Clinical Guidelines for Type 2 Diabetes

Diabetic renal disease: prevention and early management

A Collaborative Programme between:

The Royal College of General Practitioners
Diabetes UK
The Royal College of Physicians
The Royal College of Nursing

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Partner Organisations

The Royal College of General Practitioners

Diabetes UK

The Royal College of Physicians

The Royal College of Nursing
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Preface

Type 2 diabetes is affecting increasing numbers of people in the United Kingdom. Although its management can sometimes seem straightforward, the burden of serious complications and their sequelae may be considerable both for the individual concerned and for the health care services in general.

Nevertheless, many aspects of these complications can be ameliorated, even prevented in some instances, with good management of the condition. The aim of the Type 2 diabetes guideline series is to provide guidance about managing Type 2 diabetes for the whole range of clinical staff who work in primary and secondary care. This guideline and evidence review on the prevention and early management of renal disease is part in a series that also addresses other key aspects of Type 2 diabetes care: foot care, retinopathy, lipids management; management of blood pressure; and blood glucose management. Summary guidelines will be published by the National Institute for Clinical Excellence (NICE). The foot care guideline has already been published by the Royal College of General Practitioners.

This document comprises the clinical practice recommendations and the evidence review undertaken to support the development of the prevention and early management of diabetic renal disease guideline. It also contains several recommendations for areas of research, identified by the renal disease working group. For whilst the scientific literature contains a vast amount of research conducted about diabetes, only a limited amount of that research was found to be useful in addressing key clinical questions that health care professionals and patients ask about renal disease management in people with Type 2 diabetes.

These national guidelines have brought, in an explicit way, the available international research evidence together with the experience of a considerable number of health care professionals and patient representatives with substantial experience of managing Type 2 diabetes. This combination of scientific literature, professional and patient experience has produced both an evidence base and set of recommendations that can be used as they stand, or can provide the starting point for local adaptation of the guidelines.

The clinical guidelines and evidence review were constructed by a multi-professional, multi-agency collaboration. The process was led by the Royal College of General Practitioners Effective Clinical Practice Programme at its Unit based in the School of Health and Related Research at the University of Sheffield. It would not have been possible to undertake this project without the very considerable work of all the individual health care professionals and university staff, patients and their representatives who took part in the project. The support of the National Institute of Clinical Excellence and the various collaborating organisations and agencies was also a key element of allowing this work to be undertaken. I would like to thank them all.

Professor Allen Hutchinson
Programme Director

Renal disease: prevention and early management 7
1. Method of guideline development
The national clinical guideline for Type 2 diabetes

The national clinical guideline for Type 2 diabetes is comprised of a series of six inter-related guidelines that deal with different aspects of Type 2 diabetes. Throughout this document the entire series of guidelines is referred to as ‘the national guideline’. The aim of the national guideline is to provide recommendations to assist health care professionals in their management of people with Type 2 diabetes and is aimed at all health care professionals providing care to people with diagnosed Type 2 diabetes in primary and secondary care, irrespective of location. Depending on the type, stage and severity of clinical problem, the guidelines may also be valuable to those who work in the tertiary sector of diabetes care.

The constituent guidelines deal with the following areas within Type 2 diabetes:

♦ foot care (prevention and management of foot problems) (Hutchinson et al 2000)
♦ retinopathy (diabetic retinopathy: early management and screening)
♦ renal care (renal disease: prevention and early management)
♦ lipids management
♦ blood pressure management
♦ blood glucose management, including patient education

This section outlines the methodological approach that is taken to develop the national clinical guideline for Type 2 diabetes. The overall approach is the same for each constituent guideline (renal care, retinopathy etc). Where any variation in the process has occurred then this will be noted.

Each constituent guideline is developed and presented in such a way that they can stand as independent guidelines as well as part of the complete set that make up the national guideline.

Key features of the national guideline include:

- it is evidence based, where evidence is available
- in areas where evidence is lacking this is made clear, and the consensus methods used to derive recommendations are clearly described
- recommendations are explicitly linked to evidence where it is available
- the recommendations, methods and conclusions in the guideline are explicit and transparent.

The key steps taken to develop a guideline are outlined in Figure 1.
Figure 1: Outline of guideline development process

- definition of process
- review of evidence
  - review of published literature
  - review of other types of evidence
    - grey literature
    - professional opinion
    - patient views
- production of scientific report
- review of scientific report
- discussion/consensus building
- prepare draft guideline report
  - professional review
  - methodological review
  - review by other relevant bodies
- preliminary revisions
  - professional usefulness
  - methodological soundness
  - general usability
- peer review
  - final revisions
  - pre-testing
  - final guideline
Scope of the national guideline for Type 2 diabetes

The national guideline aims to cover the clinical care and management of people with diagnosed Type 2 diabetes. It does not cover people who have not been diagnosed as having Type 2 diabetes, for example those in a pre-diabetic state or people with impaired glucose tolerance or care in pregnancy. Nor does it cover issues concerned with screening for undiagnosed cases of Type 2 diabetes.

In each of the clinical areas covered by the national guideline, scoping exercises were undertaken in order to:

- develop pathways of care for the clinical areas in Type 2 diabetes
- develop key clinical questions for the constituent guidelines to address
- provide a useful mechanism for checking that all areas considered relevant were covered

For foot care, retinopathy, renal disease and blood glucose management, the pathways were initially developed by members of the Recommendations panel. These were further developed and refined by the Clinical working groups in each concerned area. For lipids and raised blood pressure, the pathways were developed from the outset by the Clinical working groups in each of these areas.

Note on nomenclature

Throughout the guideline documents we have used the classifications recommended by the World Health Organisation (WHO) (1999) and the American Diabetes Association (2001). Diabetes UK has recommended adoption of this classification (Diabetes UK, 2000, www.diabetes.org.uk).

Type 2 diabetes is described by the WHO Consultation as follows:

Type 2 (diabetes) is the most common form of diabetes and is characterised by disorders of insulin action and insulin secretion, either of which may be the predominant feature. Both are usually present at the time that this form of diabetes is clinically manifest. By definition, the specific reasons for the development of these abnormalities are not yet known.

The WHO Consultation document goes on to say:

Diabetes mellitus of this type previously encompassed non-insulin dependent diabetes, or adult onset diabetes. It is a term used for individuals who have relative (rather than absolute) insulin deficiency. People with this type of diabetes frequently are resistant to the action of insulin. At least initially and often throughout their lifetime, these individuals do not need insulin treatment to survive. This form of diabetes is frequently undiagnosed for many years because the hyperglycaemia is often not severe enough to provoke noticeable symptoms of diabetes. Nevertheless such patients are at increased risk of developing macrovascular and microvascular complications.

Where journal papers and other works are discussed in this guideline, the nomenclature that has been used in the original papers has been left unchanged. Therefore most papers cited in these guidelines refer to non-insulin dependent diabetes (NIDDM) and insulin dependent diabetes (IDDM), rather than Type 2 or Type 1 diabetes.

We acknowledge that it is now recognised that some children suffer from Type 2 diabetes (Fagot-Lampagna et al 2000). However, these guidelines refer only to the management of adults with Type 2 diabetes.
Responsibility and support for the guideline

Responsibility

The national clinical guideline was developed under the direction of the Royal College of General Practitioners Effective Clinical Practice Programme, Director: Professor Allen Hutchinson, ScHARR, University of Sheffield.

Funding

The guideline was developed with funding from the National Institute for Clinical Excellence (who took over responsibility for the National Health Service Executive, Guidelines Development Programme, with whom funding was originally agreed). Additional funding was provided by Diabetes UK (formerly British Diabetic Association).

The National Institute for Clinical Excellence is associated with the National Clinical Guideline for Type 2 Diabetes, produced by The Royal College of General Practitioners Effective Clinical Practice Unit through a funding contract. This arrangement provides the Institute with the ability to secure value for money in the use of the NHS funds invested in this organisation’s work and enables the Institute to influence topic selection, methodology and dissemination practice. The Institute considers the work of this organisation to be of value to the NHS in England and Wales and recommends that it be used to inform decisions on service organisation and delivery.

This publication represents the views of the authors and not necessarily those of the Institute.

Using the guideline

Guidelines are only one type of information that health care professionals may use when making decisions about patient care. It is assumed that this guideline, like all guidelines, will be used by health care professionals who will also bring to bear their clinical knowledge and judgement in making decisions about caring for individual patients. It may not always be appropriate to apply either specific recommendations or the general messages in this document to each individual or in every circumstance. The availability of resources may also influence decisions about patient care, including the adoption of recommendations.

The review date of this guideline is three years from publication date, by which time new, relevant results may be available that may affect the recommendations within the guideline.
Project structure

There were many groups and individuals involved in the development of the national clinical guideline (see Figure 2, Project Structure page 15). Some groups were looking at clinical areas (the Clinical working groups), others were concerned with the management and quality assurance of the guideline development process (advisory, project management, systematic reviews) and other groups were concerned with other important aspects related to the guideline (implementation and patient involvement).

Recommendations panel

The Recommendations panel had ultimate responsibility for ensuring that a valid, relevant and rigorous national clinical guideline was produced as a result of the guideline development process. It has the key role in ensuring that all areas were covered, both in those areas covered by the Clinical working groups but also to ensure that areas of care which do not neatly sit in any particular group were addressed. The Recommendations panel also ensured that issues pertinent to all Clinical working group areas, for example issues of risk for people with Type 2 diabetes, are adequately covered. The Clinical working groups in the clinical areas presented their recommendations, comments and views to this group, who had to ensure that recommendations were consistent in terms of the overall wording, presentation etc. They were also responsible for final grading of the recommendations. The Recommendations panel also had a central role in shaping what the overall national guideline looks like and the panel also acted as a quality control mechanism.

Clinical working groups

Six groups were concerned with specific clinical areas within Type 2 diabetes care. The six Clinical working groups were:

- foot care (prevention and management of foot problems)
- eye care (diabetic retinopathy: early management and screening)
- renal care (renal disease: prevention and early management)
- lipids management
- blood pressure management
- blood glucose management
The groups consisted of members of the project team (guideline methodologists, small group facilitators and systematic reviewers) together with practitioners and content experts. The chair of each group was also a member of the Recommendations panel. The groups were given remits to:

- formulate the key questions to be considered by both the evidence reviews, and the guideline, in their clinical area
- consider the evidence (both that which is presented to them and any additional evidence that the group identifies)
- consider and comment on the evidence review (undertaken by project team members)
- draft recommendations in their clinical area, for consideration by the Recommendations panel
- consider comments from the recommendations panel (and other internal reviewers) and review their recommendations if necessary
- consider external feedback from the development process, particularly from the NICE stakeholder reviews, and to make any necessary amendment proposals to the Recommendations panel

Project management group

The project management group oversaw the progress of the development of all the constituent guidelines (and thus the overall national guideline), and the whole project in general. This group dealt with management and policy issues within the project.

Advisory group

The advisory group consisted of representatives from the concerned professions, Diabetes UK, Royal Colleges and similar bodies. It offered advice and assistance on the general direction, quality and policy issues surrounding the development of the guideline. It met approximately every 6 months.

Systematic reviews group

The systematic reviews group offered advice and comment on the systematic reviews being undertaken for the guideline, ensuring that rigorous methodology was employed. It was therefore a quality assurance mechanism.

Patient organisation involvement

Diabetes UK had representation on the Advisory Group and Recommendations panel. It also had representation on individual Clinical working groups, and is represented in the review process.
Figure 2: Project structure

- Advisory Group
  - Project Management Group
  - Systematic Reviews Group
    - Foot Care Working Group
    - Eye Care Working Group
    - Renal Care Working Group
    - Lipids Management Working Group
    - Blood Pressure Working Group
    - Blood Glucose Working Group
  - Recommendations Panel
    - Renal Care Working Group
  - Implementation Group
    - Eye Care Working Group
    - Renal Care Working Group
Aim and scope of the renal care guideline

This guideline is aimed at all health care professionals providing renal care to people with diagnosed Type 2 diabetes in primary and secondary care, irrespective of location of care facilities. The guideline is not primarily aimed at health care professionals working in the tertiary care sector of diabetes renal care, although it may be useful to them.

The guideline does not address identification of undiagnosed diabetes or general management of people with diabetes (other than aspects that relate to the prevention and management of renal complications).

This section of the national guideline deals with renal care in people with diagnosed Type 2 diabetes. It does not cover the management of end-stage renal disease, renal dialysis and renal transplantation.

The initial scope of this guideline was defined by the renal care working group, which identified clinical areas and issues that it considered important in the prevention and early management of diabetic renal disease.

The recommendations are:
- evidence based wherever possible;
- explicitly linked to evidence where available;

and in some areas, where evidence is not available;
- recommendations are based on consensus of the development group(s). These are clearly stated as such.

Areas of care considered by the evidence review.

- Definitions and epidemiology of renal disease in Type 2 diabetes
- Screening for, and confirmation of, renal disease
  - screening methods
- Impact of screening on prognosis and management
- Risk, risk factors and confounders
- Interventions and progression of renal disease
  - pre-disease (primary prevention)
  - established disease (secondary treatment)

See Appendix 3 for the full clinical pathway used to identify areas of care for the review.
Evidence identification

Search strategies

The search strategies attempted to locate systematic reviews and meta analyses, randomised trials, other comparative studies, quality of life studies and economic studies using a combination of subject heading and free text searches. Extensive use was made of high quality recent review articles and bibliographies, as well as contact with subject area experts. The search strategy was also backed up by the expert knowledge and experience of group members. Searches were limited to English language citations.

The following bibliographic databases were searched

- Cochrane Trials Register
- Medline
- Embase
- Cinahl
- Healthstar
- Psyclit
- Science Citation
- Social Science Citation

using an optimally sensitive search strategy of terms and text words. All databases were searched from 1983 onwards, for most searches. However some databases were only searched from 1990 onwards in some areas, for example homocysteine. Full details of the search strategies are available from the authors. Trial registers were searched for ongoing and unpublished trials. Conference proceedings were examined using the Index to Scientific and Technical Conference Proceedings (ISI). Attempts to access the ‘grey literature’ were through the HMIC database (which included the Kings Fund, Nuffield Institute and Department of Health libraries) and SIGLE. Assessment of papers retrieved, and abstraction of data was conducted independently by reviewers (Aileen McIntosh and Dr Jean Peters) and disagreements were resolved by discussion.

In order to ensure the timeliness of the guideline, an additional review of the drug interventions was undertaken in November 2001.
Evidence grading

Evidence levels

Studies retrieved were assessed for their quality and relevance in answering the key clinical questions identified by the renal working group and the pathways of care exercise.

For studies where the concern is that of what intervention seems to be most effective, then in the assessment of those studies the key concern was the quality of the study in terms of the various aspects of study validity. Firstly, if a study can credibly demonstrate the causal relationship between treatment and outcome then it can be said to have internal validity. Secondly, if the findings can be generalised from the specific study sample to a wider population then it is said to be generalisable or to have external validity. Thirdly, if the study actually measures what it says it measures then it is said to have construct validity.

Once individual papers had been assessed for methodological quality and relevance in terms of the key clinical questions, they were graded according to the levels of evidence adapted from the US Agency for Health Care Policy and Research Classification (AHCPR, 1992). With this categorisation, six levels of evidence (for intervention studies) are available.

Following assessment for quality and relevance, papers were extracted and evidence tables produced wherever possible. Where it was not practicable to construct evidence tables then a narrative approach was used. This produced an evidence report that was presented to the renal care working group to develop evidence statements and recommendations.

### Classification of Evidence

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia:</td>
<td>evidence from meta-analysis of randomised controlled trials</td>
</tr>
<tr>
<td>Ib:</td>
<td>evidence from at least one randomised controlled trial</td>
</tr>
<tr>
<td>IIa:</td>
<td>evidence from at least one controlled study without randomisation</td>
</tr>
<tr>
<td>IIb:</td>
<td>evidence from at least one other type of quasi-experimental study</td>
</tr>
<tr>
<td>III:</td>
<td>evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies</td>
</tr>
<tr>
<td>IV:</td>
<td>evidence from expert committee reports or opinions and/or clinical experience of respected authorities</td>
</tr>
</tbody>
</table>

Adapted from Agency for Health Care Policy and Research (1992) *Acute Pain Management: Operative or Medical Procedures and Trauma* Agency for Health Care Policy and Research / US Department of Health and Human Services, Public Health Service, Rockville, MD

The AHCPR classification is most appropriate for questions of causal relationships, and is usually used to assign studies, dealing with causal relationships, to levels of evidence.
This classification however is proving to be increasingly problematic in guideline development that considers issues beyond intervention, and more specifically pharmacological interventions, and is also increasingly inadequate for assigning levels of evidence even to pharmacological intervention evidence. For example, there is no specific evidence level for systematic reviews (rather than meta-analysis). In terms of randomised controlled trials (RCTs) there is no recognition of whether the trial is considered adequately powered, or other indicators of quality.

In non-pharmacological intervention evidence the problems are considerable. RCTs may contain other information that is useful. For example, in this guideline valuable epidemiological data was available from a large RCT (the UKPDS). But it is not obvious how the evidence classification deals with this. (In this guideline we have given a level III to the epidemiological evidence from the UKPDS, and level Ia or Ib to intervention evidence.)

The classification of studies that are concerned for example with screening for a condition/disease are not well served by this classification. None of the screening studies could achieve a level of evidence higher than III using this system, no matter how good the screening study. Similarly differentiation between high quality and lower quality screening studies are obscured by giving all screening studies level III as this system requires. Although other taxonomies for classifying and assigning evidence levels to other types of study (with different research questions as their starting point) have been developed they are not yet widely used (e.g. evidence levels for studies concerned with diagnosis and prognosis are detailed in Canadian Medical Association, 1998, S3).
Derivation and grading of recommendations

The derivation of recommendations usually involves assessment of evidence, processes of interpretation and consensus to arrive at recommendations. The mix of evidence, interpretation and consensus will vary between topic areas. The grading of recommendations takes account of this and therefore variation may occur between different groups presented with the same evidence. Whilst evidence statements can be formulated without reference to the context in which clinicians practice, this is not always the case with recommendations.

The commonly used recommendation grading system is as follows:

**Grading of Recommendations**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>directly based on category I evidence</td>
</tr>
<tr>
<td>B</td>
<td>directly based on category II evidence, or extrapolated recommendation from category I evidence</td>
</tr>
<tr>
<td>C</td>
<td>directly based on category III evidence, or extrapolated recommendation from category I or II evidence</td>
</tr>
<tr>
<td>D</td>
<td>directly based on category IV evidence, or extrapolated recommendation from category I, II or III evidence</td>
</tr>
</tbody>
</table>


We have used this approach despite having reservations and concerns about its ongoing applicability to guideline development.

As with the commonly used evidence classification system, this recommendation grading system is also proving to be increasingly difficult to use. For example as mentioned earlier, screening studies can only be level III or lower evidence, therefore any recommendation from that evidence can only be a C level recommendation or lower. Similarly, epidemiological studies are also only level III or lower evidence. For example, in renal care in Type 2 diabetes, epidemiological studies may show that the presence of microalbuminuria increases the likelihood of cardiovascular events. The related recommendation to screen for microalbuminuria to detect those individuals at higher risk, can only be graded as a C level recommendation can be used. This C level recommendation does not necessarily convey the importance in clinical terms of this issue.
Areas without consensus

There may be areas where the group was unable to reach consensus on a clinical area, no matter whether evidence is available or not. Where this has happened there is scope to report that a consensual recommendation could not be reached, to present the opposing views, and leaving the final view to the user of the guidelines.

Review of the guideline

This guideline was reviewed in two rounds through public stakeholder consultation, after the methods proposed by the National Institute for Clinical Excellence. In addition, external content expert review was sought from 5 national and one international expert. These responses were collated and important issues of evidence and clinical practice were considered by the renal care working group.

Acknowledgements

The developers would like to acknowledge the help received from the Section of Information Resources, ScHARR, University of Sheffield for their substantial contribution to the systematic reviews undertaken in the development of the renal care guideline.

Additional reviewing by the NHS Centre for Reviews and Dissemination, University of York for their Effective Health Care Bulletin, Complications of diabetes: Renal disease and promotion of self-management, was also used in this evidence document. We are grateful for their help with this.
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2. Diabetic renal disease: prevention and early management

Principal recommendations
Diabetic renal disease: prevention and early management

Principal recommendations

Definitions used in this guideline

Diabetic renal disease

The presence of raised urine albumin levels and/or raised serum creatinine in Type 2 diabetes indicates an increased risk of premature cardiovascular events and to a lesser extent end-stage renal disease. If retinopathy is also present, it is likely that it is diabetic renal disease. If retinopathy is not present, the probability of another renal disease increases.

Lower-risk urine albumin excretion

Levels of microalbuminuria and/or proteinuria lower than those indicated below.

Higher-risk urine albumin excretion

Microalbuminuria - albumin:creatinine ratio greater than or equal to 2.5mg/mmol (men) or 3.5 mg/mmol (women), or albumin concentration greater than or equal to 20 mg/l

and/or

Proteinuria - albumin:creatinine ratio greater than or equal to 30 mg/mmol or albumin concentration greater than or equal to 200 mg/l.

Renal care for all people with Type 2 diabetes

♦ Arrange recall and annual review for people with Type 2 diabetes (C)
♦ Review complications and risk factors at diagnosis and at least annually thereafter (C)
♦ Measure albumin:creatinine ratio or albumin concentration annually (C)
  ♦ use a first morning urine sample where practicable (C)
  ♦ use a laboratory or near-patient test specifically for microalbuminuria (C)
♦ If microalbuminuria or proteinuria is present, repeat twice more, within one month where possible (C)
♦ Measure serum creatinine annually (C)
♦ Classify albumin excretion annually as,
  ♦ lower risk (absence of microalbuminuria or proteinuria) (C) or
  ♦ higher risk (2 out of 3 positive tests for definitions in box above) (C)
Routine care for people with lower risk albumin:creatinine ratio or albumin concentration

- Maintain tight blood glucose control (below HbA1c 6.5% to 7.5% depending on individual’s target) (A)
- Maintain tight blood pressure control (target blood pressure at or below 140/80mm Hg)

Care for people with higher risk urine albumin excretion

- If retinopathy is not present, look for a non-diabetic cause of renal disease (full history and examination, urinalysis, renal ultrasound, other tests as appropriate) (C)
- Begin therapy with an appropriate ACE inhibitor for cardiovascular/renal protection (A)
- ACE inhibitors are first choice, but combination therapy is likely in most patients. (A)
- Maintain blood pressure less than 135/75mm Hg (A)
- Measure urine albumin and serum creatinine levels at each visit (C)
- Measure, assess and manage cardiovascular risk factors aggressively (A)
- Refer for nephrological specialist opinion if serum creatinine greater than 150 μmol/l (D)
- Ensure tight blood glucose control (HbA1c below 6.5% to 7.5% depending on individual’s target) (A)

Starting ACE inhibitor therapy for patients:
- caution in patients with peripheral vascular disease/renovascular disease
- caution in patients with raised serum creatinine

In all patients, measure serum creatinine and electrolytes one week after:
- initiating ACE inhibitor therapy
- each increase in dose

*Some ACE inhibitors are not licensed for use at the blood pressure levels recommended in this guideline
3. Background to renal disease in Type 2 diabetes
Defining renal disease in Type 2 diabetes

Recommendations

Measurement of urine albumin levels and serum creatinine should be undertaken at diagnosis of Type 2 diabetes and annually thereafter. (C)

If raised urine albumin levels and retinopathy are present, manage as Type 2 diabetic renal disease. If retinopathy is not present, a non-diabetic, alternative cause of renal disease should be sought. (C)

Identify cardiovascular risk factors, at diagnosis and annually thereafter. (C)

<table>
<thead>
<tr>
<th>Definition of diabetic renal disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>The presence of raised urine albumin levels and/or raised serum creatinine in Type 2 diabetes indicates an increased risk of premature cardiovascular events and to a lesser extent end-stage renal disease. If retinopathy is also present, it is likely that it is diabetic renal disease. If retinopathy is not present, the probability of another renal disease increases.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Definition of higher risk urine albumin excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>microalbuminuria</strong> – albumin : creatinine ratio greater than or equal to 2.5 mg/mmol (men)/ greater than or equal to 3.5 mg/mmol (women) or albumin concentration greater than or equal to 20 mg/l</td>
</tr>
<tr>
<td><strong>proteinuria</strong> – albumin : creatinine ratio greater than or equal to 30 mg/mmol or albumin concentration greater than or equal to 200 mg/l</td>
</tr>
</tbody>
</table>

Evidence summary

A literature search sought to answer the following questions:

♦ What is the definition of renal disease in diabetes in patients with Type 2 diabetes?

♦ What is the gold standard for the definition of renal disease in diabetes in patients with Type 2 diabetes?

Microalbuminuria (also known as incipient nephropathy) is the earliest indicator of renal disease attributable to diabetes. Microalbuminuria relates to a range of albumin values in the urine which, while low, are above normal levels. A review of longitudinal studies has shown microalbuminuria to be predictive of total mortality, cardiovascular mortality and cardiovascular morbidity (Dineen and Gerstein 1997). These studies used different methods for detecting albumin levels in the urine and in some cases different cut-off points to define normal and abnormal urinary albumin. Collection of a timed urine sample is seen as the gold standard method for detecting
microalbuminuria (Winocour and Marshall 1998). A range of 30-300 mg/24 hours in a 24 hour urine sample, 20-200 µg/min in an overnight urine collection and 15-200 µg/min in a shorter timed sample are the conventional definitions of microalbuminuria, although some authorities believe that for Type 2 diabetes patients, the lower cut-off could be set at 10 µg/min.

Proteinuria, or macroalbuminuria, relates to a more extreme increase in the level of albumin in the urine. It represents a progression of urine albumin excretion from microalbuminuria. There is no definitive level of albumin to define the cut-off point for proteinuria in the literature. There is also overlap between the albumin ranges used to define microalbuminuria and the cut off points for proteinuria across some studies (MacLeod et al 1995). Studies showing proteinuria to be predictive of cardiovascular morbidity and mortality used a cut off point of 300 mg/24 hours in a 24 hour urine sample (Schmitz and Vaeth 1988) and >200 mg/l in a spot urine sample (Gall et al 1995).

Patients can progress from proteinuria to end stage renal failure although this outcome is relatively rare in comparison to cardiovascular mortality and morbidity (Dinneen and Gerstein 1997). The endpoints of microalbuminuria and proteinuria are discussed in greater detail in the section on the natural history of renal disease due to Type 2 diabetes.

In a cross-sectional study of 363 Danish people with Type 2 diabetes and less than 66 years of age, 50 patients were identified with persistent proteinuria (≥300 mg/24 hour). Thirty-six of these 50 patients had a kidney biopsy (6 refused, 2 did not attend, 6 biopsies could not be performed), with diabetic glomerulopathies accounting for 75% (27) of cases. Furthermore, 22% and 37% respectively of these with diabetic glomerulopathy also had proliferative or simple retinopathy, whereas none of the non-diabetic glomeropathy patients had retinopathy (Parving et al 1992).

A similar diabetic renal-retinopathy association was found in a study of 34 patients with Type 2 diabetes. Patients were categorised according to renal structure, following kidney biopsy and retinopathy was present in all those (10) with typical diabetic nephropathology, but not in those with either normal renal structure (10) or with atypical patterns of renal injury (14) (Fioretto et al 1996).

The working group felt that in the absence of a clear, consistent definition of diabetic renal disease in the literature, a consensus definition should be agreed by this working group for use throughout the guideline. This definition is as follows:

**Definition of diabetic renal disease**

The presence of raised urine albumin levels and/or raised serum creatinine in Type 2 diabetes indicates an increased risk of premature cardiovascular events and to a lesser extent end-stage renal disease. If retinopathy is also present, it is likely that it is diabetic renal disease. If retinopathy is not present, the probability of another renal disease increases.
The levels that constitute raised, or higher risk, urine albumin excretion, are for the purposes of this guideline defined as follows:

<table>
<thead>
<tr>
<th>Definition of higher risk urine albumin excretion</th>
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<tbody>
<tr>
<td><strong>microalbuminuria</strong> – albumin : creatinine ratio greater than or equal to 2.5 mg/mmol (men)/greater than or equal to 3.5 mg/mmol (women) or albumin concentration greater than or equal to 20 mg/l</td>
</tr>
<tr>
<td><strong>proteinuria</strong> – albumin : creatinine ratio greater than or equal to 30 mg/mmol or albumin concentration greater than or equal to 200 mg/l</td>
</tr>
</tbody>
</table>
Prevalence of renal disease in Type 2 diabetes

Recommendation

Refer for specialist/nephrological opinion if serum creatinine is greater than 150µmol/l, in order to counsel and prepare patient for end stage renal failure. (D)

Evidence statements

In cross-sectional studies, the prevalence of persistent microalbuminuria is approximately 20% and of proteinuria 15%. (III)

Diabetes is the single leading cause of entry into renal replacement programmes in the UK, the majority of patients having Type 2 rather than Type 1 diabetes. In the UK, 15% of people entering renal replacement therapy programmes have diabetes. (III)

The prevalence of patients with diabetes receiving renal replacement therapy is almost six times as high in the Asian and Black populations compared to White populations. (III)

Evidence

Microalbuminuria

Microalbuminuria is a stage in the development of diabetic nephropathy and the forerunner of overt diabetic nephropathy (Gupta et al 1991). Epidemiological studies of microalbuminuria have produced variable prevalence rates. Part of this variation may be explained by differences in duration of diabetes and in differences in methodology of urine collection and analysis (see Table 1). Individual factors such as posture and exertion affect albumin excretion rate (AER) (Gatling et al 1988).

There is no consensus amongst researchers. Each laboratory quotes its own normal range and a different critical albumin excretion rate (AER) predictive of future diabetic nephropathy (Gatling et al 1988), as illustrated in Table 1.

The range in prevalence for microalbuminuria in the studies in Table 1 is between 8% (Gatling et al 1988) and 32% (Bruno et al 1996). Such variation may be due to the variable methods used for urine collection, namely early morning, overnight, 24 hour and random samples, and/or different population sampling studies. Only five studies were population based (Gatling et al 1988, Klein et al 1993, Standl and Stiegler 1993, Bruno et al 1996, Bakker 1999). The rest of the studies were of clinic populations, which may bias true prevalence. The majority of the studies were in populations of European origin. Six of the studies showed prevalence figures for microalbuminuria around the 25% level (Patrick et al 1990, Mattock et al 1992, Gall et al 1991, Klein et al 1993, Allawi et al 1988, Gupta et al 1991). In addition, in those studies where data were available, microalbuminuria prevalence was higher in males than females.
### Table 1: Prevalence of microalbuminuria in people with Type 2 diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting and location</th>
<th>N =</th>
<th>Age (years)/Duration of diabetes (years)</th>
<th>Type of sample</th>
<th>Albumin excretion rate or albumin:creatinine ratio</th>
<th>Prevalence % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruno et al (1996)</td>
<td>Population Italy</td>
<td>1,574</td>
<td>65.4±10.5&lt;sup&gt;a&lt;/sup&gt; 8.2±6.6&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Timed overnight</td>
<td>20-200 µg/min</td>
<td>32 males 34 females</td>
</tr>
<tr>
<td>Lee et al (1995)</td>
<td>Hospital Korea</td>
<td>631</td>
<td>57±10&lt;sup&gt;d&lt;/sup&gt; 9.2±8&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Timed overnight</td>
<td>20-200 µg/min</td>
<td>20</td>
</tr>
<tr>
<td>Mattock et al (1992)</td>
<td>Hospital England</td>
<td>141</td>
<td>56 (40-73)&lt;sup&gt;a&lt;/sup&gt; 5 (0-14)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Timed overnight</td>
<td>≥20-200 µg/min</td>
<td>25 males 33 females 15</td>
</tr>
<tr>
<td>Marshall and Alberti (1989)</td>
<td>Hospital England</td>
<td>524</td>
<td>65 (19-86)&lt;sup&gt;a&lt;/sup&gt; 8 (1-33)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Timed overnight</td>
<td>≥30-150 µg/min</td>
<td>10</td>
</tr>
<tr>
<td>Allawi et al (1988)</td>
<td>Indians and Europids in Diabetes clinic England Indian 154 Europid 82</td>
<td>51 (28-65)&lt;sup&gt;b&lt;/sup&gt; 3 (0-22)&lt;sup&gt;b&lt;/sup&gt; 57 (27-65)&lt;sup&gt;c&lt;/sup&gt; 5 (1-19)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Timed overnight</td>
<td>albumin:creatinine ratio&gt;2.0</td>
<td>Indian = 26 Europid = 21</td>
<td></td>
</tr>
<tr>
<td>Gupta et al (1991)</td>
<td>Diabetes clinic India</td>
<td>64</td>
<td>48.7±11.0&lt;sup&gt;d&lt;/sup&gt; 6.5±5.7&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Timed day-time</td>
<td>&gt;20 µg/min</td>
<td>27</td>
</tr>
<tr>
<td>Standl and Stiegler (1993)</td>
<td>GP Germany</td>
<td>68</td>
<td>61 (56-66)&lt;sup&gt;b&lt;/sup&gt; Not stated</td>
<td>Early morning</td>
<td>30-200 mg/l</td>
<td>19 Figures not given but stated no sex differences found</td>
</tr>
<tr>
<td>Patrick et al (1990)</td>
<td>Hospital Scotland</td>
<td>149</td>
<td>60 (6-84)&lt;sup&gt;a&lt;/sup&gt; Newly diagnosed</td>
<td>Early morning</td>
<td>albumin:creatinine ratio&gt;2.5</td>
<td>26</td>
</tr>
<tr>
<td>Gall et al (1991)</td>
<td>Hospital Denmark</td>
<td>549</td>
<td>61 (10)&lt;sup&gt;b&lt;/sup&gt; 10 (7)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>24h</td>
<td>&gt;30-&lt;300 mg/24h</td>
<td>27 males 4 times higher than females (no figure given)</td>
</tr>
</tbody>
</table>

<sup>a</sup>figures are medians with 95% confidence intervals; <sup>b</sup>figures are medians with ranges; <sup>c</sup>figures are means with ranges; <sup>d</sup>figures are means with standard deviations

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### Proteinuria

The range of prevalences reported is detailed in Table 2. The prevalences reported range from 5% (Standl and Stiegler 1993) to 19% (Vijay et al 1994).
Table 2: Prevalence of proteinuria in people with Type 2 diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting and location</th>
<th>N =</th>
<th>Age (years)/Duration of diabetes (years)</th>
<th>Type of sample</th>
<th>Level of albumin</th>
<th>Prevalence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marshall and Alberti (1989)</td>
<td>Hospital England</td>
<td>524</td>
<td>65 (19-86) 8 (1-33)</td>
<td>Timed overnight</td>
<td>&gt;150 µg/min</td>
<td>6</td>
</tr>
<tr>
<td>Lee et al (1995)</td>
<td>Hospital Korea</td>
<td>631</td>
<td>61±9 14±8</td>
<td>Timed overnight</td>
<td>&gt;200 µg/min</td>
<td>14</td>
</tr>
<tr>
<td>Bruno et al (1996)</td>
<td>Population Italy</td>
<td>1,574</td>
<td>65.4±10.5 8.2±6.6</td>
<td>Timed overnight</td>
<td>&gt;200 µg/min</td>
<td>18 males 21 females 15</td>
</tr>
<tr>
<td>Klein et al (1993)</td>
<td>Population USA</td>
<td>798</td>
<td>Not stated Not stated</td>
<td>Random</td>
<td>≥300 mg/l</td>
<td>16 males 17 females 14</td>
</tr>
<tr>
<td>Standl and Stiegler (1993)</td>
<td>GP Germany</td>
<td>68</td>
<td>61 (56-66) Not stated</td>
<td>Early morning</td>
<td>&gt;200 mg/l</td>
<td>5</td>
</tr>
<tr>
<td>Vijay et al (1994)</td>
<td>Hospital India</td>
<td>600</td>
<td>54±10.5 12.4±7</td>
<td>24h</td>
<td>200-500 mg/day</td>
<td>16 males 19 females 36</td>
</tr>
<tr>
<td>Gall et al (1991)</td>
<td>Hospital Denmark</td>
<td>549</td>
<td>60 (35-76) 9 (0-20)</td>
<td>24h</td>
<td>≥300 mg/24h</td>
<td>14 males 19 females 5</td>
</tr>
<tr>
<td>Parving et al (1992)</td>
<td>Hospital Denmark</td>
<td>363</td>
<td>Not stated Not stated</td>
<td>24h</td>
<td>≥300 mg/day</td>
<td>14</td>
</tr>
</tbody>
</table>

*a figures are medians with 95% confidence intervals, b figures are medians with ranges, c figures are means with ranges, d figures are means with standard deviations

This variation may be due to differences in urine collection methods used. Prevalence of proteinuria was generally lower than for microalbuminuria with six of eight studies showing prevalence rates around 15% (Gall et al 1991, Parving et al 1992, Klein et al 1993, Vijay et al 1994, Lee et al 1995, Bruno et al 1996).

End stage renal failure

Renal disease in diabetes is a leading cause of end stage renal failure (ESRF). The proportion of patients accepted for renal replacement therapy in 1990/91 who had diabetes was 14% in the United Kingdom. The risk of nephropathy is the same for people with Type 1 and Type 2 diabetes, but as the prevalence of Type 2 diabetes is greater than Type 1, end stage renal failure secondary to Type 2 diabetes predominates (Beech et al 1992). Over an 18 month period, of 225 patients admitted for renal replacement therapy in Germany 38% had Type 2 diabetes compared with 4% with Type 1 (Lippert et al 1995).

We identified a number of surveys which showed diabetic renal disease was a leading cause of end stage renal failure although there were no data in three of the surveys to differentiate the proportion of people with Type 1 and Type 2 diabetes (Gokal 1987, Joint Working Party of the British Diabetic
A joint working party of the British Diabetic Association, the Renal Association and the Research Unit of the Royal College of Physicians (1989) carried out a survey to identify the numbers of people with diabetes with untreated severe renal failure (serum creatinine >500 µmol/l). Six regions, with a total population of 17 million people, were surveyed. One hundred and eighty-one patients with renal failure due to diabetes were identified. The overall mean number of people with diabetes who had end stage renal failure in this study was 10.3 per million in the single year.

Gokal et al (1987) followed all patients starting long-term dialysis in several large renal units in England, between 1983 and 1985. Over this period, 17% of all patients starting long-term dialysis had diabetes, and diabetes (Type 1 and 2) was given as the main reason for treatment choice for dialysis in 16% of patients (Gokal et al 1987).

Roderick et al (1994) reported on data collected from all renal units in the Thames region in 1991. This data also showed that high proportions of treated patients had diabetes. The percentage of people with diabetes receiving dialysis treatment was 15%. The percentage of people with diabetes receiving kidney transplant treatment was 10%.

### Variation by ethnicity

Studies in the UK have shown a higher prevalence of Type 2 diabetes in Asian populations. Mather and Keen (1985) carried out a survey in Southall, England, and showed that in the over 30 age group age-adjusted prevalence was 3.8 times as high in the population of Asian origin than in Whites. There was no excess of diabetes in those aged under 30. In a further survey, McKeigue et al (1988) found a prevalence rate of Type 2 diabetes in people of Bangladeshi origin aged 35 to 69 in Tower Hamlets, which was three times that of the White population.

From a study of 370 consecutive Asian and 368 consecutive White patients who had attended a diabetic clinic in Leicester for a minimum of one year, proteinuria (2 positive Albustix® tests, at least 6 weeks apart, 24 hour protein excretion >0.5g and no urinary tract infection) was found in 53 (14%) of Asian and 23 (6%) of White patients (p<0.001) (Burden et al 1986).

The higher rate of Type 2 diabetes in Asians corresponds with survey data showing a higher rate of renal events due to diabetes in this population. A study in Leicester showed the relative risk of renal replacement therapy due to diabetic nephropathy in Asians compared to Whites was 13.6 (Burden et al 1992). In this survey all cases of Asians receiving renal replacement therapy due to diabetic nephropathy had Type 2 diabetes.

Roderick et al (1996) collected survey data on 5,901 patients accepted for renal replacement therapy in renal units in England in 1991 and 1992. The patients comprised all 5,901 patients resident in England with end stage renal failure who had been accepted for renal replacement therapy in renal units in England and whose ethnic status was available from the units. Asians and Blacks were each almost six times as likely as Whites to receive renal replacement therapy for diabetic end stage renal failure.

From 19 renal units in four Thames regions, Roderick et al (1994) looked at rates of acceptance for, and prevalence of, renal replacement therapy among White, Black and Asian people (n=1002). The relative risk of acceptance (1991-2) compared with White people was 2.9 (2.3 - 3.5) for Black and 2.9 (2.4 - 3.6) for Asian, and relative risk of prevalence was 2.6 (2.4 - 2.9) for Black and 2.7 (2.5 - 3.0) for Asian.
A number of studies from the United States have examined the variation in ethnicity with end stage renal disease (ESRD). In a study of 1145 patients who initiated treatment for end stage renal disease in Ohio in 1983/84, the incidence of ESRD among patients with Type 2 diabetes was 70.6 per 100,000. When analysed by diabetic population at risk, Blacks had a higher incidence of ESRD in both types of diabetes. For Type 2 diabetes the odds ratio (95% CI) was 4.86 (3.65 - 6.47) (Stephens et al 1990).

Cowie et al (1989) examined racial differences in incidence of ESRD in the entire population of patients with diabetic ESRD in Michigan, who began treatment between 1974 and 1983. Fifty nine percent of White, and 77% of Black patients had Type 2 diabetes. The average annual incidence of ESRD in Type 2 diabetes patients, adjusted for age and sex, was 108.2 (93.5-123.0) for Blacks and 25.1 (20.8-29.5) for Whites, with a Black to White incidence ratio of 4:3 (3.36-5.25) (p≤0.0005). Incidence was higher in both Black and White males compared with females (Black males 126, 100.8 - 151.2; Black females 93.4, 76.5 - 110.3; White males 28.9, 22.2 - 35.7; White females 22.0, 16.4 - 27.6) (Cowie et al 1989).

A third study from the United States examined the incidence of treatment for diabetic ESRD among Mexican-Americans, African-Americans, and non-Hispanic Whites (Pugh et al 1995). Of the 523 people with Type 2 diabetes classified between 1987 and 1991 as new cases of ESRD, 110 (21%) were non-Hispanic White, 246 (47%) Mexican-American and 167 (32%) African-American (with differences between groups significant at p<0.001). The relative risk for age-adjusted annual incidence of treatment in African-Americans and Mexican-Americans compared with non-Hispanic Whites was 9.3 (6.2 - 14.0) and 9.2 (6.3 - 13.5) respectively (p<0.00001). Relative risks remained significant (p<0.0001) when the age adjusted Type 2 related ESRD incidence was calculated using the diabetic population denominator (African-Americans 3.8, 2.2 - 6.4 and Mexican-Americans 2.5, 1.5 - 4.2) (Pugh et al 1995).

Clinical Summary

People with Type 2 diabetes are at risk of end stage renal failure. If biochemical indicators suggest that renal function is declining, the Renal care working group and the Recommendations panel strongly recommend referral for specialist opinion at a point which provides adequate opportunity to provide information, counselling and preparation for entry into an end stage renal failure care programme.
References: background to renal disease  
(with AHCPR evidence grades where appropriate, see page 18)

Prevalence: microalbuminuria

|--------|---------------------|--------|-------------------|

Prevalence: proteinuria

|--------|---------------------|--------|-----------------------------|

End stage renal failure

|--------|---------------------|--------|-----------------------------|

Variation by ethnicity

<table>
<thead>
<tr>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>Mather and Keen (1985)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4. Natural history of renal disease in Type 2 diabetes
Progression of renal disease in Type 2 diabetes

Recommendations

Measure urine albumin and serum creatinine at diagnosis and at least annually thereafter (or other timescales recommended if other considerations demand it). (C)

Evidence statements

Approximately 25% of people have microalbuminuria at time of diagnosis of Type 2 diabetes. (III)

In those who are normoalbuminuric at diagnosis, microalbuminuria develops in approximately 15% and proteinuria in 5% within 5 years. (III)

Approximately 20% of microalbuminuric patients who survive for 10 years (with microalbuminuria) develop proteinuria, 50% remain microalbuminuric and 30% revert to normoalbuminuria. (III)

Treated, proteinuric, hypertensive people with Type 2 diabetes lose glomerular function at the rate of approximately 8 ml/min/year. There is a small amount of evidence that has suggested the rate is similar to that seen in proteinuric Type 1 patients. (III)

In prospective studies, for individuals who survive for 10 years from diagnosis of Type 2 diabetes, the risk of developing end stage renal failure is 8%. (III)
Introduction

Renal disease in diabetes has been categorised into a number of stages, according to progressively higher, abnormal levels of albumin in the urine. Those without raised albumin excretion are referred to as normoalbuminuric. The first stage of abnormal albumin excretion is referred to as microalbuminuria, while the next stage, corresponding to a higher abnormal level of albumin in urine is called proteinuria or macroalbuminuria (Mogensen 1999).

In this guideline those people with microalbuminuria or proteinuria are said to have higher risk albumin excretion.

Evidence summary

Progression in patients from normoalbuminuria

From diagnosis

Wirta et al (1996) studied 146 people with recently diagnosed Type 2 diabetes, recruited from either a hospital clinic or primary care centre in Finland, followed for six years. Twenty four hour urine samples were collected from the study population and albumin excretion rate (AER) measured. The study used an albumin excretion rate of <30 mg/24h to define normoalbuminuria and an albumin excretion rate of 30 - 300 mg/24h defined microalbuminuria. At the end of six years follow up, 129 of the 146 people were alive. Twenty four hour urine samples were collected from 109 of the 129 surviving subjects (82%), but data was incomplete for one patient. Seventy eight of the 108 patients had been normoalbuminuric at baseline, but 12 (18%) had subsequently developed microalbuminuria and two (3%) proteinuria. The rest of the 78 patients remained normoalbuminuric.

In a study by Niskanen et al (1993), 133 people with newly diagnosed Type 2 diabetes from a general practice in Finland had their albumin excretion rate measured between 1979 and 1981 and a repeat measure five years later. Twenty four hour urine specimens were collected to measure albumin excretion rate (AER). Of the 133, a total of 122 patients were followed up after five years from 125 who had survived, but missing data reduced the final data set to 108 patients. Seventy-four of these 108 had been normoalbuminuric at baseline, but 12 (18%) had subsequently developed microalbuminuria and two (3%) proteinuria. The rest of the 78 patients remained normoalbuminuric.

In established diabetes

Mattock et al (1998) examined 100 people with Type 2 diabetes, who had normal albumin excretion rates at baseline. The patients were drawn from a diabetes clinic in London and were followed for a minimum of three years and a maximum of seven years. Albumin excretion rates were measured over the course of the study using overnight urine samples. After seven years follow up, 23 people (23%) had developed microalbuminuria (albumin excretion rate 20-200 µg/min) and 6 (6%) had developed proteinuria (albumin excretion rate >200 µg/min).
Beatty et al (1995) followed up two sub-cohorts of 47 patients from an original cohort of 300 patients with Type 2 diabetes. The age and sex matched cohorts were followed up for 8 years, one cohort had microalbuminuria (Albumin concentration 35-300 mg/l) and the other urinary albumin concentrations <35 mg/l at baseline. In the latter group, only one patient progressed to microalbuminuria during the 8 years, whilst in the microalbuminuric cohort, six regressed to normoalbuminuria and five to proteinuria (>300mg/l).

In another study 176 normoalbuminuric White patients with Type 2 diabetes, from a hospital in Denmark, were followed for a median of 5.8 years. Development of microalbuminuria was defined as an albumin excretion rate (AER) of 30-299 mg/24h and proteinuria as an albumin excretion rate (AER) of ≥300 mg/24h, in at least two out of three consecutive 24 hour collections. Thirty six (20%, 95% CI 15 - 27) patients developed microalbuminuria and five (3%, CI 1 - 7) developed proteinuria (Gall et al 1997).

**Progression in patients from microalbuminuria**

**From diagnosis**

In the study by Wirta et al (1996b), twenty six patients of 108 who were followed up had microalbuminuria at baseline. Twelve of these still had microalbuminuria (46%) while five had developed proteinuria (19%) over the six years. Nine of the subjects with microalbuminuria at baseline had a normal albumin excretion rate (AER) at follow up. Regression to normoalbuminuria was predicted by low blood pressure although only one of these nine subjects began drug therapy for high blood pressure during the study period.

In the study by Niskanen et al (1993), 26 (16%) subjects had microalbuminuria from the cohort of 133 Finnish general practice patients with newly diagnosed Type 2 diabetes. Five years later, of 108 followed-up, 9 (43%) of the 26 with baseline albuminuria had reverted to a normal albumin excretion rate and 12 (57%) had persistent microalbuminuria. There were no significant differences between the nine who reverted and those with persistent microalbuminuria in terms of age, sex, body mass index and blood pressure.

A similar reversion in microalbuminuria was seen by Patrick et al (1990). In this study 149 people newly diagnosed with Type 2 diabetes from a hospital in Scotland had their albumin:creatinine ratio measured in an early morning urine specimen on diagnosis of diabetes. Microalbuminuria was defined as an albumin:creatinine ratio (ACR) >2.5 mg/mmol, while normoalbuminuria was defined as an albumin:creatinine ratio ≤2.5 mg/mmol. In the next 12 months the patients had a further three early morning urine samples analysed. If two or more of these showed an ACR >2.5 mg/mmol then persistent microalbuminuria was diagnosed. If only one showed an ACR >2.5 mg/mmol then the patient was defined as having intermittent microalbuminuria. The remainder of patients were termed as normoalbuminuric. Fifteen patients were lost to follow up and five were excluded due to initiating insulin therapy in the year after diagnosis of diabetes.

Of the 129 patients in the Patrick study with complete data available, 88 (68%) were defined as having normoalbuminuria, 20 (16%) as having intermittent microalbuminuria and 21 (16%) as having persistent microalbuminuria. Within the group with persistent microalbuminuria 18 (86%) had had an elevated albumin:creatinine ratio at baseline, the other three were initially normoalbuminuric. Among the rest of the patients with microalbuminuria at baseline (N=21), eight were lost to follow up, three had intermittent microalbuminuria and 10 had consistently normal albumin excretion. In the 10 patients who reverted to normal urine albumin excretion after follow
up, there was a significant trend for higher glycosylated haemoglobin at baseline compared with the group with persistent microalbuminuria (p<0.05).

**In established diabetes**

Mogensen et al (1984) reported on a cohort of 232 Type 2 diabetes patients from a hospital in Denmark who were followed for 10 years. One of the aims of the study was to establish whether microalbuminuria in this patient group would predict an increased likelihood of overt nephropathy (proteinuria) compared to normal levels. Microalbuminuria was defined as an albumin concentration of between 30 and 140 mg/l and proteinuria as a concentration of 140 mg/l or greater. Early morning urine samples were collected from all patients with Type 2 diabetes attending a hospital diabetes clinic in 1973. Seventy-six patients had microalbuminuria according to the study criteria. These patients were compared with people with Type 2 diabetes who had different albumin concentrations (75 patients with albumin concentrations of <15 mg/l, 53 with albumin concentrations of 16 – 29 mg/l, and 28 with albumin concentrations >140 mg/l). The groups with different albumin concentrations were similar in age, age at diagnosis of diabetes, and duration of diabetes. At 10 year follow up, repeat screening took place of these 232 patients with early morning urine samples again being measured. Twenty-two per cent of patients with microalbuminuria originally had progressed to proteinuria compared to 5% of those whose albumin levels were below 30 mg/l at baseline (p<0.001).

Beatty et al (1995) monitored 94 patients with Type 2 diabetes (47 with microalbuminuria and 47 matched controls without microalbuminuria) who were outpatients at a hospital in Northern Ireland. Microalbuminuria was defined as albumin excretion rate (AER) of 35-300 mg/l, and proteinuria as an albumin excretion rate (AER) >300 mg/l, in an early morning urine sample. Twenty-five patients in the microalbuminuric group were still alive at the eight year follow up of whom 19 were successfully followed up. Of these 19 patients five (26%) progressed from microalbuminuria to proteinuria, while eight (42%) remained microalbuminuric. Six patients (32%) reverted to a normal albumin concentration. Since there was no relative deterioration in blood pressure or glycaemic control in those who had persistent microalbuminuria compared to those who returned to normoalbuminuria, an alternative explanation given for this regression from microalbuminuria was the recognised variability in albumin excretion. An early morning collection may be more susceptible to variable measurements of albumin excretion between samples compared to a timed sample.

**Glomerular filtration rate in microalbuminuria**

Lee et al (1995b) determined the correlation between GFR and albumin excretion rate measured in overnight urine samples, in a population with Type 2 diabetes attending an outpatient clinic in Korea. A total of 284 patients took part in this cross sectional study. Sixty four people had microalbuminuria and 71 had glomerular hyperfiltration. Glomerular hyperfiltration (>140 ml/min/1.73m²) occurred in 24% (52) of normoalbuminuric and 28% (18) of microalbuminuric patients. Mean GFR of microalbuminuric patients (121.5 ± 30.1 ml/min/1.73m²) was not significantly different from that of normoalbuminurics (124.9 ± 26.4 ml/min/1.73m²) (p>0.05).

Vedel et al (1996) included 158 patients with microalbuminuria (30 - 300 mg/24h) who were less than 66 years of age. Two matched control groups were also assessed, 39 with Type 2 diabetes and normoalbuminuria (and less than 66 years of age) and 20 (age-sex matched) without diabetes or renal disease. Glomerular filtration rate measured over a 4 hour period was significantly elevated in the Type 2 diabetes group with microalbuminuria compared with the control groups (139 ± 29 ml/min
versus 115 ± 19 ml/min versus 111 ± 23 ml/min, p<0.001). Glomerular filtration rate in Type 2 patients who had not received antihypertensive treatment was elevated in microalbuminuria (n=96) compared with normoalbuminuria (n=27), 119 ± 22 versus 100 ± 14 ml/min (p<0.001).

Silverio et al (1993) carried out a cross sectional study of 71 people with Type 2 diabetes attending an outpatient clinic in Brazil. The patients were all free of proteinuria (albumin excretion rate (AER)<200 µg/min), but six were classed as having microalbuminuria (albumin excretion rate (AER) = 20 – 200 µg/min). A control group (matched for age and sex) of 44 healthy patients was used to establish a normal range for glomerular filtration. Fifteen patients had elevated glomerular filtration rate (GFR), defined as above the upper limit of normal in the control group (137.1 ml/min/1.73m²), but there was no difference between normal and hyperfiltration patients in GFR or AER. Of the six patients with microalbuminuria, only one had elevated GFR.

Progression to end stage renal failure

Hasslacher et al (1989) followed 464 patients with Type 2 diabetes and no proteinuria and no elevation of serum creatinine at the first visit, for at least two years during a fifteen year period. The patients were drawn from a diabetes outpatient clinic in Germany and were assessed for the development of proteinuria and end stage renal failure. Over the period of the study 63 died and a further 56 (12%) survivors developed proteinuria (four successive protein excretion levels of >0.5 g/24h). Forty six of those with Type 2 diabetes and proteinuria were followed for a median period of three years after onset of proteinuria. Renal failure (serum creatinine >123 µmol/l) occurred in 18 people (39%). Cumulative frequency of renal failure was approximately 63% (read from graph). The study also included a second cohort of 312 patients with Type 1 diabetes.

Progression from proteinuria (>0.5 g protein/24h) with near normal creatinine clearance (>70 ml/min/1.73m²) to the beginning of dialysis was compared in 16 people with Type 2 diabetes and 16 people with Type 1 diabetes (Biesenbach et al 1994). All the patients were followed at monthly intervals in an outpatient clinic in Austria until they started dialysis. In Type 2 patients dialysis therapy was started after a mean period of 81 (40 - 124) months, when creatinine clearance had decreased from 81 ± 6 ml/min/1.73m² to a mean clearance of 7 ± 2 ml/min/1.73m². The average rate of decline of the creatinine clearances was 0.91 ± 0.41 ml/min/month. At the beginning of the study, of the 16 patients with Type 2 diabetes, 3 were treated by diet only, and the other 13 were receiving oral antidiabetic therapy, but 8 were changed to insulin therapy. Five were receiving anti-hypertensive therapy on recruitment. At the point of initiation of dialysis treatment, 3 patients were still on a diet and 13 were receiving insulin injections. All patients were also being treated with various anti-hypertensive drugs with 8 receiving ACE inhibitors until their serum creatinine increased to ≥500 µmol/l. Elevated blood pressure levels significantly influenced the rate of progression to dialysis in both groups of patients.

Berrut et al (1997) followed 72 subjects with Type 2 diabetes who were referred to a hospital in France. The patients were followed as outpatients for a period of 22 months. Fifty one patients had normoalbuminuria and 21 had microalbuminuria (30 – 300 mg/24h). Glomerular filtration rate (GFR) was measured at baseline and follow up. GFR at baseline was similar in people who had microalbuminuria (101 ± 27 ml/min) and normoalbuminuria (91 ± 20 ml/min). During follow up GFR in the microalbuminuric group dropped by a mean of 10 ± 19 ml/min (−0.4 ± 0.9 ml/min/month of follow up) while GFR in the normoalbuminuric group remained unchanged (+4 ± 17 ml/min) (+0.2 ± 0.7 ml/min/month of follow up). The difference between the groups in change of GFR was statistically significant (p=0.0022). When adjusted to baseline GFR values, differences between microalbuminuric and normoalbuminuric groups remained statistically significant (p=0.006), with
GFR reduced by 11 ± 22% in patients with microalbuminuria versus 6 ± 17% in patients with normoalbuminuria. The drop in GFR in patients with microalbuminuria was independent of baseline GFR, patient age or follow-up time. Changes in GFR were not linked to changes in AER independently of initial AER status.

Christensen et al (1999) carried out a long-term observational study (median 55 months, range 24 - 100) of 13 normotensive to borderline hypertensive Type 2 diabetes patients with diabetic nephropathy (UAER >300 mg/24 hour in a minimum of two out of three consecutive 24 hour urine samples). Glomerular filtration rate was measured once a year, and decreased over the study period from a mean of 104 (50 - 126) to 80 (39 - 112) (p=0.002); with a median (range) rate of decline of 4.5 (~0.4 - 12) ml/min/yr. Multiple regression analysis found no significant association between baseline values of systolic and diastolic blood pressure, albuminuria, HbA1c, cholesterol, known duration of diabetes, BMI or age, with rate of decline of GFR.

Relationship of urine albumin excretion and serum creatinine

In the study by Schmitz and Vaeth (1988) 503 patients, predominantly with Type 2 diabetes, were followed for ten years. Early morning urine samples were collected from patients and urinary albumin concentration (UAC) was measured. Subjects were divided into four groups: UAC ≤15 mg/l (normal), >15 mg/l ≤UAC ≤40 mg/l, >40 <UAC ≤200 mg/l and >200 mg/l. There was a significant association between increased serum creatinine and higher UAC in an early morning sample (p<0.001). However, high serum creatinine was also present when UAC was low and vice versa, which suggests that microalbuminuria may be present before a rise in serum creatinine occurs. Serum creatinine was a significant factor in predicting total mortality (relative risk 1.81; p<0.002).

In a study by Tsalamandris et al (1994), 211 patients with either Type 1 or Type 2 diabetes were followed for a period of eight to fourteen years. Forty patients were classified into three groups depending on the presence or absence of increasing albumin excretion rate (AER) and/or reductions in creatinine clearance. In group A, 15 (eight with Type 1 and seven with Type 2 diabetes) developed a progressive increase in (AER), without a decline in creatinine clearance. In group B, 13 (six with Type 1 and seven with Type 2 diabetes) showed a progressive increase in (AER) with a decline in creatinine clearance to <90 ml/min. In Group C, 12 (four with Type 1, 8 with Type 2 diabetes) patients experienced a fall in creatinine clearance without a significant rise in albumin excretion rate (AER). In groups A and B, all 28 people developed persistent microalbuminuria (20 – 200 µg/min) or proteinuria. The 13 people in group B experienced a decline in creatinine clearance from a mean baseline of 109 ± 8 ml/min (range 59 - 163 ml/min) to a final level of 51 ± 6 ml/min (range 27 - 86 ml/min). In the 12 patients in group C, creatinine clearance declined at a similar rate of 3.9 ± 0.4 ml/min/year from a baseline of 105 ± 8 ml/min (range 63 - 147 ml/min) to a final level of 59 ± 5 ml/min (range 26 - 87 ml/min), without persistent microalbuminuria being present.

Thus the development of persistent microalbuminuria can be associated with stable or declining creatinine clearance and creatinine clearance may decline without persistent microalbuminuria developing.
Conclusion: progression to proteinuria

These studies show that over time progression can occur from normoalbuminuria to microalbuminuria and on to proteinuria in patients with Type 2 diabetes. The rate of progression varies between the studies, which reflect the different lengths of follow up, different methods for assessing urine and differences in sample populations. There is also evidence that in people with newly diagnosed diabetes and microalbuminuria, the microalbuminuria can revert to normoalbuminuria (Patrick et al 1990, Beatty et al 1995, Wirta et al 1996b). However, in some newly diagnosed patients, regression from microalbuminuria to normoalbuminuria does not occur and the microalbuminuria may represent damage which has occurred through a delay in diagnosis (Niskanen et al 1996). When reversion from microalbuminuria to normoalbuminuria does occur this may be caused by improved blood pressure or glycaemic control, perhaps as a result of therapy. Also, in some studies examining progression of renal disease, a return in some patients from microalbuminuria to normoalbuminuria occurred for unknown reasons (Patrick et al 1990, Niskanen et al 1993, Beatty et al 1995).

It is unclear from these studies whether this return is a genuine spontaneous clinical remission or the result of unreliability in baseline measurement of albumin excretion by use of a single urine sample. In two of these three studies, microalbuminuria was defined by a single early morning sample (Patrick et al 1990, Beatty et al 1995). A reference standard method for measuring albumin in the urine is a timed sample (either 24 hour or overnight), and use of untimed samples is likely to produce more variable measurements of albumin excretion than the gold standard methods (Beatty et al 1995).
Morbidity and mortality due to renal disease

Recommendations

Measure urine albumin and creatinine excretion at diagnosis of diabetes and annually thereafter. (C)

Measure albumin:creatinine ratio or albumin concentration. If microalbuminuria or proteinuria is present, repeat twice more, within one month if feasible. (C)

Following measurement of urine albumin and creatinine excretion, classify albumin excretion as being lower or higher risk. (C)

Review complications and risk factors at diagnosis and at least annually thereafter. (C)

Refer for nephrological opinion if serum creatinine greater than 150 µmol/l. (D)

Definition of higher risk urine albumin excretion

- **microalbuminuria** – albumin : creatinine ratio greater than or equal to 2.5 mg/mmol (men)/greater than or equal to 3.5 mg/mmol (women) or albumin concentration greater than or equal to 20 mg/l
- **proteinuria** – albumin : creatinine ratio greater than or equal to 30 mg/mmol or albumin concentration greater than or equal to 200 mg/l

Evidence statements

Annual measurement of urine albumin, and creatinine, and serum creatinine, is essential in assessing an individual’s risk of cardiovascular and renal disease. (III)

The presence of microalbuminuria and proteinuria are associated with a clinically important increase in cardiovascular mortality and morbidity. There is an increased risk (in mortality) of between two and four fold for patients with microalbuminuria and an increase of between five and eight fold for patients with proteinuria compared to patients without raised albumin levels. (III)

In 5 years, 32% of Type 2 patients with microalbuminuria are dead. Cardiovascular disease accounts for 53% of these deaths (38% die from ischaemic heart disease and another 15% from cardiovascular disease). (III)

Specialist referral when serum creatinine is greater than 150µmol/l allows careful preparation, planning and counselling for renal replacement therapy. (IV)
Evidence summary

Mortality due to renal disease in Type 2 diabetes

In studies following cohorts of people with Type 2 diabetes over time, reported deaths directly due to renal disease are rare, because the majority of such patients now receive renal replacement therapy and cause of death is recorded as ischaemic heart disease or stroke rather than end stage renal disease. Two cohort studies have reported mortality due to renal disease. In Gall et al (1995) the outcome of 328 patients from a hospital in Denmark were assessed in a five year follow up. During the follow up period three patients died of uraemia out of a total of 51 deaths, all of whom had proteinuria at baseline. All cause deaths ranged from 16 (8%) in 191 with normoalbuminuria at baseline through 17 (20%) in 86 with microalbuminuria to 18 (35%) in the 51 proteinuric Type 2 diabetic patients. Of the total deaths in normoalbuminuria, 9 of the 16 were attributable to cardiovascular disease and for microalbuminuria and proteinuria, there were 10 cardiovascular deaths in each group. In a Cox regression analysis, a factor 10 increase in albumin excretion rate (AER) was associated with a relative mortality risk of 1.9 (1.4 - 2.6) (p<0.001). Proteinuria was associated with a 2.5 fold (1.1 - 5.8) (p<0.05) increased cardiovascular mortality risk compared with normoalbuminuria (age adjusted multiple regression analysis).(Gall et al 1995).

In Schmitz and Vaeth, (1988) 503 patients predominantly with Type 2 diabetes, from a hospital in Denmark were followed for ten years and only eight people died of uraemia, representing 3% of deaths. Another six had uraemia or nephropathy as a secondary diagnosis. Of these renal cases ten were characterised as diabetic nephropathy, two as infection and another two were not specified. A decreasing survival probability was seen with increasing AER. The relative risks relative to AER \( \leq 15 \text{ mg/l} \) were 1.53 (p=0.007), 2.28 (p<0.001), 182 (p=0.02), for AER of \( >15 \text{ – } \leq 40 \), \( >40 \text{ – } \leq 200 \) and \( >200 \) respectively. Fifty-eight percent of deaths were caused by acute myocardial infarction, cardiac failure or stroke.

Raised urine albumin as a predictor of increased cardiovascular mortality and morbidity

Mortality as a direct result of renal disease was rare in follow up studies looking at the prognosis of people with raised urinary albumin (Schmitz and Vaeth 1988, Gall et al 1995). However, a number of studies have examined the possible link between microalbuminuria, proteinuria and mortality due to other causes.

Beilin et al (1996) examined the relationship of urine albumin excretion to cardiovascular mortality in a prospective longitudinal study (1986-93) of 666 people with predominantly with Type 2 diabetes in Perth, Australia. On entry to the study 25% had coronary heart disease, 211 (31.7%) had microalbuminuria (urinary albumin 30 - 300 mg/l) and 9.9% (65) had proteinuria (\( \geq 300 \text{ mg/l} \)). Deaths from cardiovascular disease ranged from 7.7% (30) in the normoalbuminuric group through 17.1% (36) in the microalbuminuric group to 21.5% (14) in the proteinuric group. Similarly for coronary heart disease, deaths were 6.7% (26), 12.3% (26) and 13.8% (9) respectively. The total number of deaths in the cohort was 167. After adjustment for age, sex and other risk factors the relative risks for mortality in relation to urinary albumin concentrations of 30 – 300 mg/l were: all cause 1.83 (95% CI 1.31 - 2.57) p<0.001; cardiovascular disease 2.17 (1.33 - 3.53) p<0.05; coronary heart disease 1.78 (1.04 - 3.08) p<0.05. For albumin concentrations \( >300 \text{ mg/l} \), the relative risks were 3.67 (CI 2.39 - 5.61) p<0.001; 3.54 (CI 1.86 - 6.72) p<0.001; and 2.57 (CI 1.19 - 5.53) p<0.05, respectively.
In a cohort of 108 people with Type 2 diabetes followed up at 5 years from the original 133, (132 with data) mortality in patients with diabetes with baseline albuminuria (>35 mg/24 hr) was 15.4% (4 of 26) compared with 3.8% in patients with diabetes without albuminuria (p=0.048). The cause of death was cardiovascular in 5 patients, 3 (60%) of whom had albuminuria at baseline (Niskanen et al 1993).

Of 232 patients with Type 2 diabetes followed up for 10 years, only 22% of those who were microalbuminuric (30 – 140 mg/l) were alive after 10 years compared with 57% with normoalbuminuria (<15 mg/l). The majority of deaths were cardiovascular. All cause deaths (total 142) ranged from 63 in normoalbuminuria through 59 in microalbuminuria to 20 in patients with albumin concentrations >140 mg/l. Of the 63 all cause deaths in normoalbuminuric patients, 27 were attributable to myocardial infarction or cardiac insufficiency. In microalbuminuric patients there were 59 deaths of which 45% were cardiovascular related, and in patients with UAER >140 mg/l, 30% of the 20 deaths were caused by cardiovascular problems (Mogensen 1984).

In a logistic regression analyses, Beatty et al (1995) found that microalbuminuria, age and HbA1c were significant predictors of mortality (odds ratio for microalbuminuria 3.26 (CI 1.32 - 8.04) p<0.05. Of the 32 deaths in the 94 study patients, vascular death accounted for 24 of these.

While some studies have shown a high percentage of people progressing to proteinuria over time, incidence of end stage renal failure is low (Mogensen et al 1984). However, despite the low risk to the individual patient with Type 2 diabetes, the high prevalence of proteinuria means that the numbers requiring renal replacement therapy with Type 2 diabetes are high.

**Microalbuminuria**

**Mortality/morbidity – all causes**

Dinneen and Gerstein (1997) carried out a systematic review of the literature (with meta-analyses) analysing the association between microalbuminuria, total mortality, cardiovascular mortality and cardiovascular morbidity in individuals with Type 2 diabetes. Original articles were assessed for inclusion in the review on the following predefined criteria: Type 2 diabetes was clearly defined; microalbuminuria was not assessed in the presence of bacteriuria; main outcomes (death, myocardial infarction and stroke) were clearly defined; other risk factors for atherosclerotic disease were assessed; completeness of follow up was reported; one article only from multiple reports of the same study.

The outcomes from 11 included cohort studies were summarised as odds ratios and these data were pooled to give an overall outcome for the studies. Data were reported for a total of 2138 patients who were followed up for a mean of 6.4 years. Patient age was similar across cohorts (age range: 52-75 years). All studies were carried out in Europe.

There was heterogeneity between the primary studies with respect to the methods for measuring albumin. Four studies collected early morning urine samples, one used a daytime sample, three studies collected timed overnight urine samples, one study collected a timed 24-hour urine specimen and two other studies collected shorter timed specimens. This led to a variation in definitions of microalbuminuria between studies. Even where the same urine collection method was followed there was not always consistent levels of albumin used to define microalbuminuria. Microalbuminuria was defined as an albumin excretion rate (AER) of 35 – 389 mg/24h in a 24 hour urine sample (Niskanen et al 1993). In studies using overnight urine samples as the method for detecting albumin excretion, 20 – 200 µg/min was the range in Mattock et al (1992), while two
studies quoted cut off points of >10.5 µg/min (MacLeod et al 1995) and >31 µg/min (Jarrett et al; 1984). When shorter timed collections were used in two studies, a cut off point of >15 µg/min and 15 – 200 µg/min defined microalbuminuria (Standl and Stiegler 1993, Stehouwer et al 1990). The studies using spot urine samples to measure albumin concentration had different ranges to define microalbuminuria. These were 30 – 200 mg/l (Stiegler et al 1992), 15 – 200 mg/l (Schmitz and Vaeth 1988), >15 mg/l (Neil et al 1993) and albumin creatinine ratio >2.5 (Patrick et al 1990). These various methods of urine collection may have contributed to the range in prevalence for microalbuminuria of between 12% and 36% in the eight studies in which prevalence rates could be measured.

Seven of the studies were based in a hospital setting and four were performed in a general practice setting or were population based. There were probably selection biases operating in most of the studies included in the review as only two attempted to recruit a sample truly representative of people with Type 2 diabetes in the community (Damsgaard et al 1993, Niskanen et al 1993).

The populations in the individual studies were all made up of people with Type 2 diabetes. There was variation in mean duration of diabetes in the different cohorts, ranging from newly diagnosed to thirteen years. However, in seven of the studies the mean duration was between 5.5 years and 8.5 years.

The length of follow up was different in the various studies included in the review, ranging from one year to 13 years, with a mean follow up time of 6.4 years. A follow up period of one year was sufficient for the events of interest (i.e. total mortality, cardiovascular morbidity and mortality) to occur.

Clearly, there was heterogeneity between the included studies in terms of length of follow up, methods used for assessing microalbuminuria, and duration of diabetes in the study populations. However, there was a consistent message from the outcomes of the studies. In ten of the eleven studies reporting total mortality there was a positive association between microalbuminuria and death.

**Working group discussion**

There was unanimous agreement in the renal care working group that referral for nephrological opinion when serum creatinine reaches, or is above, 150µ mol/l will allow time for careful preparation, planning and counselling for renal replacement therapy.

**Review of the evidence**

Tables 3 to 5 (following) set out the evidence on the relationship between microalbuminuria and total mortality. Table 3 summarises the eight (out of eleven) studies that reported odds ratios to assess the difference in mortality between people with normoalbuminuria and microalbuminuria. The odds ratios yielded an overall risk of 2.4 (95% CI 1.8 - 3.1). The results from the studies were not statistically heterogeneous. Excluding studies which included patients with proteinuria changed the overall odds ratio to 3.1 (CI 2.1 - 4.6).
Table 3: Odds ratios for total mortality predicted by microalbuminuria in patients with Type 2 diabetes (Dinneen and Gerstein 1997)

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting and location</th>
<th>N =</th>
<th>Type of sample</th>
<th>Length of follow up (years)</th>
<th>Microalbuminuria definition</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>odds ratio (95% CI)</td>
</tr>
<tr>
<td>Stehouwer et al (1990)</td>
<td>Hospital Holland</td>
<td>94</td>
<td>Timed (4-h)</td>
<td>3.1</td>
<td>15-200 µg/min</td>
<td>14.3 (1.5 - 342)</td>
</tr>
<tr>
<td>Stiegler et al (1992)</td>
<td>GP Germany</td>
<td>257</td>
<td>Early morning</td>
<td>3.0</td>
<td>30-200 mg/l</td>
<td>2.2 (0.6 - 7.5)</td>
</tr>
<tr>
<td>Mattock et al (1992)</td>
<td>Hospital London, UK</td>
<td>141</td>
<td>Timed overnight</td>
<td>3.4</td>
<td>20-200 µg/min</td>
<td>9.7 (2.5 - 40.5)</td>
</tr>
<tr>
<td>Damsgaard et al (1993)</td>
<td>Population Denmark</td>
<td>211</td>
<td>Spot daytime</td>
<td>10-11</td>
<td>15 µg/min</td>
<td>1.8 (1.0 - 3.3)</td>
</tr>
<tr>
<td>Niskanen et al (1993)</td>
<td>GP Finland</td>
<td>133</td>
<td>Timed 24 hour</td>
<td>5.0</td>
<td>35-389 mg/24h</td>
<td>4.6 (0.9 - 24.5)</td>
</tr>
<tr>
<td>Neil et al (1993)</td>
<td>GP England</td>
<td>236</td>
<td>Spot daytime</td>
<td>6.1</td>
<td>25-200 mg/l</td>
<td>2.0 (1.1 - 3.7)</td>
</tr>
<tr>
<td>Beatty et al (1995)</td>
<td>Hospital N Ireland</td>
<td>94</td>
<td>Early morning</td>
<td>8.0</td>
<td>35-300 mg/l</td>
<td>3.3 (1.2 - 8.9)</td>
</tr>
<tr>
<td>MacLeod et al (1995)</td>
<td>Hospital England</td>
<td>306</td>
<td>Timed overnight</td>
<td>8.0</td>
<td>&gt;10.5 µg/min</td>
<td>2.0 (1.3 - 3.3)</td>
</tr>
</tbody>
</table>

* adjusted relative risk; + adjusted odds ratio

Five of these eight studies reported adjusted risk estimates and in all five microalbuminuria remained a statistically significant independent predictor of all cause mortality. Other risk variables included in analyses in these studies were age, smoking, hypertension, hypercholesterolemia, and presence of coronary heart disease at baseline.

Three studies in the review reported relative risks for total mortality as a result of microalbuminuria at baseline. These studies are summarised in Table 4.

Table 4: Relative risk for total mortality predicted by microalbuminuria in patients with Type 2 diabetes (Dinneen and Gerstein 1997)

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting and Location</th>
<th>N =</th>
<th>Type of sample</th>
<th>Length of follow up (Years)</th>
<th>Level of albumin</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jarrett et al (1984)</td>
<td>Hospital England</td>
<td>44</td>
<td>Timed overnight</td>
<td>13.0</td>
<td>&gt;31 µg/min</td>
<td>Relative risk of mortality compared with less than 31 µg/min = 3.3</td>
</tr>
<tr>
<td>Standl &amp; Stiegler (1993)</td>
<td>GP Germany</td>
<td>228</td>
<td>Timed 1-hour</td>
<td>10.5</td>
<td>&gt;15 µg/min</td>
<td>Relative risk of mortality compared with less than 15 µg/min = 2.6</td>
</tr>
<tr>
<td>Schmitz and Vaeth (1988)</td>
<td>Hospital Denmark</td>
<td>503</td>
<td>Early morning</td>
<td>10.0</td>
<td>15-200 mg/l</td>
<td>Relative risk of mortality compared with less than 15 mg/l = 2.3</td>
</tr>
</tbody>
</table>
Studies published subsequently to the Dineen and Gerstein systematic review were identified and their results were compared to the findings of the review. Their findings are presented in Table 5 below.

Table 5: Total mortality predicted by microalbuminuria in patients with Type 2 diabetes (studies not included in Dineen and Gerstein 1997 systematic review)

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting and Location</th>
<th>N =</th>
<th>Type of sample</th>
<th>Length of follow up (Years)</th>
<th>Microalbuminuria definition</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wirta et al (1997)</td>
<td>Hospital Finland</td>
<td>150 newly diagnosed Type 2</td>
<td>24 hour sample</td>
<td>9</td>
<td>&gt;30 - &lt;300 mg/24h</td>
<td>Microalbuminuria was not a significant predictor of total mortality (no p value reported)</td>
</tr>
<tr>
<td>Beilin et al (1996)</td>
<td>Hospital Australia outpatients</td>
<td>666 people with Type 2 diabetes</td>
<td>Early morning</td>
<td>7</td>
<td>&gt;30 - &lt;300 mg/l</td>
<td>Adjusted risk ratio for elevated albumin (30-300) (including age sex and other risk factors) was 1.77 (CI 1.22 - 2.57) p=0.002</td>
</tr>
<tr>
<td>Gall et al (1995)</td>
<td>Hospital Denmark</td>
<td>328</td>
<td>24-hour</td>
<td>5</td>
<td>30 - 299 mg/24h</td>
<td>Factor 10 increase in albumin excretion rate (AER) associated with 1.9 (CI 1.4 - 2.6) relative risk of all cause death</td>
</tr>
</tbody>
</table>

Mortality/morbidity – cardiovascular causes

In six of the studies included in the Dineen and Gerstein review that reported odds ratios for cardiovascular morbidity and mortality, the pooled odds ratio was 2.0 (95% CI, 1.4-2.7). Excluding the study which had patients with proteinuria changed the pooled odds ratio to 1.8 (95% CI, 1.2-2.8). These studies are summarised in Table 6.

Table 6: Odds ratios for cardiovascular mortality and morbidity predicted by microalbuminuria in patients with Type 2 diabetes (Dineen and Gerstein 1997)

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting and location</th>
<th>N =</th>
<th>Type of sample</th>
<th>Length of follow up (Years)</th>
<th>Level of albumin</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stehouwer et al (1990)</td>
<td>Hospital Holland</td>
<td>94</td>
<td>Timed (4-h)</td>
<td>3.1</td>
<td>15 – 200 µg/min</td>
<td>2.6 (CI 0.9 - 7.8)</td>
</tr>
<tr>
<td>Stiegler et al (1992)</td>
<td>Hospital Germany</td>
<td>257</td>
<td>Early morning</td>
<td>3.0</td>
<td>30 – 200 mg/l</td>
<td>1.1 (CI 0.6 - 2.2)</td>
</tr>
<tr>
<td>Niskanen et al (1993)</td>
<td>GP Finland</td>
<td>133</td>
<td>Timed 24-hour</td>
<td>5.0</td>
<td>35 – 389 mg/24h</td>
<td>6.8 (CI 0.9 - 62.4)</td>
</tr>
<tr>
<td>Neil et al (1993)</td>
<td>GP England</td>
<td>236</td>
<td>Spot daytime</td>
<td>6.1</td>
<td>15 – 200 mg/l</td>
<td>1.9 (CI 0.8 - 4.9)</td>
</tr>
<tr>
<td>MacLeod et al (1995)</td>
<td>Hospital England</td>
<td>306</td>
<td>Timed overnight</td>
<td>8.0</td>
<td>&gt;10.5 µg/min</td>
<td>2.2 (CI 1.3 - 3.7)</td>
</tr>
<tr>
<td>Patrick et al (1990)</td>
<td>Hospital Scotland</td>
<td>149</td>
<td>Early morning</td>
<td>1</td>
<td>Albumin creatinine ratio &gt;2.5</td>
<td>2.8 (CI 0.8 - 10.0)</td>
</tr>
</tbody>
</table>
We found four relevant studies in addition to those included in Dinneen and Gerstein’s (1997) systematic review (Gall et al 1995, Beilin et al 1996, Wirta et al 1997, Mattock et al 1998). Three were likely to have been published too late to be included in the review (Beilin et al 1996, Wirta et al 1997, Mattock et al 1998). These studies are summarised in Table 7.

Three of the studies measured the effect of microalbuminuria on cardiovascular mortality (Beilin et al 1996, Wirta et al 1997, Mattock et al 1998) and in one of these studies, microalbuminuria was a significant risk factor for cardiovascular events (Beilin et al 1996). These additional studies support the conclusions of the review by Dinneen and Gerstein (1997) that microalbuminuria is a significant factor in all cause mortality and death as a result of cardiovascular events.

Table 7: Cardiovascular mortality and morbidity predicted by microalbuminuria in patients with Type 2 diabetes (studies not included in Dinneen and Gerstein 1997 systematic review)

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting and Location</th>
<th>N ≥ Type of sample</th>
<th>Length of follow up (Years)</th>
<th>Definition of microalbuminuria</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wirta et al (1997)</td>
<td>Hospital &amp; primary health care centre Finland</td>
<td>150 newly diagnosed (ND) Type 2 and 146 with duration of 5 years (KD)</td>
<td>24-hour</td>
<td>&gt;30 &lt;300 mg/24h</td>
<td>Microalbuminuria non significant predictor of CM (no p value reported)</td>
</tr>
<tr>
<td>Beilin et al (1996)</td>
<td>Hospital Australia outpatients</td>
<td>666 Type 2 diabetes (no details on selection process)</td>
<td>Early morning</td>
<td>30-300 mg/l</td>
<td>Adjusted risk ratio for elevated albumin (30 - 300 mg/l) (including age, sex and other cardiovascular risk factors) was 2.34 (1.38, 3.99) (p=0.002) for cardiovascular disease mortality and 1.78 (0.97, 3.26) (p=0.06) for coronary heart disease mortality</td>
</tr>
<tr>
<td>Mattock et al (1998)</td>
<td>Diabetes clinic England</td>
<td>146</td>
<td>Overnight</td>
<td>20-200 µg/min</td>
<td>Relative risk of coronary heart disease mortality = 1.83 (95% CI 0.56-6.04), after adjustment for other factors (not significant)</td>
</tr>
</tbody>
</table>

Proteinuria

Mortality/morbidity – all causes

We found four studies that examined the influence of proteinuria on outcomes in people with Type 2 diabetes (Schmitz and Vaeth 1988, Gall et al 1995, Beilin et al 1996, Miettinen et al 1996). These studies and their results are summarised in Tables 8 and 9.

Three of the studies were hospital based (Schmitz and Vaeth 1988, Beilin et al 1996, Gall et al 1995) whilst the fourth was a population based study (Miettinen et al 1996). In three studies, definition of proteinuria was defined using early morning samples (Schmitz and Vaeth 1988, Beilin et al 1996, Miettinen et al 1996) although the thresholds for defining proteinuria were different. Follow up was for seven years in three studies (Schmitz and Vaeth 1988, Beilin et al 1996, Miettinen et al 1996) and five years in Gall et al (1995).
Schmitz and Vaeth (1988) found that having proteinuria gave a patient a relative risk of all cause death of 1.8, whilst Beilin et al report an adjusted risk ratio of 3.58 (95% CI 2.19, 5.88) compared to someone with normal albumin levels (Table 8).

Table 8: Total mortality predicted by proteinuria in patients with Type 2 diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting and Location</th>
<th>N=</th>
<th>Type of sample</th>
<th>Length of follow up (Years)</th>
<th>Proteinuria definition</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmitz &amp; Vaeth (1988)</td>
<td>Hospital Denmark</td>
<td>503</td>
<td>Early morning</td>
<td>10</td>
<td>&gt;200 mg/l</td>
<td>Relative risk of mortality compared with albumin level less than 15 mg/l =1.8</td>
</tr>
<tr>
<td>Beilin et al (1996)</td>
<td>Hospital Australia outpatients</td>
<td>666</td>
<td>Type 2 diabetes</td>
<td>Early morning</td>
<td>30 - 300 mg/l</td>
<td>Adjusted risk ratio for all cause mortality = 3.58 (CI 2.19 - 5.88) (p&lt;0.001) compared with albumin level ≤300 mg/24 hour</td>
</tr>
</tbody>
</table>

Mortality/morbidity – cardiovascular causes

In Miettinen et al (1996), Gall et al (1995) and Beilin et al (1996) proteinuria was a significant independent factor in causing cardiovascular mortality (Table 9).

Table 9: Cardiovascular mortality and morbidity predicted by proteinuria in patients with Type 2 diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting and Location</th>
<th>N=</th>
<th>Type of sample</th>
<th>Length of follow up (Years)</th>
<th>Proteinuria definition</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miettinen et al (1996)</td>
<td>Population based Finland</td>
<td>1056</td>
<td>Early morning</td>
<td>7</td>
<td>150-300 mg/l</td>
<td>Significantly increased risk of mortality (p&lt;0.0013)</td>
</tr>
<tr>
<td>Miettinen et al (1996)</td>
<td>Population based Finland</td>
<td>1056</td>
<td>Early morning</td>
<td>7</td>
<td>&gt;300 mg/l</td>
<td>Significant increased risk of mortality (p&lt;0.001)</td>
</tr>
<tr>
<td>Gall et al (1995)</td>
<td>Hospital Denmark</td>
<td>328</td>
<td>24-hour</td>
<td>5</td>
<td>&gt;300 mg/24h</td>
<td>Proteinuria associated with increased relative risk of 2.5 for CVD mortality</td>
</tr>
<tr>
<td>Beilin et al (1996)</td>
<td>Hospital Australia outpatients</td>
<td>666</td>
<td>Type 2 diabetes</td>
<td>Early morning</td>
<td>&gt;300 mg/l</td>
<td>Adjusted risk ratio for cardiovascular mortality 3.17 (CI 1.54 - 6.53) (p&lt;0.05) and coronary heart death 2.06 (CI 0.87 - 4.86) compared with albumin level ≤300 mg/24 hour</td>
</tr>
</tbody>
</table>

Wang et al (1996) reported on the WHO Study of Vascular Disease in Diabetes. This was a 12 year follow up of 4,714 people with Type 1 or Type 2 diabetes from 10 centres around the world. Mortality rates were calculated for the sample and compared with known statistics for the population without diabetes in each centre (background population). Presence of proteinuria meant that a woman had an eight fold risk of mortality, while a man had a five fold risk of mortality compared to people with diabetes who did not have proteinuria.
References: natural history of renal disease
(with AHCPR evidence grades where appropriate, see page 18)

Progression of renal disease due to Type 2 diabetes


Mortality in renal disease due to Type 2 diabetes


Microalbuminuria: morbidity and mortality

Mogensen (1999)

Proteinuria: morbidity and mortality

III Miettinen et al (1996)
5. Risk factors for renal disease in Type 2 diabetes
Risk factors for renal disease in Type 2 diabetes

Recommendations

Measure, assess and treat aggressively cardiovascular risk factors in people with Type 2 diabetes who have microalbuminuria or proteinuria (ie those who have higher risk albumin excretion). (A)

For those people with higher risk urine albumin excretion:

- maintain blood pressure at or below 135/75 mm/Hg. (A)
- ensure good blood glucose control (HbA1c below 6.5% to 7.5%, according to the individual’s target). (A)

For those people with lower risk urine albumin excretion:

- maintain good blood pressure control (at or below 140/80mm/Hg). (A)
- maintain good blood glucose control (HbA1c below 6.5% to 7.5%, according to the individual’s target). (A)

<table>
<thead>
<tr>
<th>Definition of higher risk urine albumin excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>microalbuminuria – albumin : creatinine ratio greater than or equal to 2.5 mg/mmol (men)/greater than or equal to 3.5 mg/mmol (women) or albumin concentration greater than or equal to 20 mg/l</td>
</tr>
<tr>
<td>proteinuria – albumin : creatinine ratio greater than or equal to 30 mg/mmol or albumin concentration greater than or equal to 200 mg/l</td>
</tr>
</tbody>
</table>

Evidence statement

Risk factors for the development of microalbuminuria and proteinuria are:

- hyperglycaemia (III)
- raised blood pressure (III)
- baseline albumin excretion rate (III)

Other factors that were not strongly associated with the development of microalbuminuria and proteinuria are:

- smoking (III)
- raised serum total, LDL, cholesterol, serum triglycerides, low HDL cholesterol (III)
- higher body mass index (III)
- increased age (III)
- male sex (III)
- presence of retinopathy (III)
- raised serum homocysteine (III)
family history of diabetic renal disease (III)
race (III)

There is insufficient evidence to allow grading of individual risk factors or to attribute comparative levels of risk to individual risk factors. (III)

Reduction of blood pressure to <135/75 mm/Hg reduces the rate of progression of renal disease. (Ib)

In the UKPDS, interventions to reduce mean blood pressure from 154/87 to 144/82 mmHg were associated with a reduction in absolute risk of developing nephropathy by 8% over 6 years. (Ib)

In the UKPDS, interventions to reduce mean haemoglobin A1c from 7.9 to 7.0% were associated with an absolute risk reduction of developing nephropathy of 11% over 12 years. (Ib)

Evidence reviewed in the national Type 2 diabetes guidelines on blood pressure management and on blood glucose management, together with the British Hypertension Society guideline on the management of hypertension, all support the recommendations above.
Introduction: risk factors for renal disease in Type 2 diabetes

Studies were examined that were longitudinal in design rather than cross sectional. Longitudinal studies are better than cross sectional studies in establishing whether an outcome of interest is caused by particular risk factors under study, as they involve data collected prospectively over various time periods. Cross sectional studies, which collect data at a single point in time, can only establish an association, at a particular point in time, between the outcome and factors under investigation. Where there are only cross sectional data available on a particular risk factor or risk factors then this study design was included in the review as the next best evidence to answer the review questions.

Longitudinal studies of risk were included on the following basis: they were prospective in design; included patients with Type 2 diabetes; had clear inclusion and exclusion criteria for patients; the outcomes (development of renal disease) were clearly defined. Cross sectional studies were included on the following basis: they included patients with Type 2 diabetes; had clear inclusion and exclusion criteria for patients; the outcomes (development of renal disease) were clearly defined.

From the literature search a number of potential risk factors were identified. A variety of potential risk factors were assessed in studies of longitudinal design. These were:

- blood glucose levels
- blood pressure levels
- smoking
- lipids
- body mass index
- age
- sex
- baseline albumin excretion
- duration of diabetes
- retinopathy

Three other risk factors:

- homocysteine
- family history
- race

were covered only by studies cross sectional in design.
Evidence summary

Blood glucose

In Niskanen et al (1996) 133 people with newly diagnosed Type 2 diabetes were randomly selected from the population register of an area in Eastern Finland. The cohort was examined at recruitment (baseline exam) and then twice more, after five years and 10 years (n=88, 36 deaths, 9 missing data). The patients were assessed for microalbuminuria (defined as urine albumin excretion rate of ≥30 mg/day or ≥20 µg/min) at each examination. Haemoglobin A1c (HbA1c) levels were significantly predictive of microalbuminuria at 10 years (p=0.003), as was fasting plasma glucose (p=0.009), after adjustment for age, insulin and blood pressure.

Mattock et al (1998) found, after age adjustment, that fasting plasma glucose levels were significantly associated (p<0.05) with the development of microalbuminuria in 29 of 100 Caucasian patients, who attended a diabetes clinic in London in a single year, (adjusted odds ration 2.27, 95% CI 1.33 – 3.88). Microalbuminuria was defined as ≥20 – 200 µg/min albumin excretion rate in an overnight urine sample, on at least two occasions at either of the two follow up examinations (three and seven years after baseline).

Klein et al (1995) examined the 10 year incidence of proteinuria in a population based cohort in the United States. A total of 1,370 patients with older onset diabetes (674 on insulin, 696 not on insulin) were examined at entry into the study and then followed up on two further occasions (at four years n=987; at ten years n=533). In people with older onset diabetes treated with insulin at 10 year follow up, the incidence of gross proteinuria (albumin concentration measured by reagent strip ≥0.3 g/l) was significantly higher (odds ratio = 1.20, 95% CI 1.02 - 1.42) in those with higher glycosylated haemoglobin level. In those with older onset diabetes not on insulin, a glycosylated haemoglobin level ≥8.7% (odds ratio 2.17, 95% CI 1.30 – 3.61) was significantly associated with higher incidence of gross proteinuria at 10 years.

A second large prospective study of 574 patients followed up for a mean of 7.8 (standard deviation 0.9) years has been carried out in Israel (Ravid et al 1998). Multiple regression analysis identified HbA1c as one of three determinants of the subsequent decline in renal function. The risk for microalbuminuria was also predicted by the initial values of HbA1c, among others.

In 46 patients with Type 2 diabetes who had been monitored every two months for a mean of 4.5 years (range 3 - 6) at a diabetes clinic in South Korea, HbA1c was found to be a significant predictor (odds ratio = 2.03, 95% CI 1.17 - 4.16, p=0.023) for development of overt proteinuria, after adjustment for various factors (Song et al 1998).

Of two Japanese studies, one found that in Type 2 patients followed for six years, those patients developing microalbuminuria (albumin excretion rate ≥20 µg/min), had significantly higher blood glucose levels than those who remained normoalbuminuric (p<0.01). The relative mean level of blood glucose over the six years was 8.1 mmol/l ± SD 0.9 in the subset remaining normoalbuminuric and 9.0 mmol/l ± 0.9 in the subset developing microalbuminuria (Tanaka et al 1998). However, the second Japanese study, evaluating 1196 patients from a medical centre in Japan for a mean period of 10 years, found that fasting plasma glucose did not significantly (at the p<0.05 level) predict the development of Albustix positive albuminuria, after adjustment for sex, age, duration of diabetes, systolic blood pressure, obesity, diabetic retinopathy and insulin. All the patients had Type 2 diabetes and were free from Albustix positive albuminuria at baseline (Sasaki et al 1989).
In the United Kingdom Prospective Diabetes Study (UKPDS (33) 1998a) 3867 people with newly diagnosed Type 2 diabetes were randomised to either conventional blood glucose control or intensive blood glucose control. After nine years of follow up, a significantly greater percentage of people in the conventional treatment group had progressed to microalbuminuria (p=0.0006) and to proteinuria (p=0.03), compared to the intensive group. Over 10 years, the haemoglobin A1c (HbA1c) levels were 7.0% in the intensive treatment group and 7.9% in the conventional group. Microalbuminuria in this study was defined as urinary albumin concentration >50 mg/l, due to storage of samples at -20°C. Proteinuria was defined as an albumin concentration >300 mg/l.

Schmitz et al (1994) assessed the relationship between haemoglobin A1c (HbA1c) and the progression of albuminuria over four years, in 178 people with Type 2 diabetes. Progression was defined as a movement from normoalbuminuria (urinary albumin concentration \( \leq 15 \text{ mg/l} \)) to microalbuminuria \((>15 \text{ mg/l} - \leq 200 \text{ mg/l} \) urinary albumin concentration\) and from microalbuminuria to proteinuria (urinary albumin concentration \(>200 \text{ mg/l}\)). Progression was also defined as a 20% increase in urinary albumin concentration over the follow up period. Progressors had poorer glycaemic control (HbA1c \(8.2\% \pm 1.5\) vs \(7.7\% \pm 1.3\), p<0.05) compared with non progressors. However a multiple regression analysis in patients with at least four years and (complete) 6 years of follow-up found that HbA1c was not a significant predictor of rate of increase in albuminuria.

In Beilin et al (1996), 666 patients with Type 2 diabetes were followed for several years, in a hospital diabetes clinic in Australia. Glycated haemoglobin was significantly associated with urine albumin levels \(>30 \text{ mg/l}\) (p= 0.0001) after adjustments for other risk factors (adjusted odds ratio = 1.242).

Finally, Gall et al (1997) followed 176 people with Type 2 diabetes and normal albumin excretion rates (AER <30 mg/24h) for 6 years. A 1% difference in mean HbA1c meant a patient had a relative risk of developing microalbuminuria (AER = 30 – 299 mg/24h) or proteinuria (AER >300 mg/24h) of 1.2 (95%CI: 1.1 - 1.4). This was significant at the p<0.05 level.

Conversely, four studies did not identify blood glucose as a risk factor for renal disease (Sasaki 1989, John et al 1994, Wirta et al 1996b, Biesenbach et al 1997). Wirta et al (1996b) observed the mean blood glucose of 150 people with recently diagnosed Type 2 diabetes. The patients were drawn from a diabetes clinic in Finland and were followed for six years. The link between blood glucose and progression of urine albumin excretion rate (AER) was measured. Progression of AER was defined as the development of microalbuminuria (AER = 30 – 300 mg/24h) from normoalbuminuria at baseline, or development of proteinuria (AER >300 mg/24h) from microalbuminuria at baseline. Mean blood glucose was not found to significantly influence the progression of AER (at the p<0.05 level of significance). In a prospective follow-up study of 37 Type 2 patients, HbA1c was not associated with a decrease in the rate of creatinine clearance after adjustment for 4 other independent factors (Biesenbach et al 1997). Blood glucose was not found to be a predictor of albuminuria progression, after adjustment for other factors in patients with Type 2 diabetes in India (John et al 1994). The authors followed up a cohort of 481 Type 2 patients prospectively for 5 years. Progression of albuminuria was defined as development of microalbuminuria (>20 \(\mu\)g/min - \(\leq 200 \mu g/\text{min}\)) and proteinuria (>200 \(\mu g/\text{min}\)) and a significant increase in albuminuria within the microalbuminuric range.

**Summary**

There is a close association between the level of HbA1c and progression of albuminuria.
Blood pressure

Schmitz et al (1994) measured systolic and diastolic blood pressure in 278 people with Type 2 diabetes, from a clinic in Denmark. The influence of these two variables on progression of renal disease was measured. Progression was defined as a movement from normoalbuminuria (urinary albumin concentration $\leq 15$ mg/l) to microalbuminuria (urinary albumin concentration ($>15$ mg/l to $\leq 200$ mg/l) and from microalbuminuria to proteinuria (urinary albumin concentration $>200$ mg/l). Progression was also defined as a 20% increase in urinary albumin concentration over the follow up period. Systolic blood pressure was a significant predictor of rate of increase in albuminuria in 178 patients followed up after four years ($p=0.012$), and 135 patients followed-up for 6 years ($p=0.009$), in both cases after adjustment for average UAE, sex, age, BMI, plasma glucose, HbA$_1c$, diastolic blood pressure and baseline albuminuria.

In Beilin et al (1996) 666 people with Type 2 diabetes were followed for seven years in a hospital diabetes clinic in Australia. A significant association of systolic blood pressure with urine albumin $>30$ mg/l ($p=0.001$) was found after adjustment for other risk factors, and no association for diastolic blood pressure.

The UKPDS (UKPDS (10) 1993) found an association, after adjustment for age, between systolic blood pressure ($p<0.0001$) and urine albumin excretion in 585 patients followed from 3 months to 3 years.

In Nielsen et al (1995) 24 hour ambulatory blood pressure (systolic and diastolic) was measured at baseline (n=32) and then after a mean period of 4.6 years, (n=23) in people with Type 2 diabetes from a hospital clinic in Denmark. At the same time, urine albumin excretion rate was calculated from the mean of two 24 hour urine collections of the 23 patients followed up. Eleven patients had normoalbuminuria (albumin excretion rate $<15$ µg/min) and twelve patients had microalbuminuria (albumin excretion rate $= 15 – 200$ µg/min) at baseline. The nine patients lost to follow-up had similar baseline UAE values to those followed up. Annual progression in UAE was significantly determined by increases in systolic ($p<0.008$) and diastolic ($p<0.033$) 24 hour ambulatory blood pressure after adjustment for other independent variables. Furthermore, albuminuria increased significantly in patients taking no or a stable dose of antihypertensive therapy (n=9) compared with that in those who initiated or increased antihypertensive therapy during the follow-up (n=13) ($p=0.02$), $[1.144 (95\% CI 0.999 - 1.310)$ ratio/year versus $0.938 (95\% CI 0.839 - 1.048)$ ratio/year].

Biesenbach et al (1997) found a significant association between mean systolic blood pressure and rate of decrease of creatinine clearance ($p=0.02$) in 36 patients with Type 2 diabetes after adjustment for other potential confounders. The patients were followed up for a mean time of 61 months (SD $\pm$ 21 months) and all had persistent proteinuria ($>0.5$ g protein in 24 hour urine) due to diabetic nephropathy at recruitment, but near normal creatinine clearance ($>70$ ml/min/1.73 m$^2$).

In a study of 574 people with Type 2 diabetes of less than five years duration (mean duration $1.92 \pm 1.2$ years), initially normotensive and with normal UAE, mean blood pressure at baseline was found to be a significant ($p<0.05$) determinant for the development of microalbuminuria (albumin excretion rate $\geq 30 – 300$ mg/24h) and for duration to development of microalbuminuria after adjustment for other risk factors. The participants were drawn from a diabetes clinic in Israel and were followed for a mean of seven years (range 2 - 9 years) (Ravid et al 1998a).

Tanaka et al (1998) studied 123 Japanese patients with Type 2 diabetes for six years. Patients were matched for age and duration of diabetes, and recruited from an outpatient clinic. At baseline 74 were
normoalbuminuric (albumin excretion rate <20 µg/min) and 49 had microalbuminuria (albumin excretion rate ≥20 µg/min - <200 µg/min). The association of blood pressure with development of microalbuminuria and progression to proteinuria (albumin excretion rate>200 µg/min) was measured. Mean diastolic and systolic blood pressures were significantly higher in those who progressed from microalbuminuria to proteinuria both at baseline and at six year follow-up.

Table 10: Relationship of blood pressure to urinary albumin excretion (Tanaka et al 1998)

<table>
<thead>
<tr>
<th></th>
<th>Baseline blood pressure mm Hg</th>
<th>Follow-up blood pressure mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>Progressed from microalbuminuria to proteinuria</td>
<td>154±10</td>
<td>88±4</td>
</tr>
<tr>
<td>Remained microalbuminuric</td>
<td>136±14</td>
<td>77±7</td>
</tr>
<tr>
<td>Progressed from normoalbuminuria to microalbuminuria</td>
<td>137±14</td>
<td>76±7</td>
</tr>
</tbody>
</table>

A geographically close study was reported from South Korea (Song et al 1998). The authors found that mean systolic blood pressure was a significant predictor (odds ratio = 1.95, 95% CI 1.09 - 3.97, p=0.038) for development of overt proteinuria (UAE>200 µg/min on two consecutive occasions). Forty-six patients were monitored for a mean of 4.5 years (range 3 - 6).

Klein et al (1995) assessed the influence of a baseline blood pressure measurement upon the incidence of proteinuria after 10 years, in people with older onset diabetes. The participants were assessed separately according to whether they were on insulin therapy or not. In the group who were not taking insulin, a baseline systolic blood pressure reading of ≥146 mmHg was significantly associated (odds ratio = 2.47, 95% CI 1.49 - 4.09; p<0.05) with the development of proteinuria (defined as albumin concentration ≥0.3 g/l measured by reagent strip). Baseline blood pressure was not significantly associated with the development of proteinuria in people with older onset diabetes who were on insulin therapy. Although seven studies found an association between blood pressure and renal disease, a further six, looking at the same issue, found no significant association between the two.

Sasaki et al (1989) evaluated 1196 patients from a medical centre in Japan for a mean period of 10 years. All the patients had Type 2 diabetes and were free from Albustix positive albuminuria at baseline. Systolic but not diastolic blood pressure was found to significantly predict the development of Albustix positive albuminuria (p<0.01).

Niskanen et al (1996) followed up 133 newly diagnosed people with Type 2 diabetes for 10 years. They failed to find a significant association at the level of significance (p<0.05) between either systolic blood pressure or diastolic blood pressure, and the development of microalbuminuria (albumin excretion rate >30 – 300 mg/24h) or proteinuria (>300 mg/24h).

Wirta et al 1996 reported that mean baseline arterial blood pressure was not a significant predictor of progression of urine albumin excretion rate at follow-up in those patients with Type 2 diabetes.
who were normoalbuminuric at baseline or of proteinuria in those patients either normo or microalbuminuric at baseline (109 subjects were followed up for 6 years).

Gall et al (1997) also found that neither systolic or diastolic blood pressure significantly predicted the development of microalbuminuria (AER = 30 – 299 mg/24h) or proteinuria (AER >300 mg/24h). In this study 176 normoalbuminuric white patients with Type 2 diabetes, from a hospital in Denmark, were followed for a median of 5.8 years.

Mattock et al (1998) examined the predictive influence of diastolic and systolic blood pressure upon the development of microalbuminuria (defined as an albumin excretion rate ≥20 µg/min) in 100 people with Type 2 diabetes, who had normal albumin excretion rates at baseline. The patients were drawn from a diabetes clinic in London and were followed for a minimum of three years and a maximum of seven years. Neither systolic (odds ratio 1.33, CI 0.80 - 2.21) nor diastolic (odds ratio 1.25, CI 0.81 - 1.95) blood pressure were found to be a significant factor (at the p<0.05 level) in the development of microalbuminuria.

Finally in a prospective first year study of 481 people with Type 2 diabetes, blood pressure was not found to be a predictor of albuminuria progression, after adjustment for other factors (John et al 1994).

Summary

Overall, the larger, better designed studies found that progression to microalbuminuria and proteinuria was associated with higher levels of systolic blood pressure. Fewer studies also found an association with higher levels of diastolic blood pressure.

Smoking

In the study by Mattock et al (1998) all patients with Type 2 diabetes attending a diabetes clinic in London in a single year were followed for a minimum of three years and a maximum of seven years. One hundred and forty six patients were eligible for inclusion (no evidence of haematuria, urinary tract infection or clinical albuminuria). Thirty seven patients with microalbuminuria at the baseline examination were then excluded, as the authors were examining influence of smoking upon the development of microalbuminuria (defined as an albumin excretion rate of ≥20 µg/min in an overnight urine sample). A further nine patients did not attend any of the follow up examinations after three and seven years. Thus follow up data was available for 100 people, either at three years or at seven years. These people were classified as either current smokers or non smokers. Development of microalbuminuria was significantly higher (p<0.05) in the current smoker group, with an odds ratio of 3.72 (95% CI: 1.23 - 11.3), after adjustment for age and sex.

Smoking was also a significant factor in a different prospective follow up study. Over 700 people with older onset diabetes, who were free of complications at baseline, were re-examined after 10 years to measure the incidence of proteinuria and the contributing factors (Klein et al 1995). In this study the number of pack years was calculated for each of the participants (n=794 at 10 year follow up). Pack years were defined as the number of cigarettes smoked per day, divided by 20, multiplied by the number of years the patient had smoked. Development of proteinuria was defined as an albumin concentration of ≥0.3 g/l measured by reagent strip. The participants were divided into those on insulin therapy (n=376) and those not on insulin therapy (n=418). In both the insulin group (odds ratio = 1.11; 95% CI: 1.02 - 1.21) and non insulin group (odds ratio = 2.39; 95% CI: 1.32 - 4.32), greater total pack years smoked was significantly associated with greater risk of developing proteinuria (p<0.05), after adjustment for other risk factors.
Biesenbach et al (1997) evaluated the influence of smoking on the rate of creatinine clearance in 36 people with Type 2 diabetes (16 smokers). The patients had persistent proteinuria (>0.5 g protein in 24h urine) but near normal creatinine clearance (>7.0 ml/min/1.73m²). Taking into account other potential confounding factors such as blood glucose, blood pressure, serum lipids and proteinuria, smoking was significantly associated with the rate of decrease of the creatinine clearance (1.24 compared with 0.99 ml/min/month; p=0.01).

However, Niskanen et al (1996) did not find an effect for baseline smoking and the subsequent development of microalbuminuria, in their follow up study. In this study one hundred and thirty three people with newly diagnosed diabetes were followed for 10 years.

Likewise, whether someone was a smoker or not at study entry did not significantly (at the p<0.05 level of significance) predict development of microalbuminuria or proteinuria, in a six year follow up study of people recently diagnosed with Type 2 diabetes by Wirta et al (1996b). Similarly, in a six year follow up study of 176 people with Type 2 diabetes, Gall et al (1997) did not find a positive history of smoking to be significantly predictive in the development of microalbuminuria (AER = 30 – 299 mg/24h) or proteinuria (AER >300 mg/24h). Finally, Sasaki et al (1989) followed 1196 patients from a medical centre in Japan for a mean period of 10 years. All the patients had Type 2 diabetes and were free from Albustix positive albuminuria at baseline. Smoking was not found to significantly predict the development of Albustix positive albuminuria.

Summary

Evidence that smoking is a predictive factor on the development of microalbuminuria is equivocal (although it is associated with microvascular disease in Type 2 diabetes).

Lipids

Gall et al (1997) followed 176 people with Type 2 diabetes with normal albumin excretion rates (AER <30 mg/24h) for approximately 6 years (range 1.5 - 6 years, median 5.8 years). A 1% higher mean serum cholesterol level meant a patient had a relative risk of developing microalbuminuria (AER = 30 – 299 mg/24h) or proteinuria (AER >300 mg/24h) of 1.4 (95%CI: 1.1 - 1.7, p<0.01), after adjustment for other risk factors.

The Beilin et al (1996) study of 666 people with Type 2 diabetes followed people for seven years in a hospital diabetes clinic in Australia. A significant association of log triglyceride with urine albumin levels >30 mg/l was found (p=0.0001) after adjustment for other risk factors. No association was found with HDL or total cholesterol.

Ravid et al (1998a) collected follow up data on 574 people with Type 2 diabetes. The participants were drawn from a diabetes clinic in Israel and were followed for between two and nine years (mean 7.8 ± 0.9). Baseline total cholesterol ≥5.25 mmol/l, high density lipoprotein levels (HDL) <1.14 mmol/l and low density lipoprotein (LDL) ≥3.21 mmol/l were significant determinants of microalbuminuria (albumin excretion rate ≥30 – 300 mg/24h) in univariate analyses (all p<0.001) with odds ratio = 20.59 (CI 12.67 - 33.45) for cholesterol, 7.76 (CI 5.17 - 11.64) for HDL and 6.24 (CI 4.8 - 13.35) for LDL. After inclusion in a multiple logistic regression model, total cholesterol was a major determinant of the subsequent decline in renal function. The degree of albuminuria was also influenced by HDL values and the risk of microalbuminuria was predicted by initial values of total cholesterol and HDL. Duration to development of microalbuminuria was mainly determined by HDL and two other factors (mean blood pressure and body mass index).
The UKPDS (UKPDS (10)) found an association, after adjustment for age, between urine albumin excretion and fasting plasma triglyceride (p<0.0001) and fasting plasma LDL cholesterol (p<0.05) in 585 patients followed from three months to three years. Patients were initially treated by diet therapy but within three years 65% had been allocated to other therapies.

However Mattock et al (1998) measured serum cholesterol and triglycerides in 100 Caucasian patients with Type 2 diabetes at baseline, and then again after three years and seven years. After accounting for other potential risk variables (blood glucose, smoking, blood pressure and urine albumin excretion rate) serum cholesterol or triglycerides did not attain significant levels of effect (at the p<0.05 level of significance), in determining the development of microalbuminuria in 29 of the 100 patients.

Wirta et al (1996b) recruited 150 people recently diagnosed with Type 2 diabetes. Serum cholesterol was measured at baseline, along with urine albumin excretion rate. Microalbuminuria was defined as an albumin excretion rate of 30 – 300 mg/24h and proteinuria as an albumin excretion rate of >300 mg/24h. The influence of serum cholesterol upon progression of disease was measured over the follow up period of six years. Progression was defined as microalbuminuria at the end of the study in someone who was normoalbuminuric at baseline, and proteinuria at follow up in someone who was either normoalbuminuric or microalbuminuric at baseline. There was no significant association (at the p<0.05 level of significance) between serum cholesterol and progression of albumin excretion rate in the study.

**Summary**

The majority of studies found an association between abnormal lipid profile and increased urine albumin excretion.

**Plasma insulin**

In a population-based study, (Niskanen et al 1996) measured fasting plasma insulin in 133 people with newly diagnosed with Type 2 diabetes. The patients were resurveyed at five and ten year follow-up. In a multiple regression model, fasting insulin was not an explanatory variable for ten year urine albumin excretion (p=0.07).

One small study also reported no association. Biesenbach et al (1997) found no association between serum lipids and rate of decrease in creatinine clearance in 36 patients with Type 2 diabetes after adjustment for other confounding factors (p≥0.05).

**Body mass index**

Ravid et al (1998a) measured the body mass index (BMI) and albumin excretion rate every six months for a mean period of 7.8 years in a cohort of 574 patients who were initially free of abnormal urine albumin levels (albumin excretion rate<30 mg/24hr). In univariate analysis, higher BMI at baseline was found to be significantly predictive of microalbuminuria over the course of the study (p<0.001). After adjustment for other risk factors, the degree of albuminuria, duration to the development of microalbuminuria, and risk for microalbuminuria were all determined by BMI alongside some other variables. However this was the only study to report a significant association between BMI and renal disease; although a subgroup analysis of Schmitz et al (1994) also found an association.
Schmitz et al (1994) followed 278 people with Type 2 diabetes from a clinic in Denmark to assess the influence of BMI on progression of renal disease. Progression was defined as a movement from normoalbuminuria (urinary albumin concentration $\leq 15 \mu g/ml$) to microalbuminuria ($\geq 15$ mg/l urinary albumin concentration $\leq 200$ mg/l) and from microalbuminuria to proteinuria (urinary albumin concentration $>200$ mg/l). Progression was also defined as a 20% increase in urinary albumin concentration over the follow up period. Body mass index was not significantly correlated with progression of albuminuria in 172 patients followed up after four years ($p=0.09$), but was for 135 with six years of data ($p=0.015$), after adjustment for diastolic and systolic blood pressure, plasma glucose, HbA$_1C$, age, sex and baseline albuminuria.

In Niskanen et al (1996) the baseline BMI was measured for 133 people with newly diagnosed Type 2 diabetes. This baseline BMI was not significantly different (at the $p<0.05$ level of significance) in people who developed microalbuminuria (albumin excretion rate $>30$ mg/24h) after 10 years, compared to those who remained normoalbuminuric.

Wirta et al (1996b) did not find a significant effect for BMI at baseline for subsequent development of microalbuminuria (defined as an albumin excretion rate of $30 - 300$ mg/24h) or proteinuria (defined as an albumin excretion rate of $>300$ mg/24h).

Gall et al (1997) assessed BMI at baseline in 176 people with Type 2 diabetes, who were initially free of abnormal albumin excretion rate (AER<$30$ mg/24h). There was no significant (at the $p<0.05$ level) relationship between baseline BMI and development of microalbuminuria (AER = $30 - 299$ mg/24h) or proteinuria (AER $>300$ mg/24h).

**Summary**

The evidence of an association between basal BMI and increased albumin excretion is equivocal.

**Age**

Ravid et al (1998a) examined 574 people with Type 2 diabetes who were initially free of abnormal albumin (albumin concentration $<0.3$ mg/24h), for a mean period of 7.8 ($\pm$ 0.9) years. The study found that, after adjustment for other variables, older age was significantly associated with the degree of albuminuria ($>300$ mg/24h) in this population, drawn from a diabetes clinic in Israel ($p<0.001$).

Gall et al (1997) followed 176 people with Type 2 diabetes with normal albumin excretion rates ($<30$ mg/24h) for nearly six years. For an increase in age by one year a patient had a relative risk of developing microalbuminuria (AER $= 30 - 299$ mg/24h) or proteinuria (AER $\geq 300$ mg/24h) of 1.07 (95% CI: 1.02 - 1.12, $p<0.01$), after adjustment for other risk factors.

Sasaki et al (1989) evaluated 1196 patients from a medical centre in Japan for a mean follow-up period of 10 years. All the patients had Type 2 diabetes and were free from Albustix positive albuminuria at baseline. Age at entry into the study was found to significantly predict the development of Albustix positive albuminuria ($p<0.01$), after adjustment for other risk factors.

Davis et al (1997) used the UKPDS data to see if age at diagnosis of Type 2 diabetes affected diabetic tissue damage during the first six years of diabetes. Urinary microalbuminuria and creatinine concentrations were measured after six years. Microalbuminuria was taken as a urine creatinine regression-corrected concentration of $>50$ mg/l. From 5102 newly diagnosed Type 2 (NIDDM) patients, the patients included in the analysis were 3027 white patients aged between 35 and 65 years with data available over 6 years. Patients were divided by age at entry into five
consecutive age groups (36 - 41, 42 - 47, 48 - 53, 54 - 59 and 60 - 65 years). Age at diagnosis was not a significant marker for development of microalbuminuria at the six year follow up (p=0.09) or for initial prevalence of microalbuminuria at baseline (p=0.41).

In Wirta et al (1996b) age at baseline was investigated as a predictor of progression to microalbuminuria (albumin excretion rate >30 mg/24h) and proteinuria (albumin excretion rate >300 mg/24h). The relationship between age at baseline and progression to either microalbuminuria or proteinuria was not statistically significant.

Niskanen et al (1996) also found that age at baseline did not predict development of microalbuminuria (albumin excretion rate >30 mg – 300 mg/24h) in 133 people with newly diagnosed diabetes.

Schmitz et al (1994) followed 178 people with Type 2 diabetes for four years. The cohort was selected from an outpatient clinic in Denmark. Age was not found to correlate with progression of albuminuria after adjustment for other independent factors. Progression was defined as a movement from normoalbuminuria (urinary albumin concentration \( \leq \) 15 mg/l) to microalbuminuria (urinary albumin concentration >15 mg/l to \( \leq \) 200 mg/l) and from microalbuminuria to proteinuria (>200 mg/l). Progression was also defined as a 20% increase in urinary albumin concentration over the follow up period.

Age was not a significant factor in the development of proteinuria after 10 years, in a cohort of people with Type 2 diabetes who were free of proteinuria at baseline (Klein et al 1995). Similarly age was not a predictor of albuminuria progression in 349 patients followed up for 5 years, after adjusting for other confounders (John et al 1994).

**Summary**

The evidence of an association between age and probability of proteinuria is conflicting, although the largest study found no association at 6 year follow-up.

**Sex**

In a study by Gall et al (1997), male sex conferred a relative risk for developing microalbuminuria (AER = 30 - 299 mg/24h) or proteinuria (AER \( \geq \)300 mg/24h) of 2.6 (95% CI: 1.2 - 5.4) compared with women (p=0.02).

Sasaki et al (1989) evaluated 1196 patients from a medical centre in Japan for a mean period of 10 years. All the patients had Type 2 diabetes and were free from Albustix positive albuminuria at baseline. Male sex was found to significantly predict the development of Albustix positive albuminuria (p<0.01), after adjustment for other risk factors.

Ravid et al (1998a) surveyed 574 people with Type 2 diabetes, drawn from a diabetes clinic in Israel. After a mean follow up period of 7.8 years they did not find sex to be a significant factor in the development of microalbuminuria (AER \( \geq \)30 – 300 mg/day) or proteinuria (AER >300 mg/day), after adjustment for other variables.

Sex was not a significant factor in the development of proteinuria after 10 years, in a cohort of people with Type 2 diabetes who were free of proteinuria at baseline (Klein et al 1995). This finding was confirmed in 172 people with Type 2 diabetes followed for four years in Schmitz et al (1994). Sex did not correlate with progression of albuminuria in this cohort selected from an outpatient clinic in Denmark.
Summary

The evidence is equivocal that male sex has an increased association with increased albumin excretion.

Baseline albumin excretion

Gall et al (1997) found that increased baseline log albumin excretion rate was significantly predictive of the development of microalbuminuria (AER = 30 – 299 mg/24h) or proteinuria (AER ≥300 mg/24h). In 176 patients with Type 2 diabetes a factor ten increase in AER produced a relative risk of developing microalbuminuria or proteinuria of 11.1 (95% CI: 3.4 - 35.9, p<0.0001), after adjustment for other risk factors.

John et al (1994) examined 481 consecutive Type 2 patients attending a diabetes clinic in a hospital in South India. The effect of baseline albumin excretion rate (AER) upon the progression of urine albumin excretion rate after five years was measured. Progression was defined as a movement from normoalbuminuria (AER ≤20 µg/min) to microalbuminuria (AER>20 – 200 µg/min) or from microalbuminuria to proteinuria (AER>200 µg/min). A factor three increase in AER within the microalbuminuric range was also classed as a progression within this range. Baseline AER was significantly associated with progression of albuminuria over the five years (p=0.001).

A UKPDS report followed 585 people with Type 2 diabetes and measured albumin concentration over three years. The change in albumin concentration over the three year period was significantly associated with albumin concentration measured at three months (rs+29, p<0.0001) (UKPDS (10) 1993).

A Japanese study (Tanaka et al 1998) of Type 2 patients found that those patients who developed microalbuminuria over the six year follow-up had higher urine albumin excretion rate levels at baseline. Baseline UAER for those who were normoalbuminuric at baseline and remained so over the 6 year follow up was 4.9 µg/min (range 2 - 19), whilst those who were normoalbuminuric at baseline but developed microalbuminuria over the 6 year follow up period had a baseline UAER of 9.5 µg/min (range 2 - 19) (p<0.01). Similarly those who had microalbuminuria at baseline and remained microalbuminuric over the 6 year follow up period had a baseline UAER of 50 µg/min (range 21 – 189), whilst those who were microalbuminuric but became proteinuric over the follow up period had a baseline UAER of 62 µg/min (range 22 – 182).

Mattock et al (1998) reported that the baseline albumin excretion rate was significantly associated with the development of microalbuminuria in their age and sex adjusted multivariate analysis (odds ratio = 1.84, CI 1.09 - 3.11) of 100 patients.

One small study of 46 patients with Type 2 diabetes in South Korea found , using multiple logistic regression analysis, no relationships (odds ratio = 1.67, CI 1.02 - 3.34, p=0.083) between baseline albumin excretion and development of overt proteinuria (UAЕ>200 µg/min on two consecutive occasions) (Song et al 1998). Patients were followed up for 4.5 years on average (range 3 - 6).

Summary

Baseline albumin excretion rate is positively associated with progression to increased albumin excretion (microalbuminuria and proteinuria).
Duration of diabetes

John et al (1994) examined 481 consecutive Type 2 patients attending a diabetes clinic in a hospital in South India. The effect of duration of diabetes upon progression of urine albumin excretion rate (AER) after five years was measured. Progression was defined as a movement from normoalbuminuria (AER ≤20 µg/min) to microalbuminuria (>20 – 200 µg/min) or from microalbuminuria to proteinuria (>200 µg/min). A factor three increase in AER within the microalbuminuric range was also classed as a progression within this range. Duration of diabetes was significantly associated with progression of albuminuria (p<0.01).

In a six year follow up study of 176 people in Denmark with Type 2 diabetes, Gall et al (1997) did not find duration of diabetes to be significantly predictive in the development of microalbuminuria (AER = 30 – 299 mg/24h) or proteinuria (AER ≥300 mg/24h). Similarly, Sasaki et al (1989) found, in a study of 1196 Japanese Type 2 patients, followed up for a mean of ten years, duration of diabetes to not be a significant risk factor related to the development of persistent albuminuria, after adjustment for seven other risk factors. A third study of 46 patients in South Korea also found no relationship (odds ratio = 1.46, CI 0.85 - 2.72, p=0.181) between duration of diabetes and overt proteinuria, after adjustment for other variables (Song et al 1998).

Summary

The evidence of a link between duration of diabetes and progression to albuminuria is equivocal.

Retinopathy

In Gall et al (1997) 176 patients with Type 2 diabetes from a Danish hospital were assessed for development of microalbuminuria (AER = 30 – 299 mg/24h) or proteinuria (AER ≥300 mg/24h). After a six year follow up, those who had retinopathy were significantly more likely to develop microalbuminuria or proteinuria (relative risk 2.4, 95% CI: 1.3 - 4.7, p<0.01), after adjustment for other risk factors.

Sasaki et al (1989) followed 1196 patients from a medical centre in Japan for a mean period of 10 years. All the patients had Type 2 diabetes and were free from Albustix positive albuminuria at baseline. Presence of retinopathy was found to significantly predict the development of Albustix positive albuminuria (p<0.01) after adjustment for other risk factors.

In Beilin et al(1996) 666 people with Type 2 diabetes were followed for seven years in a hospital diabetes clinic in Australia. There was no association with retinopathy and urinary albumin >30 ml after adjustment for other factors.

Summary

There is some evidence to suggest that the presence of retinopathy is predictive of a progression to albuminuria.

Homocysteine

Chico et al (1998) examined the relationship between plasma homocysteine (plasma Hcy) and nephropathy in 90 people with Type 2 diabetes attending a diabetes clinic in Spain compared with non-diabetic age and sex matched controls. Plasma Hcy was significantly related to elevated
albumin excretion rate (defined as AER ≥20 µg/min) in the people with Type 2 diabetes (p<0.001), after adjustment for other risk factors.

In another study based in an Italian hospital outpatient cohort, Lanfredini et al (1998) examined the relationship between fasting homocysteine and post-methionine load homocysteine in 33 people with Type 2 diabetes who had either normal albumin excretion or microalbuminuria. The microalbuminuria (AER >30 - <300 mg/24h) sub-group (n=17) showed higher levels of fasting plasma homocysteine (9.05 µmol/l ± 3.83 versus 7.12 µmol/l ± 1.95, p = 0.08). There was a statistically significant difference between microalbuminuria and normoalbuminuria in post methionine load cysteine values (microalbuminuria 3.34 ± 0.37, normoalbuminuria 3.04 ± 0.35, t =-2.36, p=0.02).

The relationship between homocysteine and renal disease has also been examined in two cross-sectional studies. In the HOORN study (Hoogeveen et al 1998) a random sub-sample of 653 men and women aged 50-75 years (164 with Type 2 diabetes) were tested for presence of microalbuminuria (an albumin: creatinine ratio >30.0 mg/mmol in an early morning spot urine sample, using a modified Jaffé method) and level of serum total homocysteine. For all subjects combined, after adjustment for age, sex, impaired glucose tolerance/diabetes mellitus, hypertension, smoking and dyslipidaemia, the authors found a 5 µmol/l increment of serum total homocysteine was associated with increased risk of microalbuminuria (adjusted odds ratio 1.33, 95% CI 1.08, 1.63). Further adjustment for protein intake and serum creatinine made little difference (adjusted OR 1.28, 95% CI 1.03, 1.59). Type 2 diabetes was found not to modify the effect of serum total homocysteine on the risk of microalbuminuria (results not given).

In a cross sectional study, Smulders et al (1999) measured homocysteine in 150 patients after a 12 hour period of fasting, and in a sub-group of 50 after taking 0.1 g/kg of methionine powder dissolved in apple juice. The correlation between homocysteine and elevated albumin excretion rate (microalbuminuria = 30 – 300 mg/24h, proteinuria >300 mg/24h) was measured. There was no significant correlation (at the p<0.05 level) between levels of homocysteine either fasting or post methionine, and various degrees of albuminuria in this population drawn from a hospital diabetes outpatient clinic in Holland.

Summary

The evidence of an association between plasma homocysteine and albuminuria is equivocal.

Family history

Canani et al (1999) assessed the possible clustering of diabetic nephropathy in siblings. People with Type 2 diabetes from a diabetes clinic in Brazil, who had at least one other sibling with Type 2 diabetes of at least five years duration, were recruited to the study. Overall 90 probands and 107 siblings were included. The presence of diabetic nephropathy (albumin excretion rate ≥20 µg/min) in probands was significantly associated with sibling diabetic nephropathy, after controlling for proband fasting plasma glucose and diabetes duration (odds ratio = 3.76, 95% CI: 1.36 - 10.4, p=0.011).

Vijay et al (1999) studied two groups of siblings of people with Type 2 diabetes, matched for age, BMI and duration of diabetes. The siblings were selected from families with diabetes, attending as patients a diabetes clinic in India. Group A were siblings whose parents had persistent proteinuria, while group B were siblings whose parents were free of nephropathy. Persistent proteinuria was defined as proteinuria >500 mg/day on three consecutive occasions over six months. In group A,
seven (27%) people had microalbuminuria (30 – 300 \( \mu \text{g/min} \)) while 15 (50%) had proteinuria. This compared with only one person (3%) having abnormal albumin levels in group B. It was not stated if the distribution of different stages of renal disease between the two groups were statistically significant, but differences between Group A and Group B for microalbuminuria were not (p=0.057).

In the study by Freedman et al (1995) 52 African Americans with end stage renal disease (ESRD) due to Type 2 diabetes were matched for age, sex and race with 45 Type 2 controls without nephropathy. ESRD was attributed to Type 2 diabetes in the presence of retinopathy, proteinuria \( \geq \)300 mg/24h or 1000 mg/dl and absence of other known causes of ESRD. Nineteen of 52 ESRD cases (37%) had a 1st, 2nd or 3rd degree relative with ESRD. The equivalent figure in controls was three from 45. In this cohort, African Americans with Type 2 diabetes had an eight fold increased risk of developing ESRD in the presence of a close relative with ESRD (odds ratio = 8.06, 95% CI: 2.2 - 29.6, p<0.0005).

In Strojek et al (1997) the offspring of 56 people with Type 2 diabetes were assessed for diabetic nephropathy (AER >30 mg albumin/24h). Twenty six of the parents had nephropathy and 30 were free of the condition. Fifty-six offspring were assessed and compared with a control group (matched for age, gender and body mass index) of 30 people whose parents did not have diabetes. Albumin excretion rate was significantly higher in offspring of people with Type 2 diabetes and nephropathy than in offspring of people with Type 2 diabetes who did not have nephropathy (AER = 7.8 mg/min, range 1.04 - 19.5 compared with AER of 4.8, range 0.36 - 17.5, p<0.05).

**Summary**

There is some evidence of an association between family history of proteinuria and/or end stage renal disease and on increased chance of development of proteinuria and/or end stage renal disease.

**Race**

Cowie et al (1989) studied all black (n=470) and white (n=861) patients with end stage renal disease due to diabetes reported to the Michigan Kidney Registry, USA between 1974 and 1983. The incidence of end stage renal disease due to Type 2 diabetes (n=348) was 4.3 (3.36 - 5.25) fold higher (p\( \leq \)0.0005) among blacks after adjustment for the higher prevalence of diabetes among blacks.

Pugh et al (1995) assembled a tri-ethnic cohort from all new cases of diabetic ESRD in San Antonio between Dec 1987 and July 1991 and between Dec 1988 and July 1991 in the Dallas county, USA. All non-Hispanic whites and African-Americans and a random sample of half of the Mexican-Americans were approached for enrolment. Age adjusted incidence rates were obtained by diabetes type and by ethnic group. The majority of ESRD was caused by Type 2 diabetes (59.5% for non-Hispanic whites, 92.8% for Mexican-Americans and 84.3% for African-American). Mexican-Americans and African-Americans had 9.2 (6.3 - 13.5) and 9.3 (6.2 - 14.0) times higher incidence of treatment for ESRD caused by Type 2 diabetes compared with non-Hispanic whites (both significant at p<0.0001). The relative risks of treatment in the two ethnic groups compared to non-Hispanic whites, whilst smaller at 3.8 (2.2 - 6.4) (p<0.0001) and 2.5 (1.5 - 4.2) (p<0.001) were still significant after age adjustment using the diabetic population as the denominator. This adjusted for the higher underlying prevalence of Type 2 diabetes seen in both the African-American and Mexican-American ethnic groups.
Stephens et al (1990) studied 1145 patients initiated for treatment for end stage renal disease (ESRD) in South West Ohio, USA during 1983 and 1984 plus 508 patients who had started treatment for ESRD between 1973 and 1984 inclusive. The incidence of ESRD in people with Type 2 diabetes for blacks was 224.4 per 100,000 compared with 46.5 per 100,000 for whites (odds ratio 4.86, 95% CI: 3.65 - 6.47). The relative risk for blacks varied with age, reaching a peak of 6.9 in persons over the age of 65, with diabetes (both types included). Diabetic nephropathy alone was the primary diagnosis considered to be the cause of ESRD in 70 % of those with Type 2 diabetes.

Summary

Among people enrolled in three end stage renal disease treatment programmes in the USA, there is evidence of a preponderance of African American and Hispanic peoples. It is not clear whether this represents a true association or whether (for example) the differences reflect previous levels of health care for these groups.

Clinical summary

The prevention of progressive proteinuria and end stage renal failure is principally dependent on the management of blood pressure and of blood glucose. For people with Type 2 diabetes who do not have microalbuminuria or proteinuria, the evidence base for the management of raised blood pressure is reviewed in the guideline in this series on the management of blood pressure (Hutchinson et al 2002) and also draws on the work of the British Hypertension Society (Ramsay et al 1999). The evidence base supporting the recommendations on blood glucose targets is reviewed in the guideline in this series on blood glucose management (McIntosh et al 2002).
Relative impact of risk factors

Evidence

None of the longitudinal studies graded the risk factors they found significant in predicting the development of renal disease (in terms of relative importance). Only two studies reported odds ratios in multivariate analyses which allow a comparison between the predictive strength of variables, with a higher odds ratio implying a stronger association between a risk factor and the outcome (Klein et al 1993, Mattock et al 1998).

In a study by Mattock et al (1998) current smoking had an odds ratio of 3.7 (95% CI: 1.2 - 11.3) compared to an odds ratio of 2.3 (95% CI: 1.3 - 3.9) for fasting plasma glucose, in predicting the development of microalbuminuria.

In a study by Klein et al (1993) people with older onset diabetes were divided into those on insulin therapy and those not on insulin therapy. Odds ratios were reported for the development of proteinuria over 10 years. In the group on insulin the highest odds ratio was for a change in haemoglobin A1c (HbA1c) between baseline and follow up and an odds ratio of 1.1 (95% CI: 1.0 - 1.2) for total pack years of smoking. For the group not on insulin therapy, the most predictive variable for development of proteinuria was systolic blood pressure, with an odds ratio of 2.5 (95% CI: 1.5 - 4.0). This compared with an odds ratio of 2.4 (95% CI: 1.3 - 4.3) for total pack years smoked and 2.17 (95% CI: 1.2 - 3.8) for haemoglobin A1c (HbA1c) ≥8.7%.

The remaining studies reported variables that predicted the development of renal disease at different levels of significance (p<0.05 or p<0.01) only and thus do not allow for the relative grading of significant risk factors. Overall there is insufficient data from the studies to grade risk factors, in terms of their relative importance in influencing the development of renal disease.

Levels of risk within a given risk factor

Only five of the longitudinal studies gave quantitative information about given risk factors (Klein et al 1995, Mattock et al 1998, Ravid et al 1998a, Tanaka et al 1998, Stratton et al 2000). Of these five studies, only two reported quantifiable levels of risk for the development of renal disease (Klein et al 1995) or incidence of diabetic endpoints (Stratton et al 2000) within a particular risk factor. In the group on insulin therapy (Klein et al 1995), a 1% higher haemoglobin A1c (HbA1c) reading at baseline examination in a patient was associated with an odds ratio of developing proteinuria of 1.2 (95% CI: 1.0 - 1.4). This compared with an odds ratio of 1.1 (95% CI: 0.95 - 1.3) for a change in haemoglobin A1c (HbA1c) between baseline and four year examination was associated with an odds ratio of 1.1 (95% CI: 0.95 - 1.3) for developing proteinuria. Additionally, for people on insulin therapy, an increase of 10 in pack years smoked was associated with an odds ratio of 1.1 (95% CI: 1.0 - 1.2) for developing proteinuria after 10 years. From the UKPDS data, Stratton et al (2000) grouped 3005 individuals with newly diagnosed Type 2 diabetes according to their HbA1c mean concentration from baseline and yearly follow-up using the following categories, <6%, 6-<7%, 7-<8%, 8-<9%, 9-<10%, ≥10%. They found that, after adjustment for age, sex, ethnic group and duration of diabetes, the adjusted incidence rates for any end point related to diabetes, or for myocardial infarction and microvascular
complications, increased with each higher category of HbA1c. There was also no evidence of a threshold and the increase between the lower and upper limits (<6% and ≥10%) was threefold.

Three studies reported thresholds within a given risk factor. If a patient had a level above this threshold then they were at increased risk of developing renal disease compared to someone with a level below this threshold. Klein et al (1995) reported that a haemoglobin A1c (HbA1c) level of ≥8.7% was associated with an increased likelihood of developing proteinuria after 10 years (odds ratio of 2.5; 95% CI: 1.5 - 4.1). Ravid et al (1998a) reported an HbA1c level of ≥9.0% significantly increased the risk of developing microalbuminuria (p<0.05). Klein et al (1995) found that a systolic blood pressure level >146 mmHg was associated with an increased risk of developing proteinuria (odds ratio 2.5; 95% CI: 1.5 - 4.1). Ravid et al (1998a) found that a mean diastolic blood pressure level of >95 mmHg was significantly associated with the development of microalbuminuria. Klein et al (1995) found that if total pack years smoked was >40, the odds ratio for developing proteinuria was 2.4 (95% CI: 1.3 - 4.3) compared to someone who smoked less than 40 pack years.

The methods used to report the risk factors between studies varied. There was no consistent threshold identified for particular risk factors at which development of renal disease occurred. Only one study reported different levels of risk, within risk factors, for developing renal disease (Klein et al 1995). There is insufficient evidence from the studies as a whole to identify different levels of risk, within a given risk factor, for the development of renal disease.

Conclusion: risk factors

Significant proportions of people with Type 2 diabetes develop renal disease over time. In the longitudinal studies discussed the proportion of people developing microalbuminuria ranged from 18% (Wirta et al 1996b) to 35% (Tanaka et al 1998). The proportion of people developing proteinuria ranged from 3% (Wirta et al 1996b) to 18% (Tanaka et al 1998).

There is evidence from more than one study to suggest that higher blood glucose levels, higher blood pressure levels, increasing age, higher lipid levels, male sex, smoking, baseline albumin excretion and retinopathy are significant predictive variables in the development of renal disease in Type 2 diabetes. There is also evidence from cross sectional studies supporting the hypotheses that family history, race and homocysteine levels are correlated with renal disease in Type 2 diabetes. However it is important to note that there are also a number of studies which report negative findings (see the summaries in preceding sections and Tables 10 and 11).
Table 11: Risk factors for nephropathy (microalbuminuria and proteinuria) from longitudinal studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Subjects</th>
<th>Model</th>
<th>Blood glucose level or HbA1c</th>
<th>Blood pressure</th>
<th>Smoking</th>
<th>Lipids/Triglycerides/HDL/LDL/insulin</th>
<th>BMI</th>
<th>Age</th>
<th>Sex</th>
<th>Albumin baseline or other</th>
<th>Duration of diabetes</th>
<th>Retinopathy</th>
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<tr>
<td>Mattock et al 1998</td>
<td>100</td>
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<td>+</td>
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<tr>
<td>Biesenbach et al 1997</td>
<td>37</td>
<td>Yes</td>
<td>–</td>
<td>+</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Wirta et al 1996b</td>
<td>150</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Tanaka et al 1998</td>
<td>123</td>
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<td>+</td>
<td>–</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Ravid et al 1998</td>
<td>574</td>
<td>Yes</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td></td>
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<tr>
<td>John et al 1994</td>
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<tr>
<td>Nielsen et al 1995</td>
<td>32</td>
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<tr>
<td>Klein et al 1995</td>
<td>1370</td>
<td>Yes</td>
<td>+</td>
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<tr>
<td>Gall et al 1997</td>
<td>176</td>
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<tr>
<td>Sasaki et al 1989</td>
<td>1196</td>
<td>Yes</td>
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<td>Song et al 1998</td>
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<tr>
<td>Niskanen et al 1996</td>
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<tr>
<td>UKPDS (22) 1997</td>
<td>3027</td>
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<td></td>
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<tr>
<td>Schmitz et al 1994</td>
<td>178</td>
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<td>–</td>
<td>+</td>
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<tr>
<td>UKPDS (10) 1993</td>
<td>585</td>
<td>Yes</td>
<td>–</td>
<td>+</td>
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<tr>
<td>Beilin et al 1996</td>
<td>666</td>
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<td>+</td>
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<tr>
<td>UKPDS (33) 1998a</td>
<td>3867</td>
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<td>+</td>
<td>+</td>
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<td></td>
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</tbody>
</table>

+ = examined in study and a statistically significant risk factor;  
− = examined in study, not a significant risk factor;  
blank spaces = not examined
Table 12: Risk factors for nephropathy (microalbuminuria and proteinuria) from cross-sectional studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects</th>
<th>Homocysteine</th>
<th>Family history</th>
<th>Race</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanfredini et al 1998</td>
<td>33</td>
<td>+</td>
<td></td>
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<tr>
<td>Chico et al 1998</td>
<td>90</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canani et al 1999</td>
<td>90</td>
<td></td>
<td>+</td>
<td></td>
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<tr>
<td>Vijay et al 1999</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Stephens et al 1990</td>
<td>1145</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Pugh et al 1995</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Cowie et al 1989</td>
<td>1331</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Freedman et al 1993</td>
<td>52</td>
<td></td>
<td></td>
<td>+</td>
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<tr>
<td>Strojek et al 1997</td>
<td>56</td>
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<tr>
<td>Smulders et al 1999</td>
<td>150</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

+ = examined in study and a statistically significant risk factor;  
− = examined in study, not a significant risk factor;  
blank spaces = not examined
### References: risk factors
(with AHCPR evidence grades where appropriate, see page 18)

<table>
<thead>
<tr>
<th>Evidence Grade</th>
<th>Reference 1</th>
<th>Reference 2</th>
</tr>
</thead>
</table>
6. Screening tests for renal disease in Type 2 diabetes
Screening for diabetic renal disease

Recommendations

Measure albumin : creatinine ratio or albumin concentration at diagnosis of diabetes and annually thereafter. (C)

   use a first morning urine sample where practicable (C)
   use a laboratory or near-patient test specifically for microalbuminuria (C)

If the first result is positive, testing should be repeated on 2 further occasions (within one month where practicable) of which one should be positive to confirm the diagnosis. (C)

Measure serum creatinine annually. (C)

Following measurement, classify albumin excretion as lower risk or higher risk: (C)

<table>
<thead>
<tr>
<th>Definition of higher risk urine albumin excretion</th>
</tr>
</thead>
</table>
| **microalbuminuria** – albumin : creatinine ratio greater than or equal to 2.5 mg/mmol (men)/
  greater than or equal to 3.5 mg/mmol (women)
  or albumin concentration greater than or equal to 20 mg/l |
| **proteinuria** – albumin : creatinine ratio greater than or equal to 30 mg/mmol or
  albumin concentration greater than or equal to 200 mg/l |

Evidence statement

*Measurement of urine albumin excretion is the best screening test for diabetic renal disease.* (III)

*Measurement of serum creatinine is the best monitoring test for diabetic renal disease.* (III)

*Regular screening enables targeting of renoprotective blood pressure therapy.* (IV)

*Measurement of albumin : creatinine ratio or albumin concentration is appropriate, with cut-offs of
  2.5 mg/mmol (men) or 3.5 mg/mmol (women), or 20 mg/l, respectively.* (III)

*Most reported laboratory tests for urine albumin measurement and commercially available side-room
  tests have satisfactory sensitivities (> 80%) and specificities (> 90%) for detecting microalbuminuria.* (III)

*At a cut-off of 30 mg/l, all tests perform equally well.* (III)

*At a level of 20 mg/l, there is some variation, with only those tests designed specifically to detect
  microalbuminuria performing adequately.* (III)
Predictive studies have used timed urine collections. However, these are not necessary for screening purposes. Of the samples available, a first morning urine sample best reflects a timed urine collection and is preferable to a random sample. (III)

Optimum precision of measurement of the urine albumin:creatinine ratio is obtained using 3 first morning urine samples, collected either consecutively or at intervals. (III)

The day to day variability in albumin excretion can be as much as 40%. The variability is less in first morning samples. (III)

Urine albumin concentration is stable for 7-14 days without preservative at room temperature and also at 4°C (in the absence of urinary tract infection). At −20°C, stability has been questioned, but it appears to be satisfactory for many months at −40°C and −70°C. (III)

Note also evidence in Section 7 which identifies the renoprotective benefits of ACE inhibitors and Angiotensin II receptor antagonists, which supports the need for regular screening.
Introduction

Screening objectives

The aim of screening for diabetic renal disease is to correctly identify as many people as possible with abnormal urine albumin excretion, so that interventions can be instigated which delay the progression of renal disease or prevent end-stage renal failure and which reduce the incidence of premature cardiovascular morbidity and mortality. These interventions include the use of renoprotective blood pressure lowering drugs. The aim of this section of the review is to answer the following questions:

♦ What screening methods are available to identify renal disease, due to diabetes, in people with Type 2 diabetes?

♦ What are the best screening methods in terms of: sensitivity; specificity; cost effectiveness; patient acceptability; management of the disease?

Different types of test

We reviewed the published literature evaluating screening tests for renal disease in people with Type 2 diabetes. We searched for studies evaluating tests on a range of possible screening markers. These were:

♦ urine testing for albumin
♦ urine testing for proteins other than albumin
♦ renal biopsy
♦ serum creatinine
♦ glomerular filtration rate
♦ genetics
♦ blood pressure

We did not find any studies evaluating genetic methods, biopsy techniques, blood pressure measurement, nor urine testing for proteins other than albumin and methods for assessing glomerular filtration rate.

The majority of the studies of screening methods in the literature assess different methods for measuring albumin levels in the urine. There are essentially two types of screening test for urinary albumin. These are laboratory tests and side-room tests.

Laboratory tests (diagnostic tests)

Laboratory tests are quantitative and allow the precise measurement of very low concentrations of albumin in the urine. These include radioimmunoassay, nephelometry and immunoturbidimetric methods (Hasslacher 1993). The use of laboratory tests for screening requires sophisticated equipment usually only available in laboratories and hospitals.
Side-room tests (screening tests)

Because many people with diabetes are seen in general practice there is a need for precise screening methods that are simple, quick to apply, reliable and cost effective. In recent years progress has been made in this area and side-room tests suitable for screening have become available.

Tests included in the review

There was a range of side-room tests for measuring albumin in the urine which were evaluated in the literature. In our review we only included studies evaluating side-room tests that are currently commercially available. We carried out a search of the British National Formulary (BNF) database (2000) to identify which side-room tests were currently available to NHS general practice. The following side-room tests are listed in the BNF as suitable for urinalysis:

- Albustix® (protein)
- Albym Test® (standard dipstick test)
- Micral-Test II® (albumin)
- Micrubumintest® (albumin)
- BM-Test-GP® (glucose and protein)
- Medi-Test Combi 2® (glucose and protein)
- Medi-Test® Protein 2 (protein)
- Uristix® (glucose and protein)

We did not find evidence in our searches to evaluate Medi-Test Combi 2®, Medi-Test® Protein 2, Uristix®, BM-Test-GP® or Albym Test®. We found evidence for the Micral-Test II®, Albustix® and Micrubumintest®.

Type of urine sample

An important aspect of screening the urine for albumin is the choice of urine sample to use. Timed urine collections, either 24 hour, overnight or shorter day time are regarded as the gold standard. However timed collections are impractical to screen large numbers of subjects for microalbuminuria. Alternatives exist in the measurement of albumin concentration or albumin: creatinine ratio in either early morning or random urine samples. The issue of measurement of urine and comparisons between untimed and timed urine samples are discussed within each sub-section on screening methods.

Reference standard

We attempted to find definitive gold standard diagnostic tests for renal disease in diabetes against which screening methods should be compared. We did not find such a diagnostic standard in the literature. The screening studies we have found used laboratory methods as reference standards, either radioimmunoassay, immunonephelometry or immunoturbidimetry. Radioimmunoassay is considered to be the reference standard although it is expensive, time consuming and not suitable for the assay of small numbers of samples (Giampietro et al 1992). These techniques were used in urine samples taken at various times. Each of these methods is designed to detect very low levels of albumin in the urine.
However, one would expect varied results if any one screening test is compared to different reference standards, so that if the results of different studies are examined, one would not be comparing like with like. The section on laboratory tests attempts to evaluate the available literature assessing the effectiveness of these reference standards.

Methods of review

Inclusion criteria

We searched for studies to answer the review question and identified ninety studies which appeared relevant by title and/or abstract from our initial searches. We sifted these ninety studies and included/excluded them on the following criteria: inclusion of people with Type 2 diabetes, evaluation of a screening or diagnostic method for identifying renal disease due to diabetes against a defined reference standard. On the basis of these criteria, thirty studies were included. Thirteen of these studies evaluated side-room tests, seventeen evaluated laboratory methods and three evaluated both laboratory and side-room tests.

The screening tests identified in this review measured accuracy of screening in terms of sensitivity and specificity of the screening method evaluated. Jaeschke et al (1994) have defined sensitivity as, “the proportion of people with the target disorder in whom the test result is positive” and specificity as “the proportion of people without the target disorder in whom the test result is negative”. The ideal screening test would have a sensitivity of 100% and also a high level of specificity.

Quality criteria for included studies

The studies were assessed (although not included/excluded) on the following quality criteria contained in the Canadian Hypertension Society Consensus Conference Report (Carruthers et al 1993):-

- independent interpretation of the test procedure (without knowledge of result of reference standard);
- independent interpretation of the reference standard (without knowledge of result of test procedure);
- reproducible description of both the screening test and the reference standard;
- study population included patients suspected but not known to have the disorder of interest;
- at least 50 patients with the condition and 50 patients without the condition.

Summary of literature review

The primary focus in this section was on side-room tests as these are the initial test used by the audience of this guideline. Direct comparison between different side-room tests was not possible because the studies identified used various reference standards, methods of use of test, urine samples and definitions and ranges of microalbuminuria. However the various papers were extracted and information presented in a manner which allows a comparison. Sensitivities and specificities are the main parameters compared, as requested by the renal care working group.
The reported sensitivities ranged from 51% to 100% and the reported specificities ranged from 27% to 97%. All side-room tests achieved sensitivities of 85% and specificities of 90% in at least one study.

Summary

Overall, it appears that all the side-room tests specifically designed to identify microalbuminuria met acceptable levels of sensitivity and specificity. Reliance on the results of the single use of any one of the tests was not sufficiently reliable. Repeat tests are therefore required and confirmation by laboratory testing is advised at diagnosis.
### Table 13: Albumin:creatinine ratio - sensitivity and specificity

<table>
<thead>
<tr>
<th>Reference standard</th>
<th>Reference level for raised albumin</th>
<th>Type of urine sample</th>
<th>Outcome</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radioimmunoassay and Jaffe reaction (albumin:creatinine ratio)</strong></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Radioimmunoassay (overnight sample)</td>
<td>albumin excretion rate 30 µg/min</td>
<td>early morning</td>
<td>&gt;3.0mg/mmol</td>
<td>97</td>
<td>94</td>
<td>Hutchison et al (1988)</td>
</tr>
<tr>
<td><strong>ELISA and Jaffe reaction</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Micro-ELISA (overnight sample)</td>
<td>albumin excretion rate 30 µg/min</td>
<td>early morning</td>
<td>&gt;2.0 mg/mmol</td>
<td>96</td>
<td>100</td>
<td>Gatling et al (1988)</td>
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<tr>
<td>Micro-ELISA (overnight sample)</td>
<td>albumin excretion rate 30 µg/min</td>
<td>early morning</td>
<td>3.5 mg/mmol</td>
<td>100</td>
<td>95</td>
<td>Gatling et al (1985)</td>
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<tr>
<td>Micro-ELISA (overnight sample)</td>
<td>albumin excretion rate 30 µg/min</td>
<td>early morning</td>
<td>&gt;3.5 mg/mmol</td>
<td>88</td>
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<tr>
<td>Radioimmunoassay</td>
<td>12 mg/24h</td>
<td>24 hour</td>
<td>1.5 mg/mmol</td>
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<td>97</td>
<td>Nathan et al (1987)</td>
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<td>Radioimmunoassay</td>
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<td>96</td>
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<td>3.4 mg/mmol</td>
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<td><strong>DCA 2000</strong></td>
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<tr>
<td>Immunoturbidimetry</td>
<td>20 mg/l</td>
<td>24 hour</td>
<td>2.65 mg/mmol</td>
<td>92</td>
<td>100</td>
<td>Parsons et al (1998)</td>
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Table 13: Albumin:creatinine ratio - sensitivity and specificity (contd.)

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<th>Reference standard</th>
<th>Reference level for raised albumin</th>
<th>Type of urine sample</th>
<th>Outcome</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>Study</th>
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<td><strong>Immunoturbidimetry and Jaffe reaction</strong></td>
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<tr>
<td>Immunoturbidimetry (overnight sample)</td>
<td>albumin excretion rate 30 µg/min</td>
<td>overnight</td>
<td>4.5 mg/mmol: (women) 2.5 mg/mmol: (men)</td>
<td>Female: 100 Male: 100</td>
<td>Female: 98 Male: 89</td>
<td>Connell et al (1994)</td>
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<tr>
<td>Immunoturbidimetry (overnight urine sample)</td>
<td>albumin excretion rate 20 µg/min</td>
<td>overnight</td>
<td>2.5 mg/mmol (women) 1.8 mg/mmol (men)</td>
<td>Female: 94 Male: 94</td>
<td>Female: 92 Male: 93</td>
<td>Bakker et al (1999)</td>
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</tr>
<tr>
<td>Micro-ELISA (overnight sample)</td>
<td>albumin excretion rate 30 µg/min</td>
<td>random</td>
<td>&gt;3.0mg/mmol</td>
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<td>Gatling et al (1988)</td>
</tr>
<tr>
<td><strong>DCA 2000</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunoturbidimetry (overnight urine)</td>
<td>albumin creatinine ratio 2.5 mg/mmol (males) 3.5 mg/mmol (females)</td>
<td>not stated</td>
<td>&gt;2.5 mg/mmol (males) &gt;3.5 mg/mmol (females)</td>
<td>91</td>
<td>98</td>
<td>Poulsen et al (1998)</td>
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</table>
Table 14: Albumin concentration: sensitivity and specificity

<table>
<thead>
<tr>
<th>Reference standard</th>
<th>Reference level for raised albumin</th>
<th>Type of urine sample</th>
<th>Outcome (albumin concentration)</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radioimmunoassay</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radioimmunoassay (overnight sample)</td>
<td>albumin excretion rate 30 µg/min</td>
<td>early morning</td>
<td>&gt;17 mg/l</td>
<td>97</td>
<td>91</td>
<td>Hutchison et al (1988)</td>
</tr>
<tr>
<td><strong>Immunoturbidimetry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunoturbidimetry (overnight urine sample)</td>
<td>albumin excretion rate 20 µg/min</td>
<td>overnight</td>
<td>15 mg/l</td>
<td>Male: 98</td>
<td>Male: 89</td>
<td>Bakker et al (1999)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Female: 89</td>
<td>Female: 90</td>
<td></td>
</tr>
<tr>
<td><strong>Immunoturbidimetry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radioimmunoassay (random sample)</td>
<td>20-300 mg/l</td>
<td>random</td>
<td>20-300 mg/l</td>
<td>97</td>
<td>92</td>
<td>Sawicki et al (1989)</td>
</tr>
<tr>
<td><strong>Laser Turbidimetric</strong></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Radioimmunoassay</td>
<td>20-300 mg/l</td>
<td>random</td>
<td>20-300 mg/l</td>
<td>93</td>
<td>88</td>
<td>Sawicki et al (1989)</td>
</tr>
<tr>
<td><strong>Immunonephelometry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunonephelometry</td>
<td>15µg/min</td>
<td>overnight</td>
<td>10 mg/l</td>
<td>87</td>
<td>71</td>
<td>Kouri et al (1991)</td>
</tr>
<tr>
<td>Immunonephelometry</td>
<td>15µg/min</td>
<td>overnight</td>
<td>20 mg/l</td>
<td>60</td>
<td>97</td>
<td>Kouri et al (1991)</td>
</tr>
<tr>
<td>Reference standard</td>
<td>Reference level for raised albumin</td>
<td>Type of urine sample</td>
<td>Outcome (albumin concentration)</td>
<td>Sensitivity %</td>
<td>Specificity %</td>
<td>Study</td>
</tr>
<tr>
<td>---------------------</td>
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<td>---------------------------------</td>
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<td>--------------</td>
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</tr>
<tr>
<td>ELISA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radioimmunoassay</td>
<td>albumin excretion rate &gt;20 µg/min</td>
<td>24 hour</td>
<td>20 mg/l</td>
<td>97</td>
<td>74</td>
<td>Marbut et al (1992)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radioimmunoassay</td>
<td>albumin excretion rate &gt;20 µg/min</td>
<td>random</td>
<td>20 mg/l</td>
<td>90</td>
<td>42</td>
<td>Marbut et al (1992)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micro-ELISA</td>
<td>albumin excretion rate 30 µg/min</td>
<td>random</td>
<td>25 mg/l</td>
<td>56</td>
<td>81</td>
<td>Gatling et al (1985)</td>
</tr>
<tr>
<td>Micro-ELISA</td>
<td>albumin excretion rate 30 µg/min</td>
<td>random</td>
<td>20 mg/l</td>
<td>91</td>
<td>83</td>
<td>Bouhanick et al (1992)</td>
</tr>
<tr>
<td>Immunonephelometry</td>
<td>albumin excretion rate 30 µg/min</td>
<td>random</td>
<td>20 mg/l</td>
<td>91</td>
<td>83</td>
<td>Bouhanick et al (1992)</td>
</tr>
<tr>
<td>ELISA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micro-ELISA</td>
<td>albumin excretion rate 30 µg/min</td>
<td>early morning</td>
<td>20 mg/l</td>
<td>86</td>
<td>97</td>
<td>Gatling et al (1985)</td>
</tr>
<tr>
<td>Micro-ELISA</td>
<td>albumin excretion rate 30 µg/min</td>
<td>early morning</td>
<td>20 mg/l</td>
<td>82</td>
<td>96</td>
<td>Gatling et al (1988)</td>
</tr>
</tbody>
</table>
Table 15: Screening tests for microalbuminuria: Microbumintest®

<table>
<thead>
<tr>
<th>Reference standard</th>
<th>Reference level for raised albumin</th>
<th>Type of urine sample</th>
<th>Outcome</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radioimmunoassay</td>
<td>40-80 mg/l</td>
<td>timed overnight</td>
<td>40-80 mg/l</td>
<td>100</td>
<td>82</td>
<td>Tiu et al (1993)</td>
</tr>
<tr>
<td>Immunoturbidimetry</td>
<td>20 mg/l</td>
<td>overnight</td>
<td>20 mg/l</td>
<td>51</td>
<td>84</td>
<td>Bashyam et al (1993)</td>
</tr>
<tr>
<td>Radioimmunoassay</td>
<td>15 mg/l</td>
<td>first morning</td>
<td>15 mg/l</td>
<td>78</td>
<td>81</td>
<td>Giampietro et al 1992</td>
</tr>
<tr>
<td></td>
<td>20 mg/l</td>
<td>first morning</td>
<td>20 mg/l</td>
<td>93</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 mg/l</td>
<td>first morning</td>
<td>30 mg/l</td>
<td>100</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Radioimmunoassay</td>
<td>40 mg/l</td>
<td>first morning</td>
<td>40 mg/l</td>
<td>100</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Radioimmunoassay</td>
<td>30 mg/l</td>
<td>early morning</td>
<td>30 mg/l</td>
<td>92</td>
<td>97</td>
<td>Al-Kassab et al (1990)</td>
</tr>
<tr>
<td></td>
<td>40 mg/l</td>
<td>early morning</td>
<td>40 mg/l</td>
<td>97</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50 mg/l</td>
<td>early morning</td>
<td>50 mg/l</td>
<td>96</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Radioimmunoassay</td>
<td>15 mg/l</td>
<td>random</td>
<td>15 mg/l</td>
<td>100</td>
<td>55</td>
<td>Williams et al (1990)</td>
</tr>
<tr>
<td>Immunonephelometry (24 hour urine sample)</td>
<td>30µg/min</td>
<td>random (outpatient)</td>
<td>20 mg/l</td>
<td>83</td>
<td>82</td>
<td>Bouhanick et al 1992</td>
</tr>
<tr>
<td></td>
<td>30µg/min</td>
<td>random (hospitalization)</td>
<td>20 mg/l</td>
<td>76</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>Radioimmunoassay</td>
<td>30 mg/l</td>
<td>random</td>
<td>30 mg/l</td>
<td>91</td>
<td>97</td>
<td>Collins et al (1989)</td>
</tr>
<tr>
<td></td>
<td>40 mg/l</td>
<td>random</td>
<td>40 mg/l</td>
<td>98</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Radioimmunoassay</td>
<td>30 mg/l</td>
<td>not stated</td>
<td>30 mg/l</td>
<td>79</td>
<td>27</td>
<td>Colwell et al (1989)</td>
</tr>
</tbody>
</table>
Table 16: Screening tests for microalbuminuria: Micral-Test II®

<table>
<thead>
<tr>
<th>Reference standard</th>
<th>Reference level for raised albumin</th>
<th>Type of urine sample</th>
<th>Outcome</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>ROC</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radioimmunoassay</td>
<td>20 mg/l</td>
<td>24 hour</td>
<td>20 mg/l</td>
<td>93</td>
<td>93</td>
<td>0.95</td>
<td>Gilbert et al (1997)</td>
</tr>
<tr>
<td>Nephelometry</td>
<td>15 µg/min</td>
<td>Early morning (1 sample)</td>
<td>20 mg/l</td>
<td>64</td>
<td>88</td>
<td>0.82</td>
<td>Fernandez et al (1998)</td>
</tr>
<tr>
<td></td>
<td>20 µg/min</td>
<td>Early morning (1 sample)</td>
<td>20 mg/l</td>
<td>79</td>
<td>87</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 µg/min</td>
<td>Early morning (1 sample)</td>
<td>20 mg/l</td>
<td>86</td>
<td>80</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Immunoturbidimetry</td>
<td>Early morning/ random</td>
<td>20 mg/l</td>
<td>97</td>
<td>71</td>
<td></td>
<td>not given</td>
<td>Mogensen et al (1997)</td>
</tr>
</tbody>
</table>
Table 17: Screening tests for proteinuria: Albustix®

Albustix® are designed for detecting protein in urine, rather than albumin. However a few studies evaluated their use in detecting microalbuminuria. The findings are presented below.

<table>
<thead>
<tr>
<th>Reference standard</th>
<th>Reference level for raised albumin</th>
<th>Type of urine sample</th>
<th>Outcome</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radioimmunoassay</td>
<td>20-300 mg/l</td>
<td>Random</td>
<td>50 mg/l</td>
<td>81</td>
<td>55</td>
<td>Sawicki et al 1989</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 mg/l</td>
<td>Random</td>
<td>30 mg/l</td>
<td>90</td>
<td>71</td>
<td>Leedman et al 1987</td>
</tr>
<tr>
<td></td>
<td>30 mg/l</td>
<td>Random</td>
<td>50 mg/l</td>
<td>100</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Radioimmuno-assay</td>
<td>30 mg/l</td>
<td>24 hour urine collection</td>
<td>20 mg/l</td>
<td>70</td>
<td>79</td>
<td>Hermans et al 1994</td>
</tr>
</tbody>
</table>
Choice of urine sample for testing

Introduction

If screening for urine albumin excretion is to be part of routine diabetes care then large numbers of samples will have to be processed. As a result, urine specimens may have to be stored before assay can take place and evidence is required about the effects of sample storage (temperature and length of storage) on the accuracy of assay results, as well as on any variability in samples collected. This review examines the evidence in support of the most effective storage methods.

Evidence

Temperature and time factors

Osberg et al (1990) carried out radioimmunoassay on aliquots of urine from 101 specimens (47 subjects, 37 with Type 1 diabetes, 10 without) of fresh urine which were stored at –20°C for two, eight and 24 weeks or stored at 4°C for one, two and eight weeks. Sixty-eight of the specimens were timed, overnight collections, the other thirty-three were collected immediately after a 20 minute exercise period. The albumin concentrations in the stored urine samples were compared with an aliquot assayed on the day of collection. All samples were centrifuged before analysis for albumin. Albumin values for all stored specimens were significantly different from results for fresh specimens (p=0.0008). Albumin concentrations did not differ in aliquots stored at 4°C for up to eight weeks. However albumin concentrations in the fresh urine were significantly higher from those in the same urine samples stored at –20°C for two (p=0.01), eight (p=0.0001) and 24 (p=0.0001) weeks. There were no significant differences in the albumin level alterations in urine specimens between people with diabetes and those without, or between timed and post-exercise samples.

The effect of storage time and temperature on turbidimetric assessment of low concentration of albumin in urine was measured by Hara et al (1994). Storage at –20°C decreased albumin concentration, although the decreases varied between specimens. Storage at room temperature for two weeks or 4°C for five weeks did not significantly alter the albumin concentration. At –40°C and –80°C there were non significant changes in albumin concentration, with the smaller decreases at the latter temperature. Some specimens stored at –20°C showed a 50% decrease in albumin concentration after nine weeks while levels in specimens stored at –80°C for the same period remained unchanged.

Elving et al (1989) measured urine concentrations in overnight urine samples from 73 people with diabetes but who were non-proteinuric (≤0.3g/24 hours), using laser nephelometry. The samples were divided into four aliquots, one was stored at 4°C and assayed after two weeks and the other three were stored at –20°C and assayed at two weeks, two months and six months. The samples were centrifuged before storage and prior to assay (1500g for 15 min). Thirty three of the samples stored at 4°C were also tested after two days, and there was no statistically significant difference in albumin concentration between the two-day and two-week samples. At two weeks the 73 samples had a mean albumin concentration of 17.9 mg/l ± 28.4 mg/l. Storage for two weeks at –20°C produced no significant changes in results, compared with the 4°C, two week sample used as a reference value. However after
two months and six months of storage at –20°C significantly lower albumin concentrations were evident (p values = 0.03 and 0.005 respectively).

Vermes and Spooren (1992) compared different methods of specimen collection and storage conditions using timed-overnight urine specimens from 296 patients with Type 1, or Type 2, diabetes, plus all urine samples (i.e. 24 hour collection, first morning sample, spot urine specimen), on three consecutive days, for a further eight patients with microalbuminuria. Aliquots were stored at room temperature for seven days, 4°C for three weeks or –20°C for three months. Urine albumin excretion over the three consecutive days showed considerable day-to-day variation in each patient, but storage time and temperature did not have a significant influence on measured albumin concentration.

In Collins et al (1993) untimed spot urine samples were collected from 84 people with diabetes attending an outpatient clinic in England. The samples were collected without preservative and assayed within 48 hours after storage at 4°C. After assay, the samples were divided into six aliquots and stored at –20°C and –40°C to be assayed after 1 week, 1 month and 6 months of frozen storage. At each of these time points the samples were measured after either thawing and thorough vortex mixing or using the supernatant following centrifugation at 1500g for 10 minutes. Additionally in three patients with diabetes and one healthy control subject, 24 hour urine samples were obtained and albumin concentrations measured fresh and after one, two and seven days at –4°C or at –20°C (room temperature). There was no significant difference in albumin concentration between fresh aliquots at 4°C and those stored at either 4°C or –20°C for up to seven days. There was also no significant difference in aliquots assayed fresh at 4°C compared with storage at either –20°C or –40°C for one week, one month or six months, whether centrifuged or not.

Silver et al (1987) assayed aliquots of 20 samples stored overnight at 4°C or for a week, or at –20°C for one month. Twenty people presenting at a diabetes clinic in England provided the samples. There were no significant differences (p>0.05) between albumin concentrations for samples stored under these three different conditions.

Handling of urine sample

In a separate analysis in the same report by Collins et al (1993), spot urine samples were collected from 82 people with diabetes and 19 non-diabetic controls to assess the effect of multiple thawing and freezing on albumin concentration. After baseline assay at 4°C and within 24 hours of collection (collected without preservative), a 5 ml aliquot was stored at –20°C and albumin concentration measured every week for six weeks. Multiple freezing and thawing over a six week period at –20°C did not significantly alter albumin concentrations (p=0.99), irrespective of whether the samples were from the control group, normoalbuminuric, microalbuminuric or proteinuric diabetic patients.

Storage materials

Collins et al (1993) also tested the effect of different storage tube materials in the presence or absence of gelatine in a sample of 26 people with diabetes. Aliquots from spot samples provided by these people were stored in either polypropylene, polystyrene or borosilicate glass tubes. Another aliquot from the sample was added to a second set of similar tubes which had gelatine inserted prior to the addition of the urine. Urinary albumin levels were determined for each of these tubes after one week and one month of storage at –20°C. Storage in the different test tubes did not result in a significant change in urinary albumin after one week or one month at –20°C, although after one month of storage urinary albumin concentrations tended to be lower by an average of 7%. In tubes to which gelatine had been added this
was reduced to 4%. The significant lack of difference was retained when normoalbuminuric, microalbuminuric and proteinuric groups were analysed separately.

Summary

Based on the studies found, storage of samples at 4°C does not seem to adversely affect albumin concentration in urine. The longest period in the studies at which the samples were stored at 4°C was eight weeks (Osberg et al 1990). Storage of samples at room temperature for up to two weeks (Hara et al 1994) did not result in significantly different albumin concentrations compared with assay of fresh urine.

Freezing samples at –20°C had divergent effects on albumin concentrations in the studies. In three studies storage at –20°C reduced albumin concentrations significantly when compared with either fresh urine (Osberg et al 1990, Hara et al 1994) or compared with 4°C for two and six months (Elving et al 1989). However in the study by Collins et al (1993) storage at –20°C between one and 12 weeks did not significantly alter albumin concentrations compared with storage at 4°C for 48 hours. Similarly, storage at –20°C did not alter albumin levels compared with overnight or one week storage at 4°C (Silver et al 1987). Differences in the results between studies may be a result of different techniques or different levels of accuracy in the collection of urine.

Freezing at –40°C did not negatively effect the urine albumin concentration significantly in three studies (Hara et al 1994, Collins et al 1993, Osberg et al 1990). In Collins et al (1993) storage for up to 6 months at this temperature did not alter albumin levels compared with samples at 4°C. In Hara et al (1994) freezing at –80°C for two weeks did not effect albumin concentrations when compared with aliquots of fresh urine.

Variability in sampling

A study by Smulders et al (1998) looked at the variability in albumin levels and albumin: creatinine ratio in urine samples collected by four patients with Type 2 diabetes and microalbuminuria (AER 30-300 mg/24hour). In the first analysis of overnight and daytime samples collected over a period of 30 consecutive days, considerable variability was seen in all patients and for all parameters: albumin/24 hour; morning albumin: creatinine ratio; daytime albumin: creatinine ratio and 24 hour albumin: creatinine ratio. Overnight collections consisted of urine voided during the night and the first morning urine, immediately after rising. In general, the overnight albumin: creatinine ratio was the most constant and albumin mg/24 hours the most variable. Further analysis of the overnight samples showed no existence of any periodicity in the albumin: creatinine ratio, but did demonstrate that the optimum precision of the estimate of the actual value was obtained using three or five samples (either taken consecutively or at intervals). These findings were supported in data from two other sources: a further ten people with Type 2 diabetes and microalbuminuria with ten consecutive overnight samples (Smulders et al 1998); and 300 separate triplicate urine samples (200 24-hour samples, 100 overnight samples) all from microalbuminuric people with Type 2 diabetes. In the latter set of samples, the overnight albumin: creatinine ratio was significantly less variable (p≤0.02) than the albumin/24-hour and the 24-hour albumin: creatinine ratio sample. There was no difference (p=0.18) in variability between albumin (mg)/24-hours and the albumin: creatinine ratio. All these measurements had positively skewed sampling distributions, which were not necessarily normalised by log-transforming them.

Bakker (1999) compared the albumin concentration (ALB) (as the reference) against the albumin: creatinine ratio (ACR) , in 1171 men and 1223 women with diabetes (type not stated). Urine samples
were timed overnight and stored, if necessary, for up to four days at 4°C. Using receiver operating curves and an ALB = 20µg / min as the reference cut off value, the best discriminator values were 15 mg / l for ALB and, for ACR, 1.8g / mol for men and 2.5g/mol for women, although, for ACR, the discriminator values were dependent upon age. Bakker (1999) also reviewed the published data for sensitivity and specificity for ALB (mg/l) or ACR (g/mol) versus albumin excretion rate (mg/min) as reference. His conclusion was that ACR performed better than ALB in screening for microalbuminuria, although the disadvantage is that it needs age and sex-specific discriminator values. However whilst ACR may be the better discriminator as a screening tool for detection of microalbuminuria, it may not be the most practical option for routine clinic sampling.

Which sample?

A comparison of overnight AER and daytime albumin:creatinine ratio in 311 people (either Type 1 or Type 2, none with proteinuria) from general practices in the Poole area of England was carried out by Gatling et al (1988). A comparison of the values of different urine samples to identify microalbuminuria (AER >30µg/min), produced values for sensitivity, specificity, and predictive value as follows: daytime midstream urine albumin:creatinine ratio >3.0mg/mmol, 80%, 81%, 12; overnight urinary albumin concentration >20µg/ml , 82%, 96%, 60; overnight albumin:creatinine >3.5 mg/mmol, 88%, 99%, 72; overnight albumin:creatinine >2.0 mg/mmol, 96%, 100%, 35.

Summary

Overnight albumin:creatinine ratio sampling has the best overall specificity and sensitivity.

Clinical overview - the case for regular screening for microalbuminuria or proteinuria

This summary section considers the case for microalbuminuria screening for people with Type 2 diabetes by bringing together the work of preceding sections and also referring to the results of the reviews in the following Section 7.

There is reasonably good evidence that microalbuminuria and proteinuria can be measured qualitatively by near-patient tests and quantitatively by laboratory tests. There is also good epidemiological evidence that people with Type 2 diabetes may progress through from a normal level of urinary protein excretion to microalbuminuria and subsequently to proteinuria, indicating the onset of end stage renal failure.

If it were not possible to affect progression from microalbuminuria to proteinuria it could be argued that the only value of routine testing is to identify people who are approaching end stage renal disease. This could be done by the inexpensive and effective methods of assessing serum creatinine and urine protein excretion on an annual review. Indeed, because of the need to prepare people with failing renal function for dialysis and renal replacement programmes, this guideline does propose annual serum creatinine measurement with a recommendation for referral to a renal specialist when creatinine levels reach 150 µmol/l.

However, as previous sections of the review have shown, the presence of microalbuminuria at diagnosis, or the development of microalbuminuria, is associated with progression to proteinuria and with a higher mortality rate from cardiovascular disease and end stage renal failure. Although there is little evidence of the effectiveness of primary prevention in reducing the risk of renal failure (for example by using low
protein diets) there is now evidence of the reno-protective capacity of some classes of blood pressure lowering drugs (presented in Section 9).

These drug classes, ACE Inhibitors and Angiotensin II receptor antagonists, are effective in reducing blood pressure (although in diabetes they usually have to be prescribed in combination with other classes of drugs). Early case finding of people with microalbuminuria in Type 2 diabetes, using annual microalbuminuria screening, although