes studies accounting for approximately 70% of the total number in all selected studies.
  - ARB vs. 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 vs. 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 vs. 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 blood pressure:
  - ACEi vs. placebo no trials identified that included people with type 2 diabetes.
  - ACEi and CCB on blood pressure – 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 by Strippoli et al (2006). 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 by Kaiser et al (2003) was to assess the RCT evidence for the effects of different therapeutic blood pressure goals and interventions in the normotensive range on the decline of glomerular function. The search strategy was limited to studies of people with two years duration of type 1 or type 2 diabetes with incipient or overt

nephropathy with or without elevated blood pressure. 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 by Newman et al (2005), Strippoli et al (2005) and Strippoli et al (2006). Only two studies that considered the effect of BP targets within the normotensive range in people with type 2 diabetes were identified, namely Schrier et al (2002) and Estacio et al (2000).

Kaiser et al (2003) 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 by Jennings et al (2007) pooled analyses from the number of small studies comparing combination treatment of ACEi + ARB with ACEi alone. A total of ten studies covering both type 1 and type 2 diabetes were included in the meta-analysis. The majority of the studies were of people with type 2 diabetes. The authors concluded that the meta-analysis suggests that combined ACEi + ARB reduces 24 hour 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 (2003) 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 normalise data but less clear where data is reported as arithmetic means (presumed to reflect the skewing of the albuminuria data). Whilst 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 (Brenner et al, 2001). 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 (Parving et al, 2001). However, preservation of GFR over and above the effects of blood pressure lowering was not demonstrated in this relatively short-term study.

Studies not covered by Systematic Reviews

The ADVANCE study (ADVANCE 2007) is a multinational randomised control trial undertaken by 215 centres across 20 countries which, in addition to intensive blood glucose treatment, included a blood pressure treatment study arm. Participants were randomised 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 labeled ACEi allowed was perindopril to a maximum dose of 4mg 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 mmHg respectively, compared to placebo. The relative risk of a major microvascular event was 7.9% in the active treatment group compared to 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 (Galan et al, 2008) has indicated that lower achieved follow-up systolic blood pressure levels were associated with progressively lower renal event rates to below 110 mmHg. Renoprotective effects of blood pressuring lowering with perindopril indapamide treated were noted even among the sub group with baseline blood pressure below 120/70 mmHg.

An open label parallel prospective randomised trial (Yasuda et al, 2005) 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. The ARB and CCB treatments provided similar blood pressure 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 10 including, Jerums et al (2004), Marre et al (2004), Baba & -MIND Study Group (2001) and Fogari et al (2000) While the study by Lacourciere et al (2000) (also summarized in Table 10) has examined both ACEi and ARBs either alone of in combination.

A number of studies have specifically assessed the ARB valsartan namely Estacio et al (2006), Galle et al (2008), Hollenberg et al (2007), SMART Group (2007), Tan (2002) and Viberti (2002). The details and findings of these studies are summarized in Table 10 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 blood pressure and normoalbuminuria (Ruggenenti et al 1998; Remuzzi et al 2006). The trial was aimed at assessing the efficacy of ACEi and CCB alone and in combination. Additional agents were permitted to achieve appropriate blood pressure 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) in the study by Schram et al (2005) were assessed in 70 people with type 2 diabetes in the Netherlands. The people with type 2 diabetes were Caucasian with an average age in the randomised treatment groups of 60 to 63, hypertensive and either normoalbuminuric or early microalbuminuric (UAE < 100 mg/d). The trial was of 12 months duration after a 1 month run in and a 4 to 6 month blood pressure 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 by Strippoli et al (2006)

does not provide additional evidence for the efficacy of ARB compared to ACEi in achieving regression of microalbuminuria.

The multicentric CENTRO trial of 129 Italians with type 2 diabetes compared the ARB candesartan with the ACEi enalapril with albumin excretion rate as a secondary outcome. In the study by Rosei et al (2005) after 6 months treatment the ARB treatment group had a reduced albumin excretion rate and ACR, while the ACEi was higher. However, the baseline conditions differed between treatment groups and the majority of individuals were normoalbuminuric thus the relevance of the outcomes for individuals with microalbuminuria is questionable.

The GEMINI trial involved 1235 people with type 2 diabetes with elevated blood pressure under either a ACEi or ARB hypertension treatment randomised for treatment with two different β-blockers (carvedilol and metoprolol) (Bakris et al, 2005). 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 to 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 to 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 >=70ml/min/1.73m2 from 6 European countries (Barnett et al, 2004). 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/1.73 m^2 and was insignificant. The mean annual declines in eGFR were 3.7 ml/min/1.73 m^2 for the ARB and 3.3 ml/min/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/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 (ONTARGET 2008). Relevant secondary outcomes are kidney impairment and kidney failure requiring dialysis. The only significant differences between treatments (ACEi, ARB and ACEi+ARB) was for increased kidney impairment in the combination therapy compared to the ACEi. Further analysis of renal outcomes (Mann et al, 2008), indicated a significantly higher increase in ACR in the ACEi treatment group compared to 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 compared, 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) reported by Parving et al (2008) examined the renoprotective effects in people with type 2 diabetes with albuminuria of treatment with a direct renin inhibitor (aliskiren) in addition to maximal treatment with an ARB (losartan). Treatment

with 300 mg of aliskiren was demonstrated to reduce the ACR by 18% compared to 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 blood pressure 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 10 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 in Table 10 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 blood control in the progression of CKD namely, Muirhead et al (1999), Ravid et al (1998a), Sano et al (1994) and Trevisan & Tiengo (1995).

Table 10: 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 (mths)	Comments
ADVANCE (2007) and Galan et al (2008)	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 mmHg respectively, compared to placebo. The relative risk of a major microvascular event was 7.9% in the active treatment group compared to 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)	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)	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) MIND	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.

Study ID	Study Description	Intervention	Outcome Relevant to CKD	Follow up (mths)	Comments
Bakris et al (2005) GEMINI	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 to 5.30) over the duration of the study.
Barnett et al (2004) DETAIL	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/1.73 m^2 and was insignificant. The mean annual declines in GFR were 3.7 ml/min/1.73 m^2 for the ARB and 3.3 ml/min/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/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)	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)	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.

Study ID	Study Description	Intervention	Outcome Relevant to CKD	Follow up (mths)	Comments
ABCD Estacio et al (2000) Estacio & Schrier (1998) Schrier et al (2002)	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 stabilise 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)	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) VIVALDI	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 hr proteinuria, eGFR	12	Mean reduction in proteinuria 33% (same for both treatments). Greater renoprotection seen amongst patients with better blood pressure control.
Hollenberg et al (2007)	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.

Study ID	Study Description	Intervention	Outcome Relevant to CKD	Follow up (mths)	Comments
Jerums et al (2004)	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 stabilises AER and attenuates GFR decline in proportion to MAP in non-hypertensive people with Type 2 diabetes and microalbuminuria.
Lacourciere et al (1993)	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.
Lacourciere et al (2000)	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)	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) DIABHYCAR	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)	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 to the ACEi.

Study ID	Study Description	Intervention	Outcome Relevant to CKD	Follow up (mths)	Comments
Nakamura et al (2002)	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) and Mann et al (2008)	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) and Brenner et al (2001)	RCT, double blind Multicentre, multinational Type 2 diabetes n=1513	ARB 150mg/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.

Study ID	Study Description	Intervention	Outcome Relevant to CKD	Follow up (mths)	Comments
Parving et al (2008)	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 moths 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 to 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)	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 stabilises renal function in previously untreated patients with impaired renal function. Discontinuation of treatment results in renewed progression of nephropathy.
Ravid et al (1998a)	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.

Study ID	Study Description	Intervention	Outcome Relevant to CKD	Follow up (mths)	Comments
Rosei et al (2005) CENTRO	RCT Multicentre Type 2 diabetes Mild hypertension, either previously untreated for hypertension or unsuccessfully treated. n=129	ACEi – enalapril (20 mg/d) vs. ARB – candesartan (16 mg/d) (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) also Remuzzi et al (2006) 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)	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.

Study ID	Study Description	Intervention	Outcome Relevant to CKD	Follow up (mths)	Comments
Schram et al (2005)	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)	RCT Type 2 diabetes with microalbuminuria n=341	Valsartan vs.amlodipine	ACR	3	Valsartan – ACR 68% of baseline Amlodipine – ACR 118% of baseline Remission – 23 vs. 11% Regression – 34 vs. 16%
Tan et al (2002)	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.
The HOPE Study Group (2000)	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)	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 (1998b) Efficacy of ACEi vs. beta	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.

Study ID	Study Description	Intervention	Outcome Relevant to CKD	Follow up (mths)	Comments
UKPDS (1998d) Tight blood pressure control	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) MARVAL	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)	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 hour blood pressure alone is inadequate to reduce macroalbuminuria and additional effects of ARB (losartan) are crucial for antiproteinuric action.

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 chronic kidney disease. 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 11 with findings from key studies described in the text below.

Systematic reviews and meta-analyses:

Sandhu et al (2006) 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/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 and Croom (2007) specifically addressed the pharmacological properties of 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 to 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 to 11%) and in the DAIS trial (8% compared to 18%).

Strippoli et al (2008) 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 chronic kidney disease and with a history of coronary heart disease. These studies did not include people with moderate chronic kidney disease but without known

cardiovascular disease. In the small number of studies reporting urinary protein excretion (g/24 h) in individuals with chronic kidney disease (6 randomised 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 randomised controlled trials, 548 people). This review was unable to distinguish a specific response in individuals with diabetes.

Fried et al (2001) 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/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 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.

Randomised 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 (Costa et al, 2006). 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 (HPS) (The Heart Protection Study 2003) 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 chronic kidney disease were not studied.
- In the Greek atorvastatin and coronary heart disease evaluation (GREACE) substudy (Athyros et al, 2004) 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.
- The Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) (Koren 2005) study showed beneficial effects on GFR in individuals with type diabetes, however the study did not separately identify or assess type 2 diabetes.

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

- A multicentric double blind parallel group RCT of type 2 diabetes Swedish patients with dyslipidaemia (fasting LDL-C > 3.3 mmol/L) compared two statin treatments (rosuvastatin and atorvastatin) over a 16 week treatment period (Sorof et al, 2006). 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 (2001) 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 ($p < 0.01$).

Randomised 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 (versus placebo) in 314 people with type 2 diabetes (Canada and Europe) with mild to moderate lipid abnormalities and normo to microalbuminuria (Ansquer et al, 2005). The study length was a minimum of three years. Regression of albuminuria (defined as micro to normoalbuminuria or macro to microalbuminuria) was significantly higher in the treatment group (13 %) compared to the placebo group (11%), while progression of albuminuria was significantly lower in the treatment group (8%) compared to the placebo group (18%). Significantly more people showed no change in albuminuria in the treatment group (79%) compared to 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 blood pressure and HbA1c. The final urinary albumin was significantly correlated with either HbA1c level or blood pressure. 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 (2005) and Radermecker & Scheen (2005) report the large (9,795) 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 (Nagai et al, 2000).

Randomised 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 randomised open study of 102 people with type 2 diabetes with clinical albuminuria (UAE > 300 mg/g Cr) (Endo et al, 2006). 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 antioxidative effect of the drug.

The multifactorial intensive treatment of the STENO2 study (Gaede et al 2003b) reduced the risk of nephropathy by 50%. This long term study (mean 7.8 years) of 160 people with type 2 diabetes and microalbuminuria, utilized multifactorial interventions for modifiable risk factors for cardiovascular disease which included blood lipid control with statins and fibrates. Whilst 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 on the renal outcomes.

Table 11: 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 (mths)	Comments/Conclusions
Ansquer et al (2005) DAIS – sub group analysis	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)	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 (2003b) Steno2	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%.

Study ID	Study Description	Intervention	Outcome (relevant to CKD)	Follow up (mths)	Comments/Conclusions
Keech et al (2005) Radermecker & Scheen (2005) FIELD	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)	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)	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)	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)	RCT, double blind, parallel group Multicentre, Sweden Type 2 diabetes, dyslipidaemia (fasting LDL-C > 3.3mmol/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 week 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)	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 amongst those with diabetes.

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 summarise 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 (Cardenas et al, 2004). 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 characterised 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 blood pressure 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 MIFA over SFA may help prevent micro and macroalbuminuria (Cardenas et al, 2004).

Table 12 presents a summary of the relevant studies found by the search strategy (Appendix 3) in relation to dietary fat. With the exception of the study by Cardenas et al (2004) 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 12. 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.

Table 12: Summary of studies relevant to the assessment of the role of dietary fat

Study ID	Study Description	Intervention	Outcome (relevant to CKD)	Follow up (mths)	Comments/Conclusions
Barnard et al (2006)	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)	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)	RCT Type 2 diabetes n=11	Low fat vegan vs. Conventional low fat	UAE	3	No significant effect on UAE.
Nielsen et al (1995)	Before and after cross over. Pseudo randomised trial. Type 2 diabetes, persistent microalbuminuria n=10	Diet rich in MUF vs. Recommended high carbohydrate diet	UAE	3 week	No effect on UAE. However a potential beneficial effect on LDL/HDL ratio was detected.
Shimizu et al (1995)	Before and after non randomised 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.

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 (Shemesh et al, 1985).

The objective of the systematic review by Robertson et al (2007) was to assess the effects of dietary protein restriction on the progression of diabetic nephropathy in people with diabetes (type 1 and type 2 diabetes). The review identified 11 studies (9 RCTs and 2 before and after trials) where diet modifications were followed for at least 4 months. Before and after trials were included as it was considered that people could act as their own controls. Of these studies 8 were of people with type 1 diabetes, one type 2 diabetes and two included both type 1 and type 2 diabetes. Overall the total number of participants in the trials were 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/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 implies that patients can delay dialysis by, on average around one or two 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 (2005) was the only other RCT identified that was not reviewed by Robertson et al (2007). 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 13 includes a summary of studies identified by the search strategy (Appendix 3). The studies are characterised 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.

Table 13: Summary of studies relevant to the assessment of the role of protein restriction

Study ID	Study Design	Intervention	Outcome (relevant to CKD)	Follow up (mths)	Comments/Conclusions
Barsotti et al (1998)	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)	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)	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/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)	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 to normal diet. Microalbuminuric – only chicken reduced UAE compared to normal diet
Meloni et al (2004)	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)	RCT Type 2 diabetes, microalbuminuria n=121	Counseling 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.

Study ID	Study Design	Intervention	Outcome (relevant to CKD)	Follow up (mths)	Comments/Conclusions
Pijls et al (2002)	RCT Type 2 diabetes, microalbuminuria n=131	Dietary counseling – 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/day. No differences by end of trial. Within the intervention group individuals with reduction of at least 0.2 mg/kg/day protein compared to controls with no change – showed non significantly difference in GFR. Conclude that protein restriction is neither feasible or efficacious.
Pomerleau et al (1993)	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 week	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)	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 to casein.
Wheeler et al (2002)	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.

Restricted Salt Intake

When considering the evidence related to salt intake and CKD in people with type 2 diabetes, the following points made by Suckling et al (2007) authors based on a literature review for preparation of a Cochrane Protocol are noteworthy:

- Dietary salt is important in blood pressure 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 β production, affecting the progression of CKD.

Table 14 presents a summary of studies identified by the search strategy (Appendix 3) 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 14, 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.

Table 14: 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 (mths)	Comments/Conclusions
Houlihan et al (2000a)	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 (2002a)	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 (2002b)	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)	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)	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)	Cross over randomisation 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.

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 (Muhlhauser 1994; Yudkin 1993). The following cohort studies summarized in the text below and in Table 15, 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 vs. those who did not progress (Forsblom et al, 1998).

A number of prospective cohort studies were identified by the search strategy (Appendix 3) that have considered smoking in people with type 2 diabetes in relation to kidney function. Relevant details of these studies are summarized in Table 15. 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 namely Gambaro et al (2001). Of the 7 prospective cohort studies identified only one small study (Smulders et al 1997a) reported no significant association between smoking and the progress of albuminuria.

Chuahirun & Wesson (2002) prospectively sought predictors of renal function decline in 33 people with type 2 diabetes, successfully targeting a mean blood pressure goal of 92 mm Hg (about 125/75 mm Hg) with antihypertensives including ACEi. Initial plasma creatinine was < 1.4 mg/dL, follow-up 64.0 +/- 1.1 months. Regression analysis showed that smoking was the only examined parameter that significantly predicted renal function decline. In the 13 smokers, serum Cr increased from 1.05 +/- 0.08 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 of Chuahirun et al (2004) concluded that cigarette smoking exacerbates renal injury despite adequate blood pressure control with ACEi. 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 by Chuahirun et al (2003) 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.

The prospective cohort study reported by Cederholm et al (2005), included 6513 people with type 2 diabetes with 5 year follow up period. Smoking was identified as an independent risk factor for established microalbuminuria and for the development of microalbuminuria. Similarly the retrospective cohort study reported by Gambaro et al (2001), 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 reported by Biarnes et al (2005) was 3.19 (95% CI 1.02-9.96).

The large cohort study of people with type 2 diabetes receiving dialysis treatment by Braatvedt et al (2006), concluded that dialysis patients with a history of smoking had the highest all cause mortality.

In addition to the prospective cohort studies, a number of cross sectional studies were identified by the search strategy (Appendix 3). 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 summarised in Table 15. All of the studies identified smoking to be associated with or to be a predictor of albuminuria.

Table 15: 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 (mths)	Comments/Conclusions
Anan et al (2007)	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)	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)	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)	Cross sectional Type 2 diabetes n=1574	UAE		Smoking habits are independently related to both micro and macroalbuminuria
Cederholm et al (2005)	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)	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)	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)	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.

Study ID	Study Design	Outcome (relevant to CKD)	Follow up (mths)	Comments/Conclusions
Dean et al (1994)	Cross sectional Type 2 diabetes, normotensive n=87	UAE		Relationship if any between smoking and UAE not stated in abstract.
Forsblom et al (1998)	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)	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)	Cross sectional Type 2 diabetes n=842	UAE, ACR		Significant association found between UAE and smoking category.
Ikeda et al (1997)	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)	Cross sectional Type 1 diabetes and Type 2 diabetes Hospitals, primary health care n= >17000 type 2 diabetes	Albuminuria		Smoking was associated with poor glycaemic control and microalbuminuria
Pijls et al (2001)	Cross sectional Type 2 diabetes – primary care patients n=335	ACR		Smoking independently associated with ACR.
Savage et al (1995)	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 (1997a)	Prospective cohort Type 2 diabetes with microalbuminuria n=58	ACR	24	Smoking was not a significant predictor of the progress of albuminuria

Study ID	Study Design	Outcome (relevant to CKD)	Follow up (mths)	Comments/Conclusions
Thomas et al (2006)	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 to 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).

Summary – Prevention and Management of Chronic Kidney Disease in Type 2 diabetes?

- 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 blood pressure is strongly associated with the development of albuminuria in people with type 2 diabetes. Management of elevated blood pressure 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 blood pressure. As a consequence use of these agents is favored in the treatment of elevated blood pressure 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.

Evidence Tables: Section 2

Prevention and Management of CKD

i) Role of blood glucose control

Author (year)	Evidence (Intervention)				
	Level of Evidence		Quality Rating	Magnitude of the effect Rating	Relevance Rating
	Level	*Study Type*			
ADVANCE (2008)	II	RCT	High	High	High
Amador-Licona et al (2000)	II	RCT	Medium	Medium	Low
Bakris et al (2003) Rosigltazone	II	RCT	Medium	Medium	Medium
Davidson et al (2007)	II	RCT	High	High	Medium
De Jager et al (2005) HOME	II	RCT	High	Medium	Medium
Gaede et al (2003b) Steno2 Multifactorial – includes use of antidiabetics	II	RCT	High	High	High
Gambaro et al (2002)	II	RCT	High	High	Low
Hanefeld et al (2004)	II	RCT	High	Medium	High
Johnston et al (1998a)	II	RCT	Medium	Low	Medium
Johnston et al (1998b)	II	RCT	Medium	Low	Medium
Lebovitz et al (2001).	II	RCT	High	High	Medium
Levin et al (2000)	II	RCT	Medium (no blinding)	Medium	High
Matthews et al (2005)	II	RCT	High	Medium	High
Newman et al (2005)	I	Systematic review of RCT	High	Medium (Albuminuria) Low (GFR)	High
Ohkubo et al (1995)	II	RCT	Medium (no blinding)	High	High
Richter et al (2006) Cochrane (Pioglitazone)	I	Systematic review of RCT	High	Low	Medium
Richter et al (2007) Cochrane (Rosiglitazone)	I	Systematic review of RCT	High	Low	Medium
Saenz et al (2005) Cochrane (Metformin)	I	Systematic review of RCT	High	Low	Medium
Schernthaner et al (2004) Pioglitazone vs. Metformin	II	RCT	High	High	High
Shichiri et al (2000) Kunamoto Study	II	RCT	Medium	High	Medium
UKPDS (1998c)	II	RCT	High	High	High

(1) Magnitude of effect assessed in relation to overall outcome(s) relevant to CKD. A high effect maybe therefore be noted where there may be no significant difference between two agents, however both agents result in significant outcomes with respect to progression of CKD.

ii) Role of blod Pressure Control

a) Blood pressure as a risk factor

Author (year)	Evidence				
	Level of Evidence		Quality Rating	Magnitude of the effect Rating	Relevance Rating
	Level	*Study Type*			
ADVANCE (2007) and Galan et al (2008)	II	RCT	High	High	High
Kaiser et al (2003)	I	Systematic review of RCTs	High	Low	High
Newman et al (2005)	I	Systematic Review of RCTs	High	High (albuminuria) Medium (GFR) Low (ESKD)	High
Ravid et al (1998b)	II	Prospective cohort	High	High	High
Strippoli et al (2005) ACEs and ARBs.	I	Systematic Review of RCTs	High	High (albuminuria)	High.
Strippoli et al (2006) Antihypertensives	I	Systematic Review of RCTs	High	High (albuminuria)	High.
UKPDS (1998d) Tight blood pressure control	II	RCT	High	High	High

b) Blood pressure control as an intervention

Author (year)	Evidence				
	Level of Evidence		Quality Rating	Magnitude of the effect Rating (1)	Relevance Rating
	Level	*Study Type*			
ADVANCE (2007) and Galan et al (2008)	II	RCT	High	High	High
Agardh et al (1996)	II	RCT	High	High	Medium
Ahmad et al (1997)	II	RCT	Medium	High	Medium
Baba & -MIND Study Group (2001) MIND	II	RCT	Medium	Low	High
Bakris et al (2005) GEMINI	II	RCT	Medium	Medium	High
Barnett et al (2004) DETAIL	II	RCT	High	Medium	High
Chan et al (2000)	II	RCT	High	High	Medium
Estacio et al (2006)	II	RCT	Medium	High (UAE) Low (GFR)	High
Fogari et al (2000)	II	RCT	Medium	High	Medium
Galle et al (2008) VIVALDI	II	RCT	High	High	High
Hamilton et al (2003)	I	Systematic review of RCTs	High	High	High
Hollenberg et al (2007)	II	RCT	Medium	Medium	High
Jennings et al (2007)	I	Systematic review of RCTs	High	Medium	Medium
Jerums et al (2004)	II	RCT	High	High	Medium
Kaiser et al (2003)	I	Systematic review of RCTs	High	Low	High
Lacourciere (1993)	II	RCT	Medium	High	High
Lacourciere et al (2000)	II	RCT	High	Medium (Effect of ACEi and ARB) Low (Comparative effect of ACEi and ARB)	Medium
Lebovitz et al (1994)	II	RCT	High	High	Medium
Marre et al (2004) DIABHYCAR	II	RCT	High	Low	High
Muirhead et al (1999)	II	RCT	High	High (effects on AER) Low (comparative effect of ACEi and ARB)	Medium
Nakamura et al (2002)	II	RCT	Medium	Medium	Medium
Newman et al (2005)	I	Systematic Review of RCTs	High	High (albuminuria) Medium (GFR) Low (ESKD)	High
ONTARGET (2008) and Mann et al (2008)	II	RCT	High	Low	Medium
Parving et al (2001) and Brenner et al (2001)	II	RCT	High	High	High
Parving et al (2008)	II	RCT	High	High	Medium

Blood pressure control as an intervention (cont.)

Author (year)	Evidence				
	Level of Evidence		Quality Rating	Magnitude of the effect Rating (1)	Relevance Rating
	Level	*Study Type*			
Ravid et al (1993)	II	RCT	High (first phase) Medium (second phase)	High	Medium
Ravid et al (1998a)	II	RCT	High	High (decline in kidney function and albuminuria) Low (overt nephropathy)	High
Remuzzi et al (2006) Ruggenenti et al (1998) BENEDICT	II	RCT	High	High	High
Rosei et al (2005) CENTRO	II	RCT	Medium	Low	Low
Sano et al (1994)	II	RCT	Medium	High	Medium
Schram et al (2005)	II	RCT	Medium	Low	Medium
ABCD Schrier et al (2002) Estacio et al (2000) Estacio & Schrier (1998)	II	RCT	Medium	High	High
SMART Group (2007)	II	RCT	Medium	Medium	Medium
Strippoli et al (2005)ACEs and ARBs.	I	Systematic Review of RCTs	High	High (albuminuria)	High.
Strippoli et al (2006) Antihypertensives	I	Systematic Review of RCTs	High	High (albuminuria)	High.
Tan et al (2002)	II	RCT	High	High	Medium
The HOPE Study Group (2000)	II	RCT	High	High (reduction in risk of overt nephropathy) Low (risk of new microalbuminuria)	High
Trevisan & Tiengo (1995)	II	RCT	High	High	Medium
UKPDS (1998b) Efficacy of ACEi vs. beta	II	RCT	High	High	High
UKPDS (1998d) Tight blood pressure control	II	RCT	High	High	High
Viberti (2002) MARVAL	II	RCT	Medium	High	High
Yasuda et al (2005)	II	RCT	Medium	High	Medium

(1) Magnitude of effect assessed in relation to overall outcome(s) relevant to CKD. A high effect maybe therefore be noted where there may be no significant difference between two agents, however both agents result in significant outcomes with respect to progression of CKD.

iii) Role of blood lipid modification

Author (year)	Evidence (Intervention)				
	Level of Evidence		Quality Rating	Magnitude of the effect Rating	Relevance Rating
	Level	*Study Type*			
Ansquer et al (2005) DAIS – sub group analysis Fenofibrate	II	RCT	High	Medium	High
Athyros et al (2004) CREACE Study	II	RCT	Medium	Medium	Low
Endo et al (2006) Probucol	II	RCT	High	Medium	Medium
Fried et al (2001)	I	Systematic review of RCTs	High	Medium (eGFR) Low (proteinuria)	Low
Gaede et al (2003b) Steno2 Multifactorial – includes use of hypolipidaemics	II	RCT	High	High (however not able to assign contribution from hypolipidaemics)	High
Keating & Croom (2007) Fenofibrate	I	Systematic review of RCTs	High	Medium	High
Keech et al (2005) Radermecker & Scheen (2005) FIELD Fenofibrate	II	RCT	High	Medium	High
Koren (2005) ALLIANCE	II	RCT	Medium	Medium	Low
Nagai et al (2000) Benzafibrate and pravastatin	II	RCT	Medium	Low	Medium
Nakamura et al (2001) Statin	II	RCT	High	Medium	Low
Sandhu et al (2006) Statins	I	Systematic review of RCTs	High	Low	Medium
Sorof et al (2006)	II	RCT	High	Low	Medium
Strippoli et al (2008) Statins	I	Systematic review of RCTs	High	Low	Medium
The Heart Protection Study (2003) Simvastatin	II	RCT	High	Medium (small difference in rate of decline in eGFR)	Medium

Magnitude of effect assessed in relation to overall outcome(s) relevant to CKD. A high effect maybe therefore be noted where there may be no significant difference between two agents, however both agents result in significant outcomes with respect to progression of CKD.

iv) Role of diet modification

Author (year)	Evidence (Intervention)				
	Level of Evidence		Quality Rating	Magnitude of the effect Rating	Relevance Rating
	Level	*Study Type*			
ProteinRestriction					
Barsotti et al (1998)	III-2	Non randomised trial	Medium	Medium	Low
de Mello et al (2006)	III-1	Before and after pseudo randomised trial	High	Medium	Low
Dussol et al (2005)	II	RCT	High	Low	Medium
Gross et al (2002)	II	RCT	Medium	Medium	Low
Meloni et al (2004)	II	RCT, prospective	Medium	Low	Medium
Pijls et al (1999)	II	RCT	Medium	Medium	Medium
Pijls et al (2002)	II	RCT	Medium	Low	High
Pomerleau et al (1993)	II	RCT	Medium	Medium	Low
Robertson et al (2007)	I	Systematic Reviews of RCTs and before and after trials	High	Medium	Medium
Teixeira et al (2004)	III-2	Before and after trial	High	Medium	Low
Wheeler et al (2002)	III-2	RCT	Medium	Low	Low
Salt Restriction					
Houlihan et al (2000b)	II	RCT	Medium	Medium	Low
Houlihan et al (2002a)	II	RCT	Medium	Low (with respect to salt)	Low
Houlihan et al (2002b)	II	RCT	Medium	Medium	Low
Imanishi et al (2001)	III-2	Before and after	Medium	Low	Low
Vedovato et al (2004)	III-2	Before and after, pseudo randomisation	Medium	Medium	Low
Yoshioka et al (1998)	III-2	Before and after, Randomization of order of diet	Medium	Low	Low
Dietary Fat					
Barnard et al (2006)	II	RCT	Medium	Medium	Medium
Cardenas et al (2004)	III-2	Prospective cohort	Medium	Medium	Medium
Nicholson et al (1999)	II	RCT	Medium	Low	Low
Nielsen et al (1995)	III-1	Pseudo randomised trial	Medium	Low	Low
Shimizu (1995)	III-2	Comparative study – before and after trial.	Medium	Low	Medium

v) Role of smoking cessation

Author (year)	Evidence (Prognosis)				
	Level of Evidence		Quality Rating	Magnitude of the effect Rating	Relevance Rating
	Level	*Study Type*			
Anan et al (2007)	IV	Cross sectional	Medium	High	Low
Baggio et al (2002)	IV	Cross sectional	Medium	High	Medium
Biarnes et al (2005)	II	Prospective cohort	Medium	High	Medium
Braatvedt et al (2006)	II	Prospective cohort	High	High	Medium
Bruno et al (1996)	IV	Cross sectional	High	High	Medium
Cederholm et al (2005)	II	Prospective cohort	High	High	Medium
Chuahirun et al (2003)	II	Prospective cohort	Medium	High	Medium
Chuahirun et al (2004)	II	Prospective cohort	Medium	High	Medium
Corradi et al (1993)	IV	Cross sectional	Medium	High	Low
Dean et al (1994)	IV	Cross sectional	Medium	Low	Medium
Forsbolm et al (1998)	III-2	Retrospective cohort	Medium	High	High
Gambaro et al (2001)	III-2	Retrospective cohort	High	High	High
Gatling et al (1988)	IV	Cross sectional	Medium	High	Low
Ikeda et al (1997)	IV	Cross sectional	Medium	High	Medium
Nilsson et al (2004)	IV	Cross sectional	High	High	Medium
Pijls et al (2001)	IV	Cross sectional	High	High	High
Savage et al (1995)	IV	Cross sectional	Medium	High	Medium
Smulders et al (1997a)	II	Prospective cohort	Medium	Low	Medium
Thomas et al (2006)	IV	Cross sectional	Medium	High	Medium

Section 3: Cost Effectiveness and Socioeconomic Implication

Question

Is the prevention and management of chronic kidney disease in people with type 2 diabetes cost effective and what are the socioeconomic implications?

Practice Points

- Based on favourable cost studies, screening for microalbuminuria and treatment with antihypertensive medications should be routinely performed for the prevention and management of kidney disease in people with type 2 diabetes.

- Socio-economic factors should be considered when developing programs for prevention, and management of CKD in people with type 2 diabetes.

Evidence Statements

- Screening people with type 2 diabetes for microalbuminuria and intensive treatment of those with elevated blood pressure with ACEi and ARB antihypertensive agents is supported by cost effectiveness studies.

- Socio-economic status is an independent risk factor for CKD in people with type 2 diabetes.
  Evidence Level III

- Socio-economic status is associated with reduced access to primary medical care services and a lower level of utilisation of those services and this is likely to be associated with poorer outcomes in relation to CKD in people with type 2 diabetes.
  Evidence Level IV

Background – Cost Effectiveness and Socioeconomic Implications of Prevention and Management of CKD in Type 2 Diabetes

Cost Effectiveness

Microalbuminuria is an asymptomatic condition that affects 20-40% of people with type 2 diabetes. Of these, only about 20% are normotensive by current criteria. The rate of progression of microalbuminuria is slower in normotensive than in hypertensive people. Its significance arises from the proportion of affected people (40-80%) who subsequently develop either CVD or who develop proteinuria with eventual progression to renal failure (Palmer et al, 2008). ESKD causes a significant decline in quality of life, is expensive, and is associated with considerable mortality - approximately 15 per 100 patient years of Australians undergoing dialysis die annually (Australian and New Zealand Dialysis and Transplant Registry 2007). Based on a review of clinical trials Palmer et al (2008) estimated a risk multiplier of 3.29 for mortality in people with type 2 diabetes, elevated blood pressure and overt nephropathy compared to those with no nephropathy. In the Australian health sector, costs for provision of ESKD health care services has been projected to increase in the order of $A50M per year and reach more than $A800M by 2010 (Cass et al, 2006). This reflects the increasing prevalence of dialysis dependent patients and costs in the order of $A40,000 to $A45,000 per person per year (Craig et al, 2002). These ESKD cost projections exclude the costs associated with co-morbid conditions such as CVD as well as indirect or non-health sector costs associated with ESKD (Cass et al, 2006).

Similarly, in the US, O'Brien et al (1998) highlighted that the direct costs arising from ESKD were the most expensive of 15 different complications of type 2 diabetes. ESKD in the US costs US$53,659 per annum per patient. In comparison, ischaemic stroke has an event cost of US$40,616 and annual cost of US$9,255 and a myocardial infarction has an event cost of US$27,630 and an annual cost of US$2,185.

The cost-effectiveness of different prophylactic strategies in type 2 diabetes has not been compared. It has been estimated that the natural history of type 2 diabetes will see 17% of people developing end stage renal failure compared to 39% who will develop cardiovascular complications (Eastman et al, 1997). The latter are the dominant considerations in the elderly microalbuminuric person with type 2 diabetes and the HOPE study suggested that ACE inhibition would be justified for macrovascular protection alone in this subgroup (The HOPE Study Group 2000).

Treatment with ACEi and ARBs reduces the chance of progressing from microalbuminuria to overt proteinuria and the chance of progressing from overt proteinuria to ESKD (Strippoli et al, 2005; Strippoli et al, 2006) . However, the long-term effects (over 10 years of therapy) of ARB or ACEi on kidney function in type 2 diabetes are less clear. In addition, assessment of the effects of ARB or ACEi in normotensive, microalbuminuric people with type 2 diabetes need to take into account the potential cardiovascular benefits.

The review by Boersma et al (2006) focused on the pharmacoeconomics of ARB and ACEi treatment of people with type 2 diabetes and nephropathy. The conclusion with respect to ARBs was considered unequivocal in that the trials show both health gains and net cost savings compared to conventional treatment therapy, largely because of the high cost of dialysis and transplantation. The outcome with respect to the use of ACEi was concluded to be less clear due to the limited head-to-head trials comparing ACEi to ARB.

It has been demonstrated that aggressive blood pressure reduction in hypertensive, normoalbuminuric people with type 2 diabetes reduces the incidence of microalbuminuria (UKPDS 1998b). Taken together with the progressive lowering of recommended blood pressure thresholds for initiating treatment of elevated blood pressure (Fulcher et al, 2004), it is possible that transition rates between stages of diabetic kidney disease will be substantially lower in the future than suggested by previous studies (Ravid et al, 1993; Ravid et al, 1998).

It is important to note the assumptions inherent in cost-effectiveness analyses. A major concern about cost-effectiveness analysis is the validity of extrapolating to different populations in which costs, risk of diabetic kidney disease and effects of treatment on progression to renal failure may differ from the study population.

Socio-economic Implications

Socio-economic differentials in health are widely recognized with individuals of lower socioeconomic status (SES) having a higher risk for mortality and morbidity compared with those of higher SES e.g. (Adler & Ostrove 1999; Bello et al, 2008). These guidelines consider evidence for socioeconomic influences as they relate to outcomes relevant to the prevention and management of CKD in people with type 2 diabetes.

The increasing prevalence of type 2 diabetes has been identified as the prime cause for the increasing prevalence of ESKD in Australia (Australian and New Zealand Dialysis and Transplant Registry 2007; Dunstan et al, 2002). The duration of diabetes, age, blood pressure control and blood glucose control have been identified in the Australian population as independent risk factors for the development of albuminuria (Tapp et al, 2004). Thus the consideration of the impact of socioeconomic factors on the diagnosis, prevention and management of CKD in people with type 2 diabetes, needs to be cognisant of factors that influence the development and treatment of type 2 diabetes, or that influence the likelihood of having undiagnosed diabetes and poorly treated hypertension and blood glucose. It is reasonable to assume that socioeconomic factors that influence the diagnosis and management of type 2 diabetes will also be important factors relevant to the progression of CKD. As the evidence relating to socioeconomic influences on the, prevention, detection and diagnosis of type 2 diabetes is addressed in other type 2 diabetes guidelines, this guideline focuses on factors that relate specifically to CKD following diagnosis of type 2 diabetes.

Socio-economic status may influence the diagnosis, prevention and management of CKD in people with type 2 diabetes as a consequence of the following (Cass et al, 2004):

- Differing access to medical services.
- A differing standard of service once accessed.
- Late referral to treatment and/or specialist care.
- Differing compliance with interventions.
- Differing outcomes of interventions.
- Difference in the prevalence of risk factors (e.g. smoking).

As discussed in the overview to these guidelines, people from disadvantaged and transitional populations are disproportionally affected by type 2 diabetes and CKD. Factors contributing to the high incidence rates of ESKD in these groups include a complex interplay between genetic susceptibility, age of onset of diabetes, glycaemic control, elevated blood pressure, obesity, smoking, socioeconomic factors and access to health care. Within the Australian

population, Indigenous Australians have an excess burden of both type 2 diabetes, albuminuria and ESKD e.g. (Australian and New Zealand Dialysis and Transplant Registry 2007; Guest et al, 1993; Hoy et al, 2007; McGill et al, 1996; Preston-Thomas et al, 2007; Spencer et al, 1998) and likely represent the most marginalised group within the Australian health care setting.

Explanations offered for the excess burden of kidney disease in Indigenous populations can be categorised as (Cass et al, 2004):

- Primary renal disease explanations, for example greater severity and incidence of diseases causing ESKD.
- Genetic explanations.
- Early development explanations.
- Socio-economic disadvantage.

During 1991 – 2001, 47% of ESKD cases were attributed to diabetic nephropathy among Indigenous Australians, compared to 17% in non-Indigenous Australians. However, low kidney biopsy rates for ESKD, approximately 20% for both non-Indigenous and Indigenous Australians, indicate a potential for reporting bias with respect to diabetic nephropathy. Indigenous Australians have a higher rate of comorbidity than non-Indigenous Australians reflecting the generally poorer health of this group. It should be noted, however that type 2 diabetes constitutes the greatest excess comorbidity among Indigenous ESKD entrants (McDonald & Russ 2003a; McDonald & Russ 2003b). Socio-economic factors that influence the health of Indigenous Australians and other marginalised groups within the Australian population are likely to affect detection, prevention and management of CKD in people with type 2 diabetes. The high prevalence of type 2 diabetes causing ESKD amongst Indigenous Australians, and the association between poor control of diabetes and risk of progression of CKD, are consistent with disadvantage being a significant determinant of progression of kidney disease in diabetes.

Cass et al (2002) note that the evidence for the association between socioeconomic status and the incidence of ESKD is inconsistent. A study of the association between the level of socioeconomic disadvantage for a capital city area and the incidence of ESKD showed higher ESKD rates in more disadvantaged areas (Cass 2002). A similar study of indicators of socioeconomic disadvantage amongst Indigenous Australians (at a regional level) and the incidence of ESKD has shown a strong correlation with an overall rank of socioeconomic disadvantage. Indigenous ESKD patients are more likely to be referred to a nephrologist late in the course of their renal disease. Late referral is associated with increased mortality on ESKD treatment and is more common in disadvantaged areas. Amongst Indigenous ESKD patients, a poor understanding of their own CKD has been linked to non-compliance and reduced active involvement in their own management (Anderson et al 2008). Reduced engagement with care providers and services is a risk factor for poor outcomes with CKD care.

Evidence - Cost Effectiveness and Socioeconomic Implications of Prevention and Management of CKD in Type 2 Diabetes

Cost Effectiveness

- **Screening people with type 2 diabetes for microalbuminuria and intensive treatment of those with elevated blood pressure with ACEi and ARB antihypertensive agents is supported by cost effectiveness studies.**

The cost effectiveness of intensive blood pressure control in people with type 2 diabetes, elevated blood pressure and normoalbuminuria, has been evaluated in the UKPDS over a mean interval of 8.8 years (UKPDS 1998a). The intensive blood pressure control group (n=758) achieved a mean arterial pressure of 103 mmHg (144/82 mmHg) compared with 109 mmHg (154/87mmHg) in the usual treatment group (n=390). Use of resources driven by trial protocol and in standard clinical practice were compared. The main outcome measures were, firstly, cost effectiveness ratios calculated from use of healthcare resources and, secondly, within-trial time free from diabetes-related endpoints and projected estimates of life years gained. Compared with use of resources in standard clinical practice intensive blood pressure control was associated with an incidental cost of £1049 per extra year free from end points (costs and effects discounted at 6% per year). When the analysis was extended to life expectancy, the incremental cost per life year gained was £720, using the same discounting procedures. This analysis represents the first evidence suggesting that tight control of blood pressure for hypertensive people with type 2 diabetes offers a cost effective means of reducing the risk of complication and improving health (UKPDS 1998a).

In a further analysis of the UKPDS study, an evaluation of the cost effectiveness of intensive blood pressure control with atenolol (n=358) vs. captopril (n=758) was performed (Gray, 2001). There was no significant difference in life expectancy between groups. However, the cost per person in the captopril group was £935 greater than in the atenolol group, because of the lower drug price and fewer admissions to hospital in the atenolol group despite having higher antidiabetic drug costs. The analysis suggests that in hypertensive people with type 2 diabetes and with normal AER, control of blood pressure based on beta blockers appears superior from a cost perspective to control based on ACEi (Gray 2001). It is important to note that this does not apply to people with increased AER, in whom treatment with renin angiotensin system inhibitors has been shown to reduce AER to a greater clinical extent than treatment with other agents (Kasiske et al, 1993; Weidmann et al, 1995).

The Kidney Health Australia (KHA) report "*The Cost–Effectiveness of Early Detection and Intervention to Prevent the Progression of Chronic Kidney Disease in Australia*." (Howard et al, 2006) undertook cost effectiveness modelling of "opportunistic screening and best-practice management of diabetes, elevated blood pressure and proteinuria among Australian adults". The model outcomes were used as input to the companion KHA report by Cass et al (2006) The study modelled the health outcomes of Life Years Saved and Quality Adjusted Life Years Saved. On the basis of the models the authors concluded that the best available evidence supports screening and intensive management of three risk factors for CKD, namely diabetes, high blood pressure and protein in urine (Cass et al, 2006).

The KHA report included modelling the cost-effectiveness of screening for proteinuria and subsequent treatment with an ACEi for people with diabetes with or without elevated blood pressure. The authors noted that there was very limited data on both screening and treatment in normotensive patients, and thus model results are indicative only and suggested "some benefit under optimistic assumptions" with results considered as being of an exploratory nature only. Further trials were required in order to determine the cost effectiveness of ACEi interventions in microalbuminuric normotensive type 2 diabetes to be determined (Howard et al, 2006).

More recently Palmer et al (2008) completed a health economic analysis of screening (microalbuminuria and overt nephropathy) and optimal treatment of nephropathy in hypertensive type 2 diabetes within the US health care system. The inputs to the economic modelling was based on estimates derived from a review of clinical trials. The modelling indicated screening for early stage nephropathy and optimal treatment (use of 300 mg irbesartan) in addition to the patients current treatment, results in a 44% reduction in the cumulative incidence of ESKD. The incremental costs-effectiveness ratio was in the order of $US20,000 per QALY gained for screening and optimised treatment compared to no screening. A 77% probability that screening and optimised therapy would be considered cost effective was calculated assuming a willingness to pay threshold of $US50,000. Overall the authors considered that the modelling showed that screening and optimised treatment (with an ARB) to "represent excellent value in a US setting."

In relation to screening and treatment with an ACEi for the early detection and treatment of kidney disease, Craig et al (2002) considered that whilst this was a promising primary prevention strategy for the prevention of ESKD, there was inadequate trial data to support population wide adoption (i.e. all middle and older aged Australians). This review was not limited to people with type 2 diabetes. Based on review of clinical trials and estimates of the performance characteristics of tests for proteinuria, it was estimated that screening of 20,000 Australians (>50 years) would lead to subsequent treatment of 100 prescribed with ACEi and prevention of 1.3 cases of ESRF over 2 to 3 years. A cost benefit evaluation indicated a net cost saving to for the health care system assuming a one-off dipstick screening program in men and women over 55 based on assumed prevention of 205 cases of ESKD, 100% compliance with screening and best estimates of unit costs for screening and treatment. However, the cost effectiveness was quite sensitive to screening costs with a reversal point noted occurring at $2 per person compared to a base assumption of $0.50. Overall savings on the base assumptions were estimated at $A70,000 (2-3 years treatment costs for ESKD). Given the sensitivity of the estimates to key areas of uncertainty with respect to ESKD risk factors in the general population including, performance of screening tests and the benefits of ACEi treatment in screen-detected low risk-subjects, it remains unclear whether population wide screening for kidney disease would do "more harm than good." Presumably these uncertainties would be lower in the higher risk type 2 diabetes sub group favouring adoption of screening and treatment in this setting.

Given that microalbuminuria does not directly cause morbidity or mortality, the effectiveness of treating microalbuminuria can be assessed by comparing the cost of treatment to the savings resulting from the presumed prevention of end-stage kidney disease (Cass et al, 2006; Craig et al, 2002; Palmer et al, 2008). However, it should be emphasised that no study has followed the effects of ACEi or other intervention in normotensive, microalbuminuric people with type 2 diabetes until the development of ESKD. Nevertheless, such analysis can aid in determining which of several approaches provides the most cost-effective treatment of microalbuminuria. It should be noted that treatment of microalbuminuria is only one of

several prophylactic programs that may benefit people with diabetes, and cost-benefit analyses provide a useful tool in the efficient allocation of limited health resources.

The alternatives to screening for and treating diabetic microalbuminuria with ACEi or ARBs are to wait until elevated blood pressure (BP>130/85) or gross proteinuria develops before instigating therapy, or to treat all people with type 2 diabetes with ACEi or ARBs regardless of their urinary protein excretion. The costs and benefits for screening for albuminuria and subsequent treatment with an ARB, was considered by Palmer et al (2008) and discussed above. The costs and benefits associated with treatment of all people with type 2 diabetes with an ACEi have been modelled over the lifetime of a theoretical cohort of American people with diabetes aged 50 years at time of diagnosis and who were not receiving ACEi for other reasons by Golan et al (1999). In this model, the effectiveness of ACEi in slowing the progression of normoalbuminuria to microalbuminuria was based on only one randomised trial of 156 normotensive, middle-aged Israeli people (Ravid et al, 1998). This trial showed that ACEi therapy was associated with an absolute risk reduction of 12.5% (CI 2-23%) over 6 years. The effectiveness of ACEi is slowing the progression of microalbuminuria to diabetic kidney disease was also based on one study by (Ravid et al, 1993). In 94 normotensive middle-aged Israeli people with type 2 diabetes, AER increased over 5 years from 123 to 310 mg/24 hrs in the placebo group, and from 143 to 150 mg/24 hrs in the enalapril treatment group, showing a significant reduction in the rate of change of AER ($p<0.05$).

In the model by Golan et al (1999) the transition time from macroalbuminuria to ESKD was extrapolated from data on people with type 1 diabetes (Lewis et al, 1993). Potential costs factored into the model included screening for microalbuminuria and proteinuria, drug costs and expenses incurred in treating ESKD with either dialysis or transplantation. The model also considered the effects of treatment non-compliance on cost-effectiveness and adjusted outcomes for quality of life changes. Compared to waiting until overt proteinuria develops, treating microalbuminuria with ACEi was estimated to reduce overt proteinuria from 16.8% to 10.4%, ESKD from 2.1% to 1.9% and total mortality from 15.2% to 14.7% over 10 years (Golan et al, 1999). By comparison, treating all people with type 2 diabetes with an ACEi, rather than screening for microalbuminuria, reduced microalbuminuria from 25.3% to 18.2%, overt proteinuria from 10.4% to 9.0%, ESKD from 1.4% to 1.2% and total mortality from 14.7% to 14.6% over 10 years (Golan et al, 1999).

Angiotensin converting enzyme inhibitor treatment of overt proteinuria in normotensive, people with type I diabetes reduces the progression to end-stage renal failure by about 40% (Lewis et al, 1993). The rate of progression from gross proteinuria to end-stage renal failure is similar in people with type 1 and type 2 diabetes (Hasslacher et al, 1989). However, it can not be assumed that ACEi will have the same effect on the prevention of end-stage renal failure in people with type 2 diabetes as shown for people with type 1 diabetes. This is because of a greater contribution of age-related intrarenal atherosclerosis and glomerulosclerosis leading to a decline in the number of functioning glomeruli.

It is important to appreciate that cost-effectiveness is critically dependent on the life expectancy of the population it is applied to. Thus, treating microalbuminuria in elderly people will be less cost-effective than treating younger people. Cost-effectiveness is also reduced if more liberal criteria are used to diagnose diabetes or if screened people are unlikely to take prescribed medications (Golan et al, 1999).

Cost-effectiveness also depends on the cost of ACEi. Projections based upon the current cost of ACEi may underestimate cost-effectiveness considering that many of these agents will soon be off patent and presumably substantially cheaper (Golan et al, 1999).

Cost-effectiveness studies of screening and early treatment of diabetic kidney disease were initially performed in people with type 1 diabetes (Siegel et al, 1992). Two cost-effectiveness modelling procedures were performed, assuming conservative or optimistic effects of 50% and 75%, respectively, for ACE inhibition in slowing progression from microalbuminuria to overt kidney disease and from overt kidney disease to renal failure. The model showed that screening and treatment at the stage of microalbuminuria provided an additional 5 to 8 months of life expectancy, when compared to late intervention at the stage of overt diabetic kidney disease . Screening and treatment at the microalbuminuric stage in type 1 diabetes yielded a cost of US$16,500 per life year saved in the conservative model, and US$7,900 per life year saved in the optimistic model (Siegel et al, 1992).

Similar modelling procedures have been performed in people with type 2 diabetes. The costs of screening and treating microalbuminuria with ACEi include US$20/year for an annual check for microalbuminuria and US$320 for treatment with an ACEi. Whether this strategy increases physician/health carer time is unclear. The cost of screening for overt proteinuria is US$3 (Golan et al, 1999).

It was estimated that screening and treatment with an ACEi at the microalbuminuric stage would cost US$22,900 per life year saved, when compared to waiting till overt diabetic kidney disease develops (Golan et al, 1999). This study also suggested that treating all middle-aged people with type 2 diabetes with an ACEi would cost US$7,500 per life year saved, when compared to delaying ACEi therapy till the microalbuminuric stage (Golan et al, 1999). However, this 'treat all' approach has not been subjected to clinical trials and requires further cost-effectiveness evaluation.

The life-time cost of ACEi treatment of microalbuminuria has been calculated as $14,940, compared to $19,520 if ACEi are only introduced after gross proteinuria develops (Golan et al, 1999).

Data have been obtained on renal outcomes using angiotensin receptor blockade (Parving 2001). Hypertensive people with type 2 diabetes and microalbuminuria were treated over 2 years with irbesartan (150 mg/day or 300 mg/day) or placebo. The primary outcome was the time to the onset of diabetic kidney disease, defined by persistent albuminuria in overnight specimens, with a AER <200 µg/min and at least 30 percent higher than the base-line level. Ten of 194 people in the 300 mg/day group (5.2%) and 19 of 195 people in the 150 mg/day group (9.7%) reached the primary end-point, as compared with 30 of 201 people in the placebo group (14.9%). Cost-effective analyses have not been performed with ARB's but these results represent a 65% reduction in risk (from 14.9% to 5.2%) for the progression of microalbuminuria to macroalbuminuria with irbesartan (300 mg/day), suggesting ARB's would at least be as cost-effective as ACEi in preventing the development of CKD.

It needs to be emphasised that the above considerations apply to normotensive people with persistent microalbuminuria, who contribute approximately 20% of the total population of people with type 2 diabetes and microalbuminuria. In the larger hypertensive subgroup, antihypertensive treatment starting with an ACEi is now standard therapy.

Socio-economic Implications

- **Socio-economic status is an independent risk factor for CKD in people with type 2 diabetes *(Evidence Level III)*.**

The prevalence and incidence of CKD is associated with socioeconomic status, whereby increasing social disadvantage is an independent risk factor for CKD in people with type 2 diabetes. The following studies provide evidence relating to the influence of socioeconomic factors on CKD in people with type 2 diabetes.

White and colleagues (White et al, 2008) sought to determine whether an elevated burden of CKD is found amongst disadvantaged groups living in the US, Australia and Thailand. The study used the NHANES III, AusDiab I and InterASIA databases and identified a prevalence of diabetes of 10.6% in the US, 7.4% in Australia and 9.8% in Thailand in people 35 years or older. Crude analysis showed income in the lowest quartile, shorter duration of education and being unemployed ($p<0.01$) to significantly increase the odds of having an eGFR <60 ml/min/1.73m^2. Multivariate analysis adjusting for age and gender showed no significant association in the AusDiab data. Disadvantage appeared to affect CKD prevalence in the US via mechanisms independent of the clustering of risk factors in groups by SES. The association between disadvantage and CKD did not appear to be internationally consistent.

A cohort of 650 patients living within the boundary of Greater London who first attended a diabetes clinic between 1982 and 1985 was assessed by Weng et al (2000). Postcodes were used to determine whether the diabetes care outcomes were linked to material deprivation and place of residence. Deprivation was determined using an 'under-privileged area' UPA score based on eight variables. Proteinuria was defined as a single positive dip stick test on a morning urine sample. The mean HbA1c from deprived areas was higher than that of prosperous wards, insulin treatment was used less commonly and glycaemic control was worse. The age-adjusted prevalence of proteinuria was significantly higher ($p<0.001$) in deprived areas being 57%, 25.6% and 21.7% in deprived, intermediate and prosperous areas respectively. There was no significant difference in glycaemic control between ethnic groups. Whilst more Afro-Caribbean's live in deprived areas, a higher proportion of patients from these areas were Caucasian. Obesity, poor glycaemic control and smoking habits were identified as major risk factors in relation to socioeconomic status and increased complications arising from diabetes.

Bello et al (2008) studied the association between area-level SES and the severity of established CKD, at presentation to a renal service in the UK. The study was a retrospective cross-sectional review of 1657 CKD patients, where CKD was defined by an eGFR of <60 ml/min/1.73 m^2 for at least 6 months duration. A residential area deprivation index was used as an indicator of SES. The study identified an increasing trend in the severity of CKD (based on eGFR) at presentation to a renal unit in association with an increase in the area-level measure of deprivation. The most deprived areas also had the highest age-adjusted prevalence rate for CKD. Diabetes and hypertension explained a large part of the relationship between deprivation and severity of CKD. BMI, smoking, serum cholesterol, age and race did not fully explain the relationship.

A retrospective population study of the incidence and prognosis of CKD in the UK, which included a regional based assessment of socioeconomic deprivation, was undertaken by Drey et al (2003). The incidence of CKD was based on a serum creatinine value of $\geq$ 1.7 mg/dL

(≥ 150μmol/L) with cases identified from a review of a database of chemical pathology results. The least and most deprived quintiles had rates of 1,067 per million population (pmp) per annum (95% CI 913 to 1,221) and 1,552 pmp per annum (95% CI 1,350 – 1,754). The nature of the study did not allow for adjustment for potential confounding factors such as BMI, smoking, hypertension etc. Furthermore the cause of CKD was not able to be estimated for the majority (87%) of the cases.

A population based prospective study aimed at identifying how much of the excess risk for CKD among African Americans can be explained on the basis of racial disparities in potentially modifiable risk factors was conducted by Tarver-Carr et al (2002). The following explanations of the higher incidence of ESKD amongst African Americans were considered:

- SES
- Greater prevalence and severity of diabetes and hypertension
- Increased inherited susceptibility to kidney damage.

The study analysed baseline CKD risk factors from a non concurrent nationally representative population based cohort (NHANES II) with a 12 to 16 year follow up. Compared with white subjects, African American adults were more likely to have lower educational attainment, live below the federal poverty line and to be unmarried. They were also more likely to be current smokers, to be obese, to be physically inactive and to drink less alcohol. They had a higher prevalence of diabetes and hypertension as well as higher SBP and GFR. The age-adjusted incidences of all-cause CKD and treated ESKD were 2.7 and 8.9 fold higher amongst African Americans. The age-adjusted incidence of kidney disease attributable to diabetes was almost 12 times higher in African Americans. After adjustment for age and gender, sociodemographic factors, lifestyle factors and clinical factors, the excess risk of CKD among African Americans reduced from a relative risk of 2.69 (1.50-4.82) to 1.95 (1.05-3.63); explaining 44% of the excess risk. Diabetes and hypertension alone accounted for 32% of the excess risk. The differences according to ethnicity were greater with middle aged than older adults. The authors concluded that interventions aimed at reducing racial disparity in CKD risk should focus on primary prevention and improved treatment of diabetes and hypertension, lifestyle modification, and elimination of health disparities attributable to socioeconomic status.

The Fremantle Diabetes Study reported by Davis et al (2007), a longitudinal observational study in a community based clinically-defined type 2 diabetes patient cohort, compared the ACR in self-identified Aboriginal and Torres Strait Islanders (n=18) with Anglo Celt type 2 diabetes patients (n=819), who represent the largest ethnic group within the patient community. The Aboriginal and Torres Strait Islander patients were significantly younger at diagnosis but had similar diabetes duration. Despite similar glycaemic management, the Indigenous patients had higher HbA1c. The geometric mean ACR was significantly higher in Aboriginal compared to Anglo Celt patients [10.1 (1.1-93.6) vs. 2.9 (0.7-12.4) mg/mmol respectively]. The SBP and DBP were lower and the smoking rate three times higher than in the Anglo Celt patients. Even though Aboriginal and Torres Strait Islander patients had a higher number of GP visits each year, they were less likely to have received diabetes education or to self monitor blood glucose. Overall there was no significant difference in the proportion of each group that died during the mean follow up period of 9.3 ± 3.2 years, however the age at death was 18 years younger in the Aboriginal group. Aboriginal patients had a twofold higher risk of dying than Anglo Celts. Amongst other variables, urinary ACR was an independent predictor of all-cause mortality in Aboriginal and Torres Strait Islander and Anglo Celt patients. The Fremantle Study, although the small number of Indigenous patients reduces the ability to draw inferences about the urban Indigenous population,

suggests that sustained high-level glycaemia and smoking are likely determinants of albuminuria in the Indigenous patients.

- **Socio-economic status is associated with reduced access to primary medical care services and a lower level of utilisation of those services and this is likely to be associated with poorer outcomes in relation to CKD in people with type 2 diabetes *(Evidence Level IV).***

The mechanisms by which social disadvantage increases the risk of CKD have not been fully elucidated. However, social disadvantage appears to influence the stage of CKD at which specialist referral takes place, which in turn has negative implications for individual outcomes. Access to and utilisation of primary care medical services may also be lowest amongst those of highest social disadvantage and greatest need, thereby limiting the ability for implementation of interventions shown to prevent or reduce progression of CKD.

Consideration of access to medical services needs to take into account both services related to prevention as well as specialist care for the management of CKD. Consistent with the study by Davis et al (2007), the socially disadvantaged are likely to be less educated in aspects of primary prevention and management. In relation to CKD, the timing of referral to a nephrologist might further influence the progression of CKD and overall outcomes. The meta analysis by Chan and colleagues (Chan et al, 2007) examined the outcomes in patients with CKD referred late to a nephrologists. The analysis did not distinguish between the cause of CKD nor conduct sub group analyses for diabetes. Overall, 20 studies (total sample size 12 749) examining the effect of late referral met inclusion. The definition of late referral varied from 1 month to 6 months. There was a significantly increased overall mortality in the late referral group compared to the early referral group (relative risk 1.99 95% CI, 1.66 to 2.39) and a significantly longer duration of hospital stay. However, the mean serum creatinine and creatinine clearance at time of referral were not significantly different between the groups.

Cass et al (2003), investigated the association between area level measures of socioeconomic disadvantage and the proportion of ESKD patients who were referred late for renal replacement therapy. The analysis, which utilized the ANZDATA database, considered the timing of referral to a nephrologists and the postcode of residence at the start of treatment. Late referral was defined as those who required dialysis within 3 months of referral. The analysis was restricted to capital cities and excluded overseas visitors and those where ESKD was caused by disease with very short course. The ABS Statistical Sub-Division (SSD) level socioeconomic data from the 1996 census was used for the assessment.

Of the total of 3334 patients (April 1995 – December 1998), 889 (26.7%) were found to have been referred late with a high variability between SSDs. There was a significant correlation between late referral and disadvantage ($r=-0.36$, $p=0.01$), with a higher proportion of late referral being associated with the more disadvantaged regions. Areas with higher incidence of ESKD in population terms were also areas where a higher proportion of patients were referred late. Issues of access, availability and quality of care are all potentially relevant to late referral. Disadvantaged areas had both an increased population burden of ESKD and a greater risk of delayed access to specialist renal services which is then associated with a poorer outcome. The study concludes that despite an overall improvement in the prevention and care of chronic diseases, with regard to chronic renal failure, there is a failure to address the needs of general practitioners and the public especially in disadvantaged areas. Of interest, late referral was found not to be related to geographical access to dialysis units (Cass et al 2003).

Overland and colleagues analysed information on the number of diabetic individuals and number of services for selected Medicare item codes by NSW postcodes using the Health Insurance Commission data file (Overland et al, 2002). The analysis was conducted for the 1996 calendar year and indicated that people at most disadvantage were less likely to be under the care of a GP (OR 0.41 0.40-0.41) or consultant physician (0.50 0.48-0.53) despite this group having the highest prevalence of diabetes. Once under care, slightly more were likely to undergo HbA1c or microalbuminuria screening (1.04 1.00-1.10 and 1.22 1.12-1.33) but less likely to undergo lipid or HDL cholesterol (0.81 0.48-0.53 and 0.85 0.79-0.90). Thus whilst disadvantaged people had poor access, once in the health system the level of monitoring received was similar. They note, however that the majority of medical practitioners are located in capital cities yet the majority of people in NSW at most social disadvantage live outside the Sydney metropolitan area. In addition the gap between Medicare reimbursement and the amount charged by medical practitioners is often greater in rural areas. People at most social disadvantage may be selectively disadvantaged in regard to access to health care services in the current system. The reluctance to test the most socially disadvantaged group for lipid abnormalities may reflect the cost of lipid lowering treatment (at the time of the survey).

The relationship between social disadvantage and access to GPs is further demonstrated in the study by Turrell et al (2004) who conducted an analysis of 1996 to 1997 Medicare data to evaluate associations between utilization of GPs, socioeconomic disadvantage, geographic remoteness and Indigenous status. The review was undertaken at the level of Statistical Local Areas (SLA) after assigning an Index of Relative Socio-economic Disadvantage (IRSD) and Accessibility/Remoteness Index of Australia (ARIA). The proportion of Indigenous Australians was calculated from the number of self-identified persons of Aboriginal and Torres Strait Islanders background. In relation to socioeconomic disadvantage the following points were noted:

- The number of full time equivalent GPs decreased with decreasing socioeconomic status and increasing remoteness of SLAs.
- The proportion of Indigenous Australians increased with decreasing socioeconomic status and increasing remoteness of SLAs.
- The utilization rate of GP services decreased markedly with the remoteness of the SLA and to a lesser extent with decreasing socioeconomic status.
- There was an interaction between remoteness and socioeconomic disadvantage such that:
  - in highly accessible areas average GP utilization rate increased with decreasing SES
  - in remote/very remote areas, the average GP utilization rate decreased with decreasing SES.

The authors concluded that in areas of adequate GP supply, ready geographic and financial access, equity of access appears to prevail. However, in socioeconomically disadvantaged areas where GPs are least accessible and affordable, the principle of equity of access to services is compromised. Furthermore, these latter areas are also those with highest medical needs.

Summary – Cost Effectiveness and Socio-econmic Implications of Prevention of CKD

- The best available evidence supports screening and intensive management of the three risk factors for CVD, namely diabetes, high blood pressure and protein in urine.

- Screening for albuminuria in people with type 2 diabetes has been modelled as being cost effective due to the anticipated reduction in CVD events and the reduction in the number progressing to ESKD. The modelling shows cost effective outcomes both with respect to life years saved as well as quality adjusted life years saved.

- Similarly treatment of albuminuria with ACEi and ARB antihypertensive agents is a cost effective approach to reducing CVD outcomes and progression to ESKD.

- The cost effectiveness of treating normotensive microalbuminuric type 2 diabetes patents with an ACEi and/or ARB antihypertensive agent has yet to be established.

- Further studies on the benefits of ACE inhibition in preventing ESKD in normotensive microalbuminuric people with type 2 diabetes would allow better estimates of the cost-effectiveness of this treatment. However it may be difficult to ethically justify such studies

- The prevalence and incidence of CKD is associated with socioeconomic status, whereby increasing social disadvantage is an independent risk factor for CKD in people with type 2 diabetes.

- The mechanisms by which social disadvantage increases the risk of CKD have not been fully elucidated. However, social disadvantage influences access and utilisation of medical services, thereby limiting the ability for implementation of interventions shown to prevent or reduce progression of CKD.

Evidence Tables: Section 3

Cost Effectiveness and Socioeconomic Implications

Cost-effectiveness

Author (year)	Evidence				
	Level of Evidence		Quality Rating	Magnitude of the effect Rating	Relevance Rating
	Level	*Study Type*			
Cass et al (2006)	N/A	Modelling	High	High	High
Craig et al (2002)	N/A	Modelling	High	Medium	High
Golan et al (1999)	N/A	Modelling	Medium	High	Medium
Gray et al (2001)	N/A	Trial based economic evaluation	High	Medium	Medium
Howard et al (2006)	N/A	Modelling	High	Medium	High
Palmer et al (2008)	N/A	Modelling	High	High	Medium
Siegel et al (1992)	N/A	Modelling	Medium	High	Medium
UKPDS (1998a)	N/A	Trial based economic evaluation	High	High	Medium

Socioeconomic implications

Author (year)	Evidence				
	Level of Evidence		Quality Rating	Magnitude of the effect Rating	Relevance Rating
	Level	*Study Type*			
Bello et al (2008)	IV	Cross-sectional	Medium	High	Medium
Cass et al (2003)	III-3	Retrospective cohort	Medium	High	High
Chan et al (2007)	I	Systematic review and meta analysis	High	High	Medium
Davis et al (2007)	II	Prospective cohort	Medium	High	Medium
Drey et al (2003)	III-3	Retrospective cohort	Low	High	Medium
Overland et al (2002)	IV	Cross-sectional	Medium	High	High
Tarver-Carr et al (2002)	II	Prospective cohort	Medium	High	Medium
Turrell et al (2004)	IV	Cross-sectional	Medium	High	High
Weng et al (2000)	III-3	Retrospective cohort	Medium	High	Medium
White et al (2008)	IV	Cross-sectional	High	Medium	High

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APPENDICES

Appendix 1: Search yield table

Guideline Search Strategy and Yield

Electronic databases searched:

- Medline
- EMBASE
- Cochrane Library
- CINAHL
- HTA
- DARE

Terms used to search the databases:

Detailed in search strategy and terms tables (Appendix 3). The tables include search terms used for Medline search and Cochrane. These search terms have been modified as appropriate for other databases.

Search inclusion criteria:

See general and specific inclusion and exclusion criteria (Appendix 3). Where possible searches were limited by the English language and human research. Literature searches were completed on the following dates:

- Question 1: March 28, 2008.
- Question 2:
    - Blood Glucose - April 3, 2008
    - Blood Pressure - March 18, 2008
    - Blood Lipids – March 27, 2008
    - Dietary Factors – March 28, 2008
    - Smoking Cessation – April 1, 2008.
- Question 3:
    - Cost effectiveness - August 1, 2008
    - Socioeconomic implications - January 5, 2009.

No additional formal searching of the electronic databases was performed after these dates. However, if important and relevant studies published after these dates were identified or brought to our attention before the completion of the guideline (March, 2009) they have been included.

Abbreviations and explanation of table headings

Identified = number of articles which matched the mesh terms listed or contained the text terms in each particular database
Relevant = those articles considered relevant to the questions being asked after viewing titles or abstracts

Articles identified by other strategies = including articles or reports suggested by the Expert Advisory Group or other experts or public submissions
Total for Review = those articles considered relevant to the question after viewing titles and abstracts, contained original data or were systematic reviews of original articles and met the inclusion/exclusion criteria
Total no. reviewed and graded = articles used to generate the evidence for the identified question . These articles have been summarised and graded

Total no. reviewed and graded = articles used to generate the evidence for the identified question . These articles have been summarised and graded

Questions		No. articles identified (all databases combined)	No. relevant articles	Articles identified by other strategies	Total for review	Total no. reviewed and graded	Level I	Level II	Level III	Level IV	Highest level of evidence
1	How should kidney function be assessed and how often?	1688	954	6	960	58		12	35	11	II
2	How should CKD be prevented and/or managed in people with type 2 diabetes										
	What is the role of blood glucose control?	907	187	4	185	21	4	17			I
	What is the role of blood pressure control?	1875	630	12	642	42	6	38			I
	What is the role of blood lipid modification?	416	112	3	115	15	4	11			I
	What is the role of diet modification?	1493	474	1	475	23	1	14	8		I
	What is the role of smoking cessation?	861	140	1	476	18		6	1	11	II
3.	Is the prevention and management of CKD in people with type 2 diabetes cost effective and what are the socioeconomic implications?	1424 (cost effectiveness) 24 (socioeconomic implications)	114 (cost effectiveness) 12 (socioeconomic implications)	4 (cost effectiveness) 18 (socioeconomic implications)	118 (cost effectiveness) 30 (socioeconomic implications)	8 (cost effectiveness) 10 (socioeconomic implications)	NA** 1	NA 2	NA 3	NA 4	I

* Reports/publications that did not appear in the search but were suggested by members of the Expert Advisory Group and as a result of public submissions.

** Level not assigned due to a number of the studies being models.

Appendix 2: Inclusion and exclusion criteria

Generic criteria used to determine the suitability of articles for review

Inclusion criteria

The following are the criteria of articles to be included in the literature review:

- Present original data or reviews of original data
- Focus on kidney disease in type 2 diabetes or include a cohort with type 2 diabetes and renal outcomes
- Address one or more of the specified research question
- Applicable to diabetes care or prevention in Australia
- Conducted in humans
- Conducted in appropriate population for the question being addressed
- Other specific inclusion criteria for each guideline

Exclusion criteria

- Studies of inappropriate patient population
- Articles and reviews which present the author's opinion rather than evidence
- Small review articles where the material is covered more adequately by more recent/or more comprehensive reviews
- In vitro and animal studies
- Genetic studies that are not clinically applicable

Specific criteria used to determine the suitability of articles for review (CKD guideline)

- Interventions that focus on the assessment, prevention and management of kidney disease in people with type 2 diabetes.
- Where two or more articles appear to report data from the same group of subjects, only the most complete article should be used to generate data for the analyses.
- The sample size should be 50 or more.
- Exclude studies of inappropriate populations (small studies in populations not relevant to the Australian population).
- Post hoc analyses unless they provide significant additional information not already covered in the original study report.
- For question 2 (prevention and management of CKD – role of dietary modification) studies of population size less than 50 have and short duration have been included due the small number of large trials.

Appendix 3: Search strategies and terms

General

The symbol / after a word indicates that it is a MeSH term and any article found by this method has been allocated to this subject heading used in the database; .mp indicates that that word was searched as a keyword in the database; *indicates that the search was more directly focused. Other abbreviations used were: ACR refers to: albumin-to creatinine.mp OR ACR mp; Antihypertensives refers to: Antihypertensive agents/ OR Antihypertensive.mp OR Blood pressure lowering.mp; Decline in GFR refers to: decline in GFR.mp OR decline in glomerular filtration rate.mp; GFR refers to: GFR.mp OR glomerular filtration rate.mp; GFR = glomerular filtration rate; AER = albumin excretion rate. The symbol C indicates results from Cochrane database search. A list of specific intervention agents for blood pressure, blood glucose and blood lipids, used in the Cochrane search are listed at the end of the search strategy table.

Question		Searches	Result
1.	How should kidney disease be assessed and how often?	**Total for Question**	
		(albuminuria/ OR proteinuria/) AND (gold standard OR sensitivity OR specificity)	60 (C)
		(albuminuria/ OR proteinuria/ OR kidney function tests/ OR glomerular filtration rate/ OR glomerular filtration rate.tw OR gfr.tw OR estimated glomerular filtration rate.tw OR proteinuria/ OR creatinine/) [1]	90407
		(albumin excretion rate.tw OR aer.tw OR acr.tw OR dipstick$.tw OR serum creatinine.tw OR ratio$.tw OR assess$.tw OR "Sensitivity and Specificity"/ OR snesitivity.tw OR "review"/) [2]	30000946
		a.mp AND ([1] AND [2]) AND Diabetes Mellitus, Type 2	1688 954 (after 1999)
		(kidney function tests/ OR glomerular filtration rate/ OR glomerular filtration rate.tw OR gfr.tw OR estimated glomerular filtration rate.tw OR proteinuria/ OR creatinine/) AND Diabetes Mellitus, Type 2/	1708
		(kidney function tests/ OR glomerular filtration rate/ OR glomerular filtration rate.tw OR gfr.tw OR estimated glomerular filtration rate.tw OR proteinuria/ OR creatinine/) AND Diabetes Mellitus, Type 2/ - LIMIT to "reviews (sensitivity)"	936

Question		Searches	Result
		(kidney function tests/ OR glomerular filtration rate/ OR glomerular filtration rate.tw OR gfr.tw OR estimated glomerular filtration rate.tw OR proteinuria/ OR creatinine/) AND Diabetes Mellitus, Type 2/ - LIMIT to "etiology (sensitivity)"	741
		Diabetes Mellitus, Type 2/ AND (Proteinuria/ OR Albuminuria/)	2230
		Diabetes Mellitus, Type 2/ AND (Proteinuria/ OR Albuminuria/) - LIMIT to "review (sensitivity)"	1260
		Diabetes Mellitus, Type 2/ AND (Proteinuria/ OR Albuminuria/) - LIMIT to "etiology (sensitivity)"	1083
		[Diabetes Mellitus, Type 2/ AND (Proteinuria/ OR Albuminuria/) - LIMIT to "review (sensitivity)"] OR [Diabetes Mellitus, Type 2/ AND (Proteinuria/ OR Albuminuria/) - LIMIT to "etiology (sensitivity)"]	1663 915 (after 1999)
		Diabetes Mellitus, Type 2/ AND (Proteinuria/ OR Albuminuria/ OR Glomerular Filtration Rate)	470
		Diabetes Mellitus, Type 2/ AND (Proteinuria/ OR Albuminuria/ OR Glomerular Filtration Rate) – LIMIT to "reviews (sensitivity)	250
		Diabetes Mellitus, Type 2/ AND (Proteinuria/ OR Albuminuria/ OR Glomerular Filtration Rate/) – LIMIT to "etiology (sensitivity)	201
		Diabetes Mellitus, Type 2/ AND (Proteinuria/ OR Albuminuria/ OR Glomerular filtration rate/ OR Kidney function tests)	302 (C)
2.	How should kidney disease be prevented and/or managed?	**Total for Question**	
	Role of blood pressure	Diabetes Mellitus, Type 2 AND (Angiotensin-converting enzyme inhibitors/ OR aldosterone antagonisits/ OR angiotensin II Type 1 receptor blockers/ OR calcium channel blockers/ OR hydroxymethylglutaryl-coa reductase inhibitors/) [1]	1875
		[1] AND (meta analysis OR clinical trial.mp,pt.)	574

Question		Searches	Result
		Diabetes Mellitus, Type 2/ AND antihypertensive agents/ [2]	1817
		[2] AND (meta analysis OR clinical trial.mp.pt.)	501
		Diabetes Mellitus, Type 2/ AND Antihypertensive agents/ [3]	495 (C)
		[3] AND (antihypert* OR angiotensin* near inhibit OR angiotensin* near block OR aldoster* NEAR antag* OR calcium near channel blocker* OR Hyrdoxymethylglutaryl* near inhibit* OR [antihypertensive list][#]	129 (C)
	Role of blood glucose		
		Diabetes Mellitus, Type 2/ AND ((hypoglycaemic agents/ OR HbA1* OR glycaem* OR glycem*) AND (Albuminuria/ OR Proteinuria/))	457
		Diabetes Mellitus, Type 2/ AND (Hypoglycaemic agents/ OR HBA1* OR glycaem* OR glycem* OR gluc* near control* OR hypogly* next agent* OR [hypoglycaemic agent list]## [1]	204 (C)
		[1] AND (Proteinuria/ OR Albuminuria/ proteinu* OR albuminu*)	6 (C)
	Role of blood lipids		
		Diabetes Mellitus, Type 2/ AND (Anticholesteremic Agents/ OR Antilipemic Agents/ OR lipid.tw OR LDL.tw.) AND (albumin$.tw OR Albumnuria/ OR Proteinuria/) [2]	416
		limit [2] to clinical trial, all.	100
		Diabetes Mellitus, Type 2/ AND (Type NEXT 2 AND diabetes) AND (Anticholesteremic Agents/ OR Antilipemic Agents/ OR antichol* OR antilip* OR lipid.tw OR LDL.tw. OR albuminuria.tw OR proteinuria.tw OR Albumnuria/ OR Proteinuria/ OR [agent list]###)	12 (C)
	Role of Dietary Modification		
	Salt Restriction	Diabetes Mellitus, Type 2/ AND (Sodium dietary/ OR dietary salt OR dietary sodium OR ((salt* OR sodium*) AND (restict* OR intake* OR change*))) [1]	319
		limit [1] to clinical trial, all	85

Question		Searches	Result
		(Diabetes Mellitus, Type 2/ or type near 2) AND (Sodium dietary/ OR dietary salt OR dietary sodium OR ((salt* OR sodium*) AND (restict* OR intake* OR change*)))	3 (C)
	Role of dietary protein	Diabetes Mellitus, Type 2/ AND (Dietary Proteins/ OR protein* diet* OR protein OR diet) [1]	600
		limit [1] to clinical trial, all	130
		Diabetes Mellitus, Type 2/ AND (Dietary Proteins/ OR protein* diet* OR protein OR diet)	9 (C)
	Dietary fat	Diabetes Mellitus, Type 2 AND (Diet, fat-restricted/ OR saturat* OR monounsatur* OR polyunsat*) [1]	575
		limit [1] to clinical trial, all	174
		[2] AND (Albuminuria/ OR Proteinuria)	3
		(Diabetes Mellitus, Type 2/ OR Type NEXT 2 diabetes) AND ((Diet, fat-restricted/ OR saturat* OR monounsatur* OR polyunsat*)	29 (C)
	Smoking Cessation		
		Diabetes Mellitus, Type 2/ AND (Smoking/ OR Smoking Cessation/)	861
		Diabetes Mellitus, Type 2/ AND (Smoking/ OR Smoking Cessation/) AND (Proteinuria/ OR Albuminuria)	112
		Diabetes Mellitus, Type 2/ AND (Smoking/ OR Smoking Cessation/ OR smoking OR smok* near/3 cess*)	28 (C)
3.	Is the prevention and management of chronic kidney disease in people with type 2 diabetes cost effective and what are the socioeconomic implications?		
	Cost Effectiveness		
		Diabetes Mellitus, Type 2/ AND (Economics/ OR cost.tw OR cost effect*.tw) [1]	1424
		(Kidney Diseases/ OR Proteinuria/ OR Albuminuria) [2]	355 594
		[1] AND [2] [3]	134
		Limit [3] to English	114
	Socioeconomic Implications		

Question		Searches	Result
		Diabetes Mellitus, Type 2/ AND (Kidney Diseases/ OR Proteinuria/ OR Albuminuria) [1]	5247
		(Socioeconomic factors/ OR Socioeconomic factors.tw OR social disadvantage.tw) [2]	257 941
		[1] AND [2]	24
		Limit [3] to English	24

Notes

[#] Acebutolol or Adrenomedullin or Alprenolol or Amlodipine or Atenolol or Bendroflumethiazide or Bepridil or Betaxolol or Bethanidine or Bisoprolol or Bretyliu* or Bupranolol or Captopril or arteolol or Celiprolol or Chlorisondamine or Chlorothiazide or Chlorthalidone or Cilazapril or Clonidine or Cromakalim or Cyclopenthiazide or Debrisoquin or Diazoxide or Dihydralazine or Dihydroalprenolol or Diltiazem or Doxazosin or Enalapril or Enalaprilat or Epoprostenol or Felodipine or Fenoldopam or Fosinopril or Guanabenz or Guanethidine or Guanfacine or Hexamethonium or Hexamethoniu* or Hydralazine or Hydrochlorothiazide or Hydroflumethiazide or Indapamide or Indoramin or Isradipine or Kallidin or Ketanserin or Labetalol or Lisinopril or Losartan or Mecamylamine or Methyldopa or Metipranolol or Metolazone or Metoprolol or Mibefradil or Minoxidil or Muzolimine or Nadolol or Nicardipine or Nicorandil or Nimodipine or Nisoldipine or Nitrendipine or Nitroprusside or Oxprenolol or Pargyline or Pempidine or Penbutolol or Pentoliniu* or Perindopril or Phenoxybenzamine or Phentolamine or Pinacidil or Pindolol or Piperoxan or Polythiazide or Prazosin or Propranolol or Protoveratrines or Ramipril or Reserpine or Saralasin or Teprotide or Ticrynafen or Timolol or Todralazine or Tolazoline or Trichlormethiazide or Trimethaphan or Veratru* or Vincamine or Xipamide

Acarbose or acetohexamide or buformin or carbutamide or chlorpropamide or glipizide or gliclazide or glyburide or insulin or insulin next isophane or insulin next long-acting or metformin or phenformin or tolazamide or tolbutamide

Azacosterol or Chitosan or Cholestyramine or Clofibrate or Clofibric next Acid or Dextrothyroxine or Doxazosin or Hydroxymethylglutaryl* next Reductase next Inhibitors or Lovastatin or Meglutol or Pravastatin or Probucol or Simvastatin or trans* next *chlorobenzaminomethyl* next cyclohexane or Bezafibrate or Butoxamine or Clofenapate or Clofibrate or Clofibric or Colestipol or Gemfibrozil or Halofenate or Meglutol or Nafenopin or Niacin or Niceritrol or Procetofen or Pyridinolcarbamate or Simvastatin or Triparanol

Appendix 4: NHMRC Evidence Statement Grading Forms

Key question(s): How should kidney function be assessed and how often in people with type 2 diabetes?		Evidence table ref:
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
(A) Cohort studies (prognosis level II) demonstrate that microalbuminuria predicts overt nephropathy and accelerated decline in GFR. **(B)** Cross sectional studies (diagnosis level III) provide data on the accuracy of AER and ACR. **(C)** Cohort and cross sectional studies (diagnosis Level III) provide data on estimation of GFR. Note: the prognostic studies that are evidence for (A) use the tests described in (B) and (C). It is therefore impossible to separate the prognostic implications and the tests completely and therefore these issues have been graded as one recommendation.	~~A~~	Several Level I or II studies with low risk of bias
	B	One or two Level II studies with low risk of bias or SR/multiple Level III studies with low risk of bias
	~~C~~	Level III studies with low risk of bias or Level I or II studies with moderate risk of bias
	~~D~~	Level IV studies or Level I to III studies with high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Lower level of consistency for eGFR studies.	~~A~~	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	~~C~~	Some inconsistency, reflecting genuine uncertainty around question
	~~D~~	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Persistent microalbuminuria confers an approximately 5 fold increase in risk of overt nephropathy over 10 years. In addition microalbuminuria is a risk factor for CVD and ESKD.	A	Very large
	~~B~~	Moderate
	~~C~~	Slight
	~~D~~	Restricted
4. Generalisability		
	A	Evidence directly generalisable to target population
	~~B~~	Evidence directly generalisable to target population with some caveats
	~~C~~	Evidence not directly generalisable to the target population but could be sensibly applied
	~~D~~	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability		
	A	Evidence directly applicable to Australian healthcare context
	~~B~~	Evidence applicable to Australian healthcare context with few caveats
	~~C~~	Evidence probably applicable to Australian healthcare context with some caveats
	~~D~~	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base	B	
2. Consistency	B	
3. Clinical impact	A	
4. Generalisability	A	
5. Applicability	A	

Indicate any dissenting opinions

RECOMMENDATION

What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.

GRADE OF RECOMMENDATION

B

Kidney status in people with type 2 diabetes should be assessed by: annual screening for albuminuria; AND annual estimation of glomerular filtration rate (eGFR) and continue annual screening for all albuminuria and eGFR in the event of negative screening test.

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	~~YES~~
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	~~NO~~
Will the implementation of this recommendation require changes in the way care is currently organised?	~~YES~~
	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation?	~~YES~~
	NO

NHMRC Evidence Statement Grading Form

Key question(s): How should chronic kidney disease be prevented and/or managed in people with type 2 diabetes? **Role of blood glucose control.**		Evidence table ref:
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Several Level 1 and Level II intervention studies demonstrate that glycaemic control reduces the development and progression of CKD in people with type 2 diabetes.	A	Several Level I or II studies with low risk of bias
	~~B~~	One or two Level II studies with low risk of bias or SR/multiple Level III studies with low risk of bias
	~~C~~	Level III studies with low risk of bias or Level I or II studies with moderate risk of bias
	~~D~~	Level IV studies or Level I to III studies with high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Glycaemic control consistently shown to affect the progression of albuminuria in people with type 2 diabetes, however the evidence of the effect of glycaemic control on ESKD and rate of decline in GFR is either inconsistent or limited.	~~A~~	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	~~C~~	Some inconsistency, reflecting genuine uncertainty around question
	~~D~~	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Risk reductions in the order of 30% for progression to microalbuminuria with intensive glycaemic control are indicated by trials.	A	Very large
	~~B~~	Moderate
	~~C~~	Slight
	~~D~~	Restricted
4. Generalisability		
	A	Evidence directly generalisable to target population
	~~B~~	Evidence directly generalisable to target population with some caveats
	~~C~~	Evidence not directly generalisable to the target population but could be sensibly applied
	~~D~~	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability		
	A	Evidence directly applicable to Australian healthcare context
	~~B~~	Evidence applicable to Australian healthcare context with few caveats
	~~C~~	Evidence probably applicable to Australian healthcare context with some caveats
	~~D~~	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
6. Evidence base	A	
7. Consistency	B	
8. Clinical impact	A	
9. Generalisability	A	
10. Applicability	A	

Indicate any dissenting opinions

RECOMMENDATION	GRADE OF RECOMMENDATION	
What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.	A	

Blood glucose control should be optimised aiming for a generalised HbA1c target ≤ 7%.

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	~~YES~~
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	~~NO~~
Will the implementation of this recommendation require changes in the way care is currently organised?	~~YES~~
	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation?	~~YES~~
	NO

NHMRC Evidence Statement Grading Form

Key question(s): How should chronic kidney disease be prevented and/or managed in people with type 2 diabetes? Role of blood pressure control.		Evidence table ref:
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Several Level I and II (aetiology and intervention) studies evaluating the progression of CKD in people with type 2 diabetes in association with blood pressure control and use of antihypertensive agents in hypertensive and normotensive people.	A	Several Level I or II studies with low risk of bias
	~~B~~	One or two Level II studies with low risk of bias or SR/multiple Level III studies with low risk of bias
	~~C~~	Level III studies with low risk of bias or Level I or II studies with moderate risk of bias
	~~D~~	Level IV studies or Level I to III studies with high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
High level of consistency with respect to association between blood pressure and progression of albuminuria. Less consistency for some specific renal endpoints and interventions due to smaller number of trials.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	~~C~~	Some inconsistency, reflecting genuine uncertainty around question
	~~D~~	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The trials indicate risk reduction in development of microalbuminuria in T2DM patients of approximately 30%. The trials indicate risk of progression from microalbuminuria to macroalbuminuria to be reduced and regression from microalbuminuria to normoalbuminuria to be increased in T2DM patients by approximately 40 to 50%.	A	Very large
	~~B~~	Moderate
	~~C~~	Slight
	~~D~~	Restricted
4. Generalisability		
Studies either exclusively type 2 diabetes or mixed type 1 and type 2 diabetes.	A	Evidence directly generalisable to target population
	~~B~~	Evidence directly generalisable to target population with some caveats
	~~C~~	Evidence not directly generalisable to the target population but could be sensibly applied
	~~D~~	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability		
	A	Evidence directly applicable to Australian healthcare context
	~~B~~	Evidence applicable to Australian healthcare context with few caveats
	~~C~~	Evidence probably applicable to Australian healthcare context with some caveats
	~~D~~	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Hypertension is a key risk factor for macrovascular complications, including stroke, myocardial infarction and heart failure in T2DM patients, which indicates a need to treat hypertension irrespective of the risk or presence of albuminuria.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
11. Evidence base	A	
12. Consistency	B	Lower consistency for some renal endpoints and interventions.
13. Clinical impact	A	
14. Generalisability	A	
15. Applicability	A	

Indicate any dissenting opinions

RECOMMENDATION	GRADE OF RECOMMENDATION	
What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.	A	

In people with type 2 diabetes and microalbuminuria or macroalbuminuria, ARB or ACEi antihypertensives should be used to protect against progression of kidney disease.

The blood pressure 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.

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	~~YES~~
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	~~NO~~
Will the implementation of this recommendation require changes in the way care is currently organised?	~~YES~~
	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation?	~~YES~~
	NO

NHMRC Evidence Statement Grading Form

Key question(s): How should chronic kidney disease be prevented and/or managed in people with type 2 diabetes? Role of smoking cessation.		Evidence table ref:
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
Several prospective cohort studies (aetiology level II) and retrospective cohort studies (aetiology level III) indicate smoking as an independent risk factor in the progression of CKD.	A	Several Level I or II studies with low risk of bias
	~~B~~	One or two Level II studies with low risk of bias or SR/multiple Level III studies with low risk of bias
	~~C~~	Level III studies with low risk of bias or Level I or II studies with moderate risk of bias
	~~D~~	Level IV studies or Level I to III studies with high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Smoking is consistently identified as an independent risk factor for CKD.	A	All studies consistent
	~~B~~	Most studies consistent and inconsistency can be explained
	~~C~~	Some inconsistency, reflecting genuine uncertainty around question
	~~D~~	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Smoking has been identified as an independent risk factor for CKD in people with type 2 diabetes, however the magnitude of risk has not been defined.	~~A~~	Very large
	B	Moderate
	~~C~~	Slight
	~~D~~	Restricted
4. Generalisability		
	A	Evidence directly generalisable to target population
	~~B~~	Evidence directly generalisable to target population with some caveats
	~~C~~	Evidence not directly generalisable to the target population but could be sensibly applied
	~~D~~	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability		
	A	Evidence directly applicable to Australian healthcare context
	~~B~~	Evidence applicable to Australian healthcare context with few caveats
	~~C~~	Evidence probably applicable to Australian healthcare context with some caveats
	~~D~~	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Whilst the magnitude of the effect of smoking on CKD has not been defined, smoking influences a range of health endpoints relevant to the management of type 2 diabetes and other chronic disease.

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
16. Evidence base	B	
17. Consistency	A	
18. Clinical impact	A-B	Magnitude of effect of smoking on progression of CKD in type 2 diabetes patients has not been defined, however smoking has been identified as an independent risk factor.
19. Generalisability	A	
20. Applicability	A	

Indicate any dissenting opinions

RECOMMENDATION	GRADE OF RECOMMENDATION	
What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.	B	

People with type 2 diabetes should be informed that smoking increases the risk of chronic kidney disease.

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	~~YES~~
	NO
Are there any resource implications associated with implementing this recommendation?	~~YES~~
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
	~~NO~~
Are the guideline development group aware of any barriers to the implementation of this recommendation?	~~YES~~
	NO

Appendix 5: Overview of Guideline Development Process and Methods

National Evidence Based Guidelines for the Prevention and Management of Type 2 Diabetes

Overview of Guideline Development Process and Methods

Prepared by
The Diabetes Unit
Menzies Centre for Health Policy
The University of Sydney

for the
Diabetes Australia Guideline Development Consortium

Last updated 5 May 2009

Table of Contents

List of Tables:

Purpose and Structure of the Document

Purpose

This 2008-9 series of guidelines for type 2 diabetes updates and builds on the original suite of evidence based diabetes guidelines which were initiated in 1999 under funding from the Department of Health and Ageing (DoHA) to the Diabetes Australia (DA) Guideline Development Consortium. Under the initial diabetes guideline project, six evidence based guidelines for type 2 diabetes were endorsed by the NHMRC. The purpose of the initial guidelines and the current guidelines is to provide systematically derived, objective guidance to:

1. Improve quality and consistency of care and reduce inappropriate variations in practice by assisting clinicians' and consumers' understanding of and decisions about treatment and management options
2. Inform fund holders and health service planners about the effectiveness and feasibility of the various options
3. Assist researchers and research authorities to highlight i) areas of diabetes prevention and care for which there is inconclusive evidence and ii) areas of deficiency in the evidence which require further or definitive research.

The specific purpose of this current project which commenced in early 2008 was to update two of the previous guidelines - Primary Prevention, and Case Detection and Diagnosis – and to develop three new guidelines, one for Blood Glucose Control, one for Chronic Kidney Disease and one for Patient Education.

Structure

This *Overview of the Guideline Development Process and Methods* outlines the rationale for the guidelines and the organisational structure, methods and processes adopted for the Type 2 Diabetes Guideline project, including the Blood Glucose Control Guideline. The guidelines are structured to present the recommendations, practice points, evidence statements, documentation of search strategies and search yield and a textual account of the evidence underpinning each recommendation.

Final format and implementation

The contract between the DoHA and the DA Guideline Development Consortium makes provision for locating and synthesising the available evidence on the five index areas into guideline recommendations and describing the objective justification for the recommendations. Thus, the contract covers the development of the guidelines up to and including endorsement by the NHMRC but does not include implementation of the guidelines.

However, following endorsement by the NHMRC there will need to be an independent process of consultation with potential guideline users to determine the final format of the guidelines for wide dissemination to clinicians and consumers. Once this format has been agreed, an implementation strategy to encourage and facilitate the widespread uptake of the guidelines in everyday practice will need to be developed and actioned at national and state

and territory level. It is our understanding that the DoHA has developed an implementation plan and strategies and is currently obtaining internal sign-off on these before enacting them.

1.0 Introduction and Overview

1.1 Diabetes as a health burden

Results of the national diabetes prevalence survey, AusDiab (Dunstan et al, 2002), which was conducted on representative sample of some 11,000 people across Australia, found a prevalence of diabetes of 7.4% in people aged 25 years or older. Another 16.4% of the study population had either impaired glucose tolerance or impaired fasting glucose. AusDiab also confirmed that there is one person with undiagnosed diabetes for every person with diagnosed diabetes. Findings from the second phase of AusDiab, a 5-year follow-up survey of people who participated in the baseline study, have indicated that every year eight out of every 1,000 people in Australia developed diabetes (Barry et al, 2006). This, together with the increasing number of new cases of pre-diabetes, obesity, the metabolic syndrome, and kidney disease, has demonstrated that abnormal glucose metabolism is exerting a major impact on the health of Australians (Magliano et al, 2008).

Diabetes has a demonstrably high health and cost burden (Colagiuri et al, 2003; AIHW, 2008) resulting from its long term complications which include:

- heart disease and stroke
- foot ulceration, gangrene and lower limb amputation
- kidney failure
- visual impairment up to and including blindness
- erectile dysfunction

The health burden of diabetes is described in more detail throughout the guideline series but to put these complications in perspective, it is worth noting here that, in Australia, diabetes is the most common cause of:

- blindness in people under the age of 60 years
- end stage kidney disease
- non-traumatic amputation

Diabetes is heavily implicated in deaths from cardiovascular disease (CVD) but, due to death certificate documentation deficiencies; this link is believed to be substantially under reported. At a global level, diabetes is predicted to increase dramatically in the next decade or two (IDF, 2006). With an ageing and increasingly overweight and physically inactive population, and a cultural mix comprising numerous groups known to be at high risk of type 2 diabetes, Australia is a prime candidate for realising the projected increases.

Due to sheer numbers, the major proportion of the total diabetes burden is attributable to type 2 diabetes which is the most common form of diabetes and accounts for approximately 85% of all diabetes in Australia. Type 2 diabetes occurs predominantly in mature adults with the prevalence increasing in older age groups. However, in high risk populations such as Aboriginal and Torres Strait Islander people it may become manifest much earlier.

These guidelines focus exclusively on type 2 diabetes in non-pregnant adults. Like type 1 diabetes, type 2 diabetes is characterised by high blood glucose levels. However, unlike type 1 diabetes, the key feature of type 2 diabetes is insulin resistance rather than insulin deficiency. Consequently, its treatment does not necessarily require insulin and in many people, particularly in the initial years following diagnosis, type 2 diabetes can be successfully

managed with dietary and general lifestyle modification alone or in combination with oral anti-diabetic medications. Insulin therapy may be required if and when oral medication becomes ineffective in lowering and maintaining the blood glucose within an acceptable range. Assiduous attention to the management of elevated blood pressure, lipid problems and overweight is also required as these common features of type 2 diabetes markedly increase the risk of long term complications.

1.2 Key components and principles of diabetes care

Key components of care
In 1995, the NSW Health Department identified three key components of diabetes care, stating that …. 'there is consensus supported by published literature that diabetes care and outcomes can be improved by providing access for all people with diabetes to:

- information about their condition and self care education
- ongoing clinical care to provide optimal metabolic control
- screening for and appropriate treatment of complications' (Colagiuri R et al, 1995).

These and the principles of care below were included in the initial suite of guidelines for type 2 diabetes and remain as valid now as they were then.

Principles of care
The particular expression of the universally accepted diabetes care principles set out below was abbreviated from those developed by the UK Clinical Advisory Group (CSAG, 1994) and later summarised by the NSW Health Expert Panel on Diabetes (New South Wales (NSW) Department of Health, 1996) and was further adapted for this project:

- People with diabetes should have access to timely and ongoing care from a diabetes team. This should ideally include a doctor, nurse and dietitian with specific training and experience in the management of diabetes. Additional expertise, for example in podiatry, social work, behavioural psychology and counselling, should be available as required as should referral access to specialist services for the management of identified complications

- People with diabetes are entitled to access to opportunities for information, education and skills acquisition to enable them to participate optimally in their diabetes management

- People with diabetes are entitled to access high quality health services regardless of their financial status, cultural background, or place of residence

- For people with diabetes from community groups who may have special needs eg people from Aboriginal, Torres Strait Islander or culturally and linguistically diverse backgrounds and the elderly, diabetes care should be specifically tailored to overcoming access barriers and providing opportunities for optimising diabetes care and outcomes

- Diabetes teams should routinely evaluate the effectiveness of the care they provide

1.3 Rationale for the Guidelines

The magnitude of the impact of diabetes on individuals and society in Australia is manifest in its status as a National Health Priority Area since 1996 and the current attention directed to it by the Council of Australian Governments' National Reform Agenda which seeks to address and avert a greater impact on productivity than already exists as a result of diabetes.

For tangible and lasting benefits, evidence based information is required which synthesises new and existing evidence to guide primary prevention efforts and assist clinicians to identify and treat modifiable primary risk factors, accurately diagnose type 2 diabetes, assess metabolic control, provide effective routine care, and make appropriate and timely referrals.

Since the initial suite of NHMRC diabetes guidelines was released there has been a vast improvement in both the volume and quality of the evidence about preventing type 2 diabetes which is detailed in the Primary Prevention Guideline. Nonetheless, there remain grave concerns that the rapidly increasing prevalence of obesity combined with decreasing levels of physical activity will continue to impact negatively on the incidence and prevalence of diabetes unless addressed as a mater of urgency. Consequently, the Primary Prevention Guideline also cites some of the emerging evidence about environmental influences on food consumption and physical activity.

Type 2 diabetes represents a complex interaction of patho-physiological factors and its prevention and successful management requires clinicians and public health practitioners to maintain a thorough understanding of these interactions especially since there is now irrefutable evidence that both the onset of diabetes and the onset of its complications can be prevented or significantly delayed. Given the typically long pre-clinical phase of type 2 diabetes and that half of all people with diabetes are undiagnosed, the Case Detection and Diagnosis Guideline is an important component of this suite of guidelines.

Integral to the successful management of diabetes is self care knowledge and skills, and the capacity of the person with diabetes to adapt their lifestyle to optimise their physical and psychological well being. The Patient Education Guideline presents evidence addressing these issues.

The care of type 2 diabetes is predominantly carried out by general practitioners, often under 'shared care' arrangements with local Diabetes Centres and/or private endocrinologists. In remote Australia, and even in more densely settled rural regions, the population base is insufficient to support specialist diabetes teams and the general practitioner may not have local access to specialist referral and support. Regardless of geographical factors, standards of diabetes clinical care in Australia are known to be variable. The Chronic Kidney Disease Guideline sets out diagnostic criteria and therapies for achieving the treatment targets to guide the identification, prevention and management of kidney disease in people with diabetes.

Microvascular complications (retinopathy, nephropathy and neuropathy) and the increased risk of macrovascular complications (ischemic heart disease, stroke and peripheral vascular disease) are associated with reduced life expectancy and significant morbidity in type 2 diabetes. Using therapeutic interventions to lower blood glucose and achieve optimal HbA1c levels is critical in preventing diabetes complications and improving the quality of life. The Blood Glucose Control Guideline examines the evidence and the relationships among these issues.

1.4 Funding source

The Type 2 Diabetes Guidelines project is funded by the DoHA under a head contract with DA as convenor of the Guideline Development Consortium. The development of the guidelines is managed in partnership with DA by The Diabetes Unit at the University Sydney under the direction of A/Professor Ruth Colagiuri.

1.5 The Guideline Development Consortium

The Guideline Development Consortium led by DA comprises organisations representing consumers, specialist diabetes practitioners and primary care physicians and includes:

- The Australian Diabetes Society (ADS)
- The Australian Diabetes Educators Association (ADEA)
- The Royal Australian College of General Practitioners (RACGP)
- The Diabetes Unit – Menzies Centre for Health Policy (formerly, the Australian Health Policy Institute), the University of Sydney.

Additionally there are a number of collaborators:

- The NSW Centre for Evidence Based Health Care (University of Western Sydney)
- The Cochrane Renal Review Group (Westmead Children's Hospital)
- The Cochrane Consumer Network
- The Caring for Australians with Renal Impairment Guidelines Group (CARI),
- Kidney Health Australia.

1.6 The scope of the Guidelines

The brief for the Guideline Development Project was to prepare a set of evidence based guidelines for type 2 diabetes to NHMRC standard.

The Type 2 Diabetes Guidelines target public heath practitioners, clinicians (medical, nursing and allied health), diabetes educators and consumers and were designed to be appropriate for use in a wide variety of practice settings. The guidelines focus on care processes and interventions that are primarily undertaken in the non-acute setting ie they do not deal with highly technical procedural interventions such as renal dialysis.

1.7 Use of the Guidelines

Guidelines are systematically generated statements which are designed to assist health care clinicians and consumers to make informed decisions about appropriate treatment in specific circumstances (Field MJ & Lohr, 1990).

Guidelines are not applicable to all people in all circumstances at all times. The recommendations contained in these guidelines are a general guide to appropriate practice and are based on the best information available at the time of their development. The clinical guidelines should be interpreted and applied on an individual basis in the light of the health care practitioner's clinical experience, common sense, and the personal judgments of consumers about what is appropriate for, and acceptable to them.

1.8 Review date

New information on type 2 diabetes is continually and rapidly becoming available. The Project Management Team and Steering Committee recommend that these guidelines are reviewed and revised at least every three years after publication. We anticipate this will be June 2012.

1.9 Economic analysis

Assessment of economic impact i.e., analysing the cost implications of recommendations has become a mandatory component of guideline development.

1.10 Socio-economic impact

The Expert Advisory Groups for each guideline were encouraged to adopt a framework that is recommended by the NHMRC to identify, appraise and collate evidence of the impact of socioeconomic position and other markers of interest eg income, education, occupation, employment, ethnicity, housing, area of residence, lifestyle, gender.

2.0 Organisational structure and staffing

The organisational structure of the Guideline Development Project (Figure 1) comprises:

- A Steering Committee
- Project Management Team
- Expert Advisory Groups
- Guidelines Assessment Register Consultant
- Research Officers
- Research team

The Steering Committee consists of a representation from each of the Consortium members, the Guideline Project Medical Advisor, and the DoHA. Refer to Appendix i for Terms of Reference. The Project Steering Committee provides guidance and directions to the project and to the DoHA via DA. The main role was to oversee the project progress and timeline.

Expert Advisory Groups (EAGs) were established for each of the five guideline areas. They have a core composition of a consumer, a general practitioner, content experts nominated by the Australian Diabetes Society and the Australian Diabetes Educators Association, and other representation as appropriate. Consumers on the expert advisory groups were provided by Diabetes Australia as being representative of people with type 2 diabetes who are experienced in acting as consumer representatives and who had a detailed understanding of issues affecting people with diabetes. Terms of Reference of the EAGs is provided in Appendix ii. Lists of the individual members of each of the EAGs are provided in each guideline.

The Project Management Team. The Diabetes Unit, at Menzies Centre for Health Policy (formerly, the Australian Health Policy Institute), University of Sydney was subcontracted by DA to manage the project on behalf of the Consortium. The Diabetes Unit provides guidance on methods, technical support, data management, co-ordinates the input of the EAGs and supervises the project staff on a daily basis. The Project Management Team consists of the Director of the Diabetes Unit, the CEO of Diabetes Australia and the project's Medical Advisor.

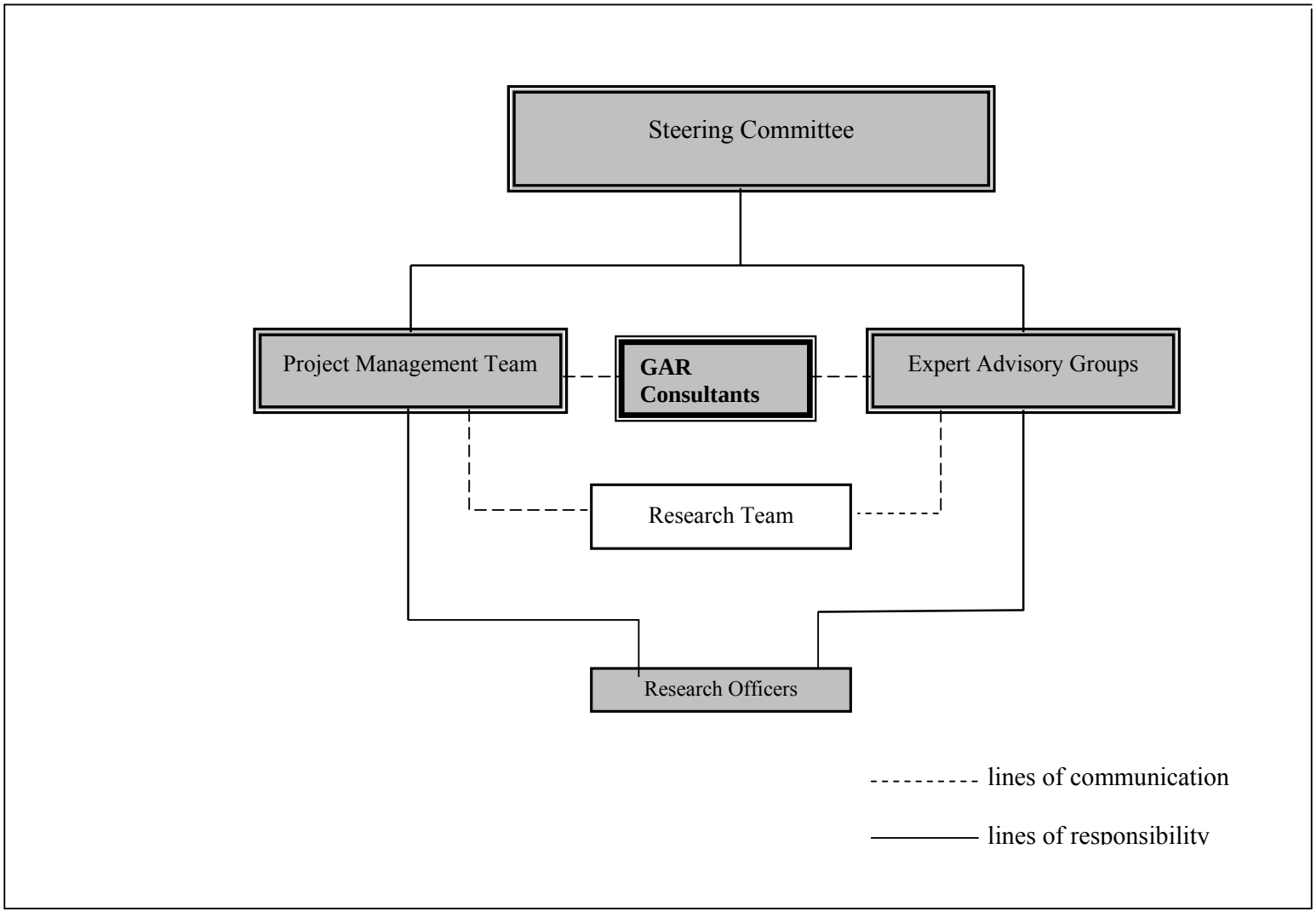
Guidelines Assessment Register (GAR) consultans. The NHMRC nominated a GAR consultant for each guideline (except the Blood Glucose Control guideline) to provide guideline developers with support in relation to utilising evidence-based findings and applying the NHMRC criteria. Specifically, the GAR consultants provided advice on evaluating and documenting the scientific evidence and developing evidence-based recommendations based on the scientific literature and NHMRC procedures.

Research Officers were recruited or seconded from a variety of research and health care disciplines and given additional training to conduct the literature searches, and review, grade and synthesise the evidence under the supervision of the Senior Research and Project Manager, Dr Seham Girgis, the Chairs of the EAGs and the Project Management Team.

Research Team refers to the Project Director, Senior Project Manager, Research Officers, and the project's Medical Advisor.

.

Figure 1: Organisational Structure



3.0 Methods

3.1 Development of Protocols

At the beginning of the project, a Methods Manual was developed for the EAGs and project staff. The Manual was based on the NHMRC *Standards and procedures for externally developed guidelines* (NHMRC, 2007) and the series of handbooks on the development, implementation and evaluation of clinical practice guidelines published by the NHMRC from 2000–03. The NHMRC Standards and procedures document (NHMRC, 2007) introduced an extended set of levels of evidence and an approach to assessing a body of evidence and grading of recommendations. These standards and handbooks have superseded *A guide to the development, implementation and evaluation of clinical practice guidelines* (NHMRC, 1999), which formed the basis of the initial suite of NHMRC guidelines for type 2 diabetes.

The NHMRC has introduced a requirement for guidelines to consider issues related to cost-effectiveness and socioeconomic impact. Two publications in the NHMRC toolkit for developing clinical practice guidelines have been used to address these issues - how to compare the costs and benefits: evaluation of the economic evidence (NHMRC, 2001) and using socioeconomic evidence in clinical practice guidelines (NHMRC, 2003).

The Methods Manual developed for the project contains definitions, procedures and protocols, descriptions of study type classifications, checklists and examples of steps and methods for critical appraisal of the literature. It also includes the revised level of evidence and the minimum requirements for formulating NHMRC evidence based guidelines.

3.2 Guideline Development Process

From the literature and expert opinion the following steps were identified as central to the process of identifying sources of rigorously objective, peer reviewed information and reviewing, grading, and synthesising the literature to generate guideline recommendations:

1. Define specific issues and generate clinically relevant questions to guide the literature searches for each guideline topic.
2. Search the literature systematically using a range of databases and search strategies.
3. Sort the search yield on the basis of relevance to the topic area and scientific rigour.
4. Document the search strategy and the search yield.
5. Critically review, grade and summarise the evidence.
6. Assess the body of evidence according to the published NHMRC standard and formulate guideline statements and recommendation/s in accordance with the evidence.
7. Formulate the evidence statements and recommendations.
8. Conduct quality assurance throughout all these steps.

Step 1: Defining issues and questions to direct the literature searches

Each EAG was asked to define key issues for the guideline and to generate a set of questions focusing on clinically relevant issues to guide the literature searches. These critical clinical issues also formed the focus of the guideline recommendations and accompanying evidence statements. A generic framework was developed and centred on issues such as:

- What are the key treatment/management issues for this area?
- What anthropometric, clinical or behavioural parameters need to be assessed?
- Should everyone be assessed or are there particular risk factors which warrant selective testing or preventative treatment?
- What assessment techniques should be used?
- How often should the assessment be done?
- How should the results be interpreted?
- What action should follow from the results (if abnormal) e.g., management, further investigation, referral?
- What are the overall costs of using the intervention? (particularly in relation to changes in costs if changes to management are recommended)
- What is the impact of socioeconomic position and other markers of interest e.g., income, education, occupation, employment, ethnicity, housing, area of residence, lifestyle, gender.

EAGs were also advised to frame each question using the **'PICO'** elements as follows: **P**opulation **or P**roblem; **I**ntervention (for a treatment intervention question), **or I**ndicator or exposure (for a prognosis or aetiology or question), **or I**ndex test (for a diagnostic accuracy question); **C**omparator; and **O**utcome.

The resulting questions developed by each EAG are presented at the beginning of each guideline and again in the Search Strategy and Yield Table.

Step 2: Searching the literature

NHMRC clinical practice guidelines are required to be based on systematic identification and synthesis of the best available scientific evidence (NHMRC, 2007). A number of systematic strategies were used in this project to identify and assess scientific information from the published literature. 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 Reviewers Handbook (Higgins JPT et al). Several strategies were used to identify potentially relevant studies and reviews from the literature such as:

Electronic Databases
Searches were carried out using the following databases:

- Medline
- Cochrane Library: Databases of Systematic Reviews, DARE, Controlled Trials Register, Central, HTA.
- Additional databases searched where indicated included:
  Embase
  Cinahl
  Psycho Info
  Eric
  Other (where appropriate) such as Internet, Expert sources, Hand searching of reference lists at the end of relevant articles.

Key words
The key words (MeSH terms and some free text terms) used when searching these electronic databases are presented in detail in the Search Strategy and Yield Table at the end of each guideline topic. The EAGs limited their searches through a number of methods including:
- specification of temporal constraints (e.g. 1999-2008 for the updated guideline)
- language constraints (English only)
- where there were overwhelming amounts of literature or if there was a large volume of poor quality research, some groups imposed limits by experimental design to exclude the less rigorous forms of research.

Details of specific inclusion criteria for the EAG are also presented, together with the key words, at the end of each individual guideline.

Consultation with colleagues
The EAGs were encouraged to gather relevant information/articles from other experts and colleagues. The Project Management Team collated the questions developed by each EAG to direct the literature searches and highlight overlapping questions and requested EAGs and Research Officers to send any articles identified as applicable to other guideline topics to the EAG.

Step 3: Sorting the search yield

Two or more members of each EAG were responsible for sorting through the search results by scanning the lists of titles and abstracts generated by the electronic database searches, highlighting potentially relevant articles and requesting printed full articles. Full articles were retrieved and those which were relevant were assessed for quality. Articles were considered relevant if they provided direct or indirect information addressing one or more of the specified 'clinical issues' questions and were applicable to diabetes care or prevention in Australia.

Sorting according to study design

Articles with original data were sorted according to study design. Articles with the most rigorous experimental designs were reviewed in the first instance. Articles conducted to other study designs were included if they added new information not found in the papers of highest levels of evidence. Relevant papers were sorted as follows:

- Meta-analysis, systematic review of randomised controlled trials (interventions)
- Randomised controlled trials (RCT)
- Cohort studies
- Case control studies
- Case series, pre-post or post studies

Exclusion criteria

Articles were not included for review if it was apparent that their relevance to formulating a guideline recommendation was non-existent or negligible. Examples of reasons for non review included criteria such as:

- Studies of inappropriate patient population(s) for the question being addressed (epidemiology, specific diet)
- Hypothesis/mechanism/in vitro study/animal studies
- Genetic studies that are clinically inapplicable
- Non-systematic reviews which presented the author's opinion rather than evidence

Step 4: Documenting the search strategy and its yield

The search strategy (terms and limits) and yield were documented and are available for viewing in a table at the end of each guideline. In brief, the Search Strategy and Yield Table recorded details about the:

1. Questions being investigated
2. Electronic databases searched
3. MeSH terms and key words used to search the database
4. Methods for limiting the searches
5. Number of articles identified by each search
6. Number of articles relevant from that search
7. Number of relevant articles identified through other search processes
8. Number of articles obtained for review
9. Number of relevant articles which were systematic reviews, RCTs or well designed population based studies, quasi-experimental and other (these were documented in the tables according to the updated NHMRC Evidence Levels I –IV).
10. Number of articles reviewed
11. Highest level of evidence found for each question

Step 5. Critically reviewing, grading and summarising the evidence

All relevant articles were reviewed and critically assessed using checklists recommended by the NHMRC (2000) (NHMRC, 2000a; NHMRC, 2000b).The NHMRC checklist sets out an explicit standardised approach to reviewing and incorporating scientific evidence into clinical practice guidelines.

In addition, Research Officers were asked to construct tables to summarise extraction of data and to provide a brief summary of the key results for each article.

Overall assessment of individual studies
At the conclusion of reviewing each article, the reviewers rated the evidence in a summary form as shown in (Table 1) using the following criteria:

- *Levels of evidence*
  The 'interim' NHMRC levels of evidence (NHMRC, 2007) was used in this project to assess levels of evidence for a range of study designs (Appendix iv).
- *Quality rating*
- *Magnitude of effect*
- *Relevance rating*

Criteria for quality of evidence, magnitude of effect, and relevance of evidence were based on those provided by the NHMRC (2000a &b). These criteria are presented in Appendix iv.

Table 1: Example of an Overall Assessment Report

Assessment Category	**Rating**			
	Value	Low	Medium	High
Level of evidence				
Quality rating				
Magnitude of effect				
Relevance rating				

These assessments were then used in the evidence tables which summarises basic information about **Each Study** reviewed, including an overall assessment of the evidence (Table 2).

Table 2: Example of an evidence table with overall study assessment

Author, Year	**Evidence**				
	Level of Evidence		***Quality Rating***	***Magnitude of Effect Rating***	***Relevance Rating***
	Level	***Study Type***			
Author X (1999)	III-2	Cohort	High	Low	High

Step 6. Assessing the body of evidence and formulating guideline evidence statements and recommendations

In addition to considerations of the rigour of the research providing the evidence (Tables 1 and 2), principles for formulating guideline evidence statements and recommendations were derived consistent with the NHMRC recommended standard '*The NHMRC Standards for External Developers of Guidelines* (NHMRC, 2007).

For each identified clinical question, evidence statements are based on an assessment of all included studies for that question (**the Body of Evidence**). The NHMRC considers the following five components in judging the overall body of evidence (NHMRC, 2007) as specified in the '*NHMRC Body of Evidence Matrix'* (Table 3):

- The evidence base, in terms of the number of studies, level of evidence and quality of studies (risk of bias).
- The consistency of the study results.
- The potential clinical impact of the proposed recommendation.
- The generalisability of the body of evidence to the target population for the guideline.
- The applicability of the body of evidence to the Australian healthcare context.

Based on the body of evidence, recommendation/s was formulated to address each of the identified clinical questions for the area. Recommendation/s was written as an action statement.

Principles for formulating the guideline recommendation/s

In the course of the face-to-face meetings of the EAGs, and from published sources, principles were identified re-affirming the need for guideline recommendations to:

- Be developed systematically and objectively by synthesising the best available evidence.
- Have potential to improve health and related outcomes whilst minimising possible harms.
- Be clinically relevant and feasible.
- Take account of ethical considerations, and acceptability to patients.
- Centre on interventions which are accessible to those who need them.
- Propose activities within the scope of the role of those expected to use the guidelines e.g., interventions which could be expected to be conducted in routine general practice.

Grading of recommendation/s

The grading of each recommendation reflects the strength of the recommendation (Table 4) and is based on 'The *NHMRC Standards for External Developers of Guidelines* (NHMRC, 2007).

In face-to-face meetings, the EAG, initially graded each of the five components of the NHMRC Body of Evidence Matrix (Table 3) for each recommendation and then determined the overall grade for the body of evidence by summing the individual component grades (Appendix v).

Cost effectiveness analyses that were based on modelling, could not be evaluated using the NHMRC 'Body of Evidence Matrix'. Hence, cost-effectiveness recommendations were not graded.

Table 3: NHMRC Body of Evidence Matrix

Component	A	B	C	D
	Excellent	**Good**	**Satisfactory**	**Poor**
Evidence base	several level I or II studies with low risk of bias	one or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	level III studies with low risk of bias, or level I or II studies with moderate risk of bias	level IV studies, or level I to III studies with high risk of bias
Consistency	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population for the guideline	population/s studied in the body of evidence are similar to the target population for the guideline	population/s studied in body of evidence different to target population for guideline but it is clinically sensible to apply this evidence to target population	population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

Table 4: 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 recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Step 7. Articulate the guidelines

For each guideline, clinical questions identified by EAGs are addressed in separate sections in a format presenting:

- *Recommendation(s*) - including grading.
- *Practice Point (s)* – including expert consensus in absence of gradable evidence.
- *Evidence Statements* - supporting the recommendations.
- *Background* - to issues for the guideline.
- *Evidence* - detailing and interpreting the key findings.
- *Evidence tables* - summarising the evidence ratings for the articles reviewed.
  At the end of the guideline, references and Search Strategy and Yield Tables documenting the identification of the evidence sources were provided.

To ensure consistency between the guidelines, a template was designed for writers to use when drafting the guidelines.

Step 8. Methods for Quality Assurance across the project

To ensure optimal accuracy and consistency within and between guideline areas, the Project Management Team conducted a range of quality assurance activities throughout the project:

Quality Assurance, Procedures and Protocols

- The provision of a Methods Manual which provides written instructions to the Chairs of the EAGs and research staff identifying the steps and processes to be followed.

- The provision to the EAGs of a selection of key published resource material relevant to the development of the guidelines (NHMRC tool kit 2000-2003; NHMRC, 2007).

- Specification and training of research staff on the search process.

Quality Assurance, Methods

- The appointment of a Senior Research Officer to the Project Management Team to advise on research methods, and provide a resource and support service to the research staff.

- The establishment of a Methods Advisory Group.

- The development of questions based on key clinical issues for each guideline topic to focus and guide the literature searches and the formulation of the guideline recommendations. As previously indicated, these are listed at the beginning of each guideline and the Search Strategy and Yield Table at the end of the guideline.

- The Project Management Team collated and reviewed the questions and undertook a Delphi - like process with the Chairs of EAGs to refine these questions. In addition, all EAGs and the Project Management Team reviewed the combined questions during one of the three face-to-face meetings.

- The design and provision to Chairs of EAGs and Research Officers of standardised forms documenting aspects of the search strategy used, the search yield, and the inclusion and exclusion of articles for review. A completed Search Strategy and Yield Table follows each guideline topic.

- The Senior Research Officer reviewed:
  - all search terms used to ensure that the searches were comprehensive and that the approach was similar across groups.

  - the documentation of the search process.

- The GAR Consultants worked closely with the Senior Research Officer and EAGs. The GAR Consultants provided advice on evaluating and documenting the scientific evidence, developing evidence-based recommendations based on the scientific literature, and NHMRC procedures.

- Double culling of the search yield for each guideline topic by project staff and members of the EAG.

- Double reviewing of a sample of completed reviews for each guideline topic by the Senior Research Officer or an experienced Research Officer, or by a member of the relevant EAG.

- Review of the completed recommendations and written description of the literature review for each guideline area was undertaken to check for:
  - appropriate use of references
  - accurate application of evidence ratings
  - congruence between the recommendations and evidence statements
  - consistency between recommendations
  - clarity of the literature review findings

4.0 Consultation Process

The organisational structure for the Type 2 Diabetes Guidelines Development Project was designed to involve and ensure consultation between the Guideline Development Consortium (DA, ADS, ADEA, RACGP) and the Diabetes Unit. A number of other strategies were employed to ensure wide consultation with a range of stakeholders and interested groups and individuals.

Initial Consultation
Prior to commencement of the project, initial consultation included contacting relevant professional organisations to discuss the guideline development and to seek nomination of content experts.

Internal Consultation
The internal communication and interaction between the Project Management Team and the research officers included fortnightly meetings, email communications, and regular telephone contact. In addition, for each guideline, there was individual informal meetings between the research officers and their project managers.

The Project Steering Committee
The Project Steering Committee comprised representatives from various organisations (who should be consulting with their colleagues in that organisation) include:

- Diabetes Australia (Mr Matt O'Brien)
- Medical Advisor (Professor Stephen Colagiuri)
- Australian Diabetes Society (Dr Maarten Kamp)
- Australian Diabetes Educators Association (Ms Jane Giles)
- Royal Australian Collage of General Practice (Professor Mark Harris)
- Department of Health and Ageing (Ms Suzanne Prosser)
- The Diabetes Unit, Menzies Centre for Health Policy (Associate Professor Ruth Colagiuri)

During the course of the project, DA convened two face-to-face meetings and three teleconferences of the Project Steering Committee members to provide guidance and direction to the project.

Expert Advisory Groups
The EAGs consulted formally through the inclusion of specific interest groups on the individual EAG. Examples include dietitians, clinicians, educators, researches, and consumers.

Communication strategies with EAG members included:

- Face-to-face meetings
  - an initial meeting to scope the coverage of the guideline and view the processes required to develop it, identify and agree on the roles of the EAG.
  - a final meeting to review and grade the recommendations and body of evidence form.

- Email communication seeking advice on research questions and search terms and requesting review of material developed.

- Chairs and individual members of EAGs, consulted with additional content experts regarding approaches and clinical/content issues as required.

Consultation with Guidelines Assessment Register (GAR) Consultants.
The GAR consultant for each guideline provided guideline developers with support in relation to utilising evidence-based findings and applying the NHMRC criteria. GAR consultants attended face-to-face meetings with EAGs. They provided advice on evaluating and documenting the scientific evidence and developing evidence-based recommendations based on the scientific literature and NHMRC procedures.

Consultation with Consumers
Consumer representatives were selected and appointed by Diabetes Australia for each EAG to ensure the consideration of people with type 2 diabetes with respect to their acceptability of the proposed guideline recommendations.

Public Consultation
All guidelines went through a formal public consultation process. This process was as follows:

- The guidelines were released for public consultation by Diabetes Australia through the NHMRC designated public consultation process between August and October 2008.

- The call for submissions was advertised in the national public press and a front page website advertisement was placed on the Diabetes Australia website, which linked to a full website advertisement.

- The NHMRC also advertised the draft guidelines in their 'bulletin'.

- Key stakeholder organisations (Appendix vi) were notified directly by email of the availability of the guidelines for public review and requested to comment. The emailed notice provided a link to the advertisement on the Diabetes Australia website.

- As a result of public consultation, submissions were received and referred to the Project Management Team:
  - six submissions relating to the Primary Prevention Guideline
  - four submissions relating to Case Detection and Diagnosis Guideline
  - two submissions relating to Patient Education
  - two submissions relating to Chronic Kidney Disease
  - five submissions relating to Blood Glucose Control
  - one submission did not relate to any of the guidelines but made comments on the overall process of the guideline development which was subsequently referred to the Diabetes Australia Guideline Consortium Steering Committee.

- The issues raised in these submissions were considered and consulted about internally and externally by the guideline developers and were reviewed by the Project Management and Research Teams, the Medical Advisor, the relevant EAG, and the GAR Consultant.

- Key issues from the submissions for each guideline were summarised into table form and corresponding responses addressing each issue were presented in separate documents entitled *"Response to Public Consultation on … "* and accompanied the guideline drafts presented to independent review by the NHMRC.

- Changes to the guidelines as a result of public consultation and as a result of independent review by the NHMRC were incorporated into the revised final guidelines.

Informal Consultation

Further consultation occurred throughout the project with a wide variety of groups and individuals in response to particular issues and needs. For example, the Chronic Kidney Disease Guideline has been reviewed by the CARI peer reviewers and presented at the Dialysis, Nephrology Transplant 2009 Workshop, Lorne Victoria. Comments from the peer reviewers and from the workshop have been incorporated into the subsequent revision of the draft guideline.

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APPENDICES

Appendix i: Terms of Reference of Steering Committee

Type 2 Diabetes Guidelines Project

1. Scope

The Steering Committee is a composite body which provides guidance and direction to the project and advice in relation to the project to the Department of Health and Ageing via Diabetes Australia.

2. Function

The role of the Steering Committee is to oversight and monitors the project progress and timelines.

3. Membership

The Steering Committee will comprise representatives from the following organisations:

- Diabetes Australia
- The Diabetes Unit, Australian Health Policy Institute
- Australian Diabetes Society
- Australian Diabetes Educators Association
- Royal Australian College of General Practitioners
- Medical Advisor
- Consumer – person with type 2 diabetes nominated by Diabetes Australia.

The Department of Health and Ageing (the Department) will be represented in an advisory role.

The final composition of the Steering Committee, the operating procedures and the Chair of the Committee will be agreed by the Department.

If a representative is unable to attend a meeting/teleconference they may nominate a proxy representative from their own organisation.

4. Quorum and Voting

The quorum for Steering Committee meetings is to be 50% of membership plus one additional member.

The Steering Committee shall always attempt to achieve consensus. In the event of decisions requiring a vote, each member of the Committee shall exercise a single vote. Decisions will be by a majority and the Chair shall have a casting vote.

5. Communication

The Steering Committee will communicate directly with Diabetes Australia who in turn will liaise with the Department. Communication between the Steering Group and other teams and groups is essential and will be facilitated by the Chair of the Committee.

Frequency of Meetings

The Steering Committee will meet on at least five occasions throughout the contract period. These meetings will comprise two face-to-face meetings and three teleconferences, throughout the contract period.

6. Executive and Operational Support

The Steering Group Secretariat will be provided by Diabetes Australia. The Secretariat will provide support in writing minutes and co-ordinating meetings

7. Funding

The costs of travel, accommodation, meeting location (or teleconference) expenses and other activities proposed by the Steering Committee will be agreed and borne by Diabetes Australia.

Appendix ii: Terms of Reference for Expert Advisory Groups

Type 2 Diabetes Guidelines Project

Purpose

The Expert Advisory Groups (EAGs) for the National Evidence Based Guidelines for Type 2 Diabetes are convened by The Diabetes Unit, Menzies Centre for Health Policy (formerly Australian Health Policy Institute), The University of Sydney under the head agreement between Diabetes Australia and the Department of Health and Ageing to support the development of the guidelines by providing:

1. Overall technical and content advice and critical comment

2. Input into the development or revision of research questions to guide the literature reviews

3. Guidance on search terms and for the literature review

4. Review of drafts of the guidelines and recommendations at critical points along the continuum of their development

5. Perspectives on the feasibility and applicability of the guidelines from the perspective of their own disciplines and their peers and colleagues

Duration

The EAGs are convened for the duration of the project. It is anticipated this will cover approximately 18 months up to end 2008.

Frequency of Meetings

It is anticipated that there will be three meetings of the EAGs mainly by teleconference with one face-to-face meeting at commencement.

The EAG members may also be asked to comment on emailed information from time to time.

Expenses

Reasonable expenses for travel to meeting will be reimbursed on presentation of original receipts

Conflict of Interests

EAG members are asked to declare any/all perceived conflict/s of interest

Appendix iii: NHMRC Evidence Hierarchy, designations of 'levels of evidence' according to type of research question

Level	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening Intervention
I	A systematic review of level II Studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation	All or none	All or none	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study ▪ Interrupted time series without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

(Source: NHMRC 2007)

Appendix iv: Study Assessment Criteria

I. Study quality criteria

Systematic reviews

1. Were the questions and methods clearly stated?
2. Is the search procedure sufficiently rigorous to identify all relevant studies?
3. Does the review include all the potential benefits and harms of the intervention?
4. Does the review only include randomised controlled trials?
5. Was the methodological quality of primary studies assessed?
6. Are the data summarised to give a point estimate of effect and confidence intervals?
7. Were differences in individual study results adequately explained?
8. Is there an examination of which study population characteristics (disease subtypes, age/sex groups) determine the magnitude of effect of the intervention?
9. Were the reviewers' conclusions supported by data cited?
10. Were sources of heterogeneity explored?

Randomised controlled trials

1. Were the setting and study subjects clearly described?
2. Is the method of allocation to intervention and control groups/sites independent of the decision to enter the individual or group in the study ?
3. Was allocation to study groups adequately concealed from subjects, investigators and recruiters including blind assessment of outcome?
4. Are outcomes measured in a standard, valid and reliable way?
5. Are outcomes measured in the same way for both intervention and control groups?
6. Were all clinically relevant outcomes reported?
7. Are factors other than the intervention e.g. confounding factors, comparable between intervention and control groups and if not comparable, are they adjusted for in the analysis?
8. Were >80% of subjects who entered the study accounted for at its conclusion?%
9. Is the analysis by intention to intervene (treat)?
10. Were both statistical and clinical significance considered?
11. Are results homogeneous between sites? (Multi-centre/multi-site studies only).

Cohort studies

1. Are study participants well-defined in terms of time, place and person?
2. What percentage (%) of individuals or clusters refused to participate?
3. Are outcomes measured in a standard, valid and reliable way?
4. Are outcomes measured in the same way for both intervention and control groups?
5. Was outcome assessment blind to exposure status?
6. Are confounding factors, comparable between the groups and if not comparable, are they adjusted for in the analysis?
7. Were >80% of subjects entered accounted for in results and clinical status described?
8. Was follow-up long enough for the outcome to occur
9. Was follow-up complete and were there exclusions from the analysis?
10. Are results homogeneous between sites? (Multicentre/multisite studies only).

Case-control studies

1. Was the definition of cases adequate?

2. Were the controls randomly selected from the source of population of the cases?
3. Were the non-response rates and reasons for non-response the same in both groups?
4. Is possible that over-matching has occurred in that cases and controls were matched on factors related to exposure?
5. Was ascertainment of exposure to the factor of interest blinded to case/control status?
6. Is exposure to the factor of interest measured in the same way for both case and control groups in a standard, valid and reliable way (avoidance of recall bias)?
7. Are outcomes measured in a standard, valid and reliable way for both case and control groups?
8. Are the two groups comparable on demographic characteristics and important potential confounders? and if not comparable, are they adjusted for in the analysis?
9. Were all selected subjects included in the analysis?
10. Was the appropriate statistical analysis used (matched or unmatched)?
11. Are results homogeneous between sites? (Multicentre/multisite studies only).

Diagnostic accuracy studies

1. Has selection bias been minimised
2. Were patients selected consecutively?
3. Was follow-up for final outcomes adequate?
4. Is the decision to perform the reference standard independent of the test results (ie avoidance of verification bias)?
5. If not, what per cent were not verified?
6. Has measurement bias been minimised?
7. Was there a valid reference standard?
8. Are the test and reference standards measured independently (ie blind to each other)
9. Are tests measured independently of other clinical and test information?
10. If tests are being compared, have they been assessed independently (blind to each other) in the same patients or done in randomly allocated patients?
11. Has confounding been avoided?
12. If the reference standard is a later event that the test aims to predict, is any intervention decision blind to the test result?

(Sources: adapted from NHMRC1999, NHMRC 2000a, NHMRC 2000b, Liddle et al 96; Khan et 2001)

Study quality – Rating

The following was used to rate the quality of each study against the study type criteria listed above.

High: all or all but one of the criteria were met

Medium: 2 or 3 of the criteria were not met

Low: 4 or more of the criteria were not met

II. Classifying magnitude of the effect

Ranking	Statistical significance		Clinical importance of benefit
High	Difference is statistically significant	AND	There is a clinically important benefit for the full range of estimates defined by the confidence interval.
Medium	Difference is statistically significant	AND	The point estimate of effect is clinically important BUT the confidence interval includes some clinically unimportant effects
Low	Difference is statistically significant OR Difference is not statistically significant (no effect) or shows a harmful effect	AND AND	The confidence interval does not include any clinically important effects The range of estimates defined by the confidence interval includes clinically important effects.

(Source: adapted from the NHMRC classification (NHMRC 2000b)

III. Classifying the relevance of the evidence

Ranking	Relevance of the evidence
High	Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival *Or* Evidence of an effect on a surrogate outcome that has been shown to be predictive of patient-relevant outcomes for the same intervention
Medium	Evidence of an effect on proven surrogate outcomes but for a different intervention *Or* Evidence of an effect on proven surrogate outcomes but for a different intervention and population
Low	Evidence confined to unproven surrogate outcomes.

(Source: adapted from the NHMRC classification (NHMRC 2000b)

Appendix v: NHMRC Evidence Statement Form

Key question(s):			Evidence table ref:
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*			
	A	Several Level I or II studies with low risk of bias	
	B	one or two Level II studies with low risk of bias or SR/multiple Level III studies with low risk of bias	
	C	Level III studies with low risk of bias or Level I or II studies with moderate risk of bias	
	D	Level IV studies or Level I to III studies with high risk of bias	
2. Consistency *(if only one study was available, rank this component as 'not applicable')*			
	A	All studies consistent	
	B	Most studies consistent and inconsistency can be explained	
	C	Some inconsistency, reflecting genuine uncertainty around question	
	D	Evidence is inconsistent	
	NA	Not applicable (one study only)	
3. Clinical impact *(Indicate in the space below if the study results varied according to some <u>unknown</u> factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*			
	A	Very large	
	B	Moderate	
	C	Slight	
	D	Restricted	
4. Generalisability			
	A	Evidence directly generalisable to target population	
	B	Evidence directly generalisable to target population with some caveats	
	C	Evidence not directly generalisable to the target population but could be sensibly applied	
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply	
5. Applicability			
	A	Evidence directly applicable to Australian healthcare context	
	B	Evidence applicable to Australian healthcare context with few caveats	
	C	Evidence probably applicable to Australian healthcare context with some caveats	
	D	Evidence not applicable to Australian healthcare context	

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	Rating	Description
1. Evidence base		
2. Consistency		
3. Clinical impact		
4. Generalisability		
5. Applicability		

Indicate any dissenting opinions

RECOMMENDATION	GRADE OF RECOMMENDATION	
What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.		

IMPLEMENTATION OF RECOMMENDATION *Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.*	
Will this recommendation result in changes in usual care?	YES
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
	NO
Are the guideline development group aware of any barriers to the implementation of this recommendation?	YES
	NO

Appendix vi: Key stakeholder organisations notified of public consultation

- Diabetes Australia State and Territory member organisations including:
    - Australian Diabetes Society
    - Australian Diabetes Educators Association

- University Schools of Nursing, Medicine, Podiatry, Nutriton/ Dietetics
- Australian Podiatry Association
- Australian Podiatry Council
- Eyes on Diabetes
- Cooperative Centre for Aboriginal Health
- Australian Centre for Diabetes Strategies
- Public and private Diabetes Centres throughout Australia (for which we were able to obtain email addresses)
- State and Federal health departments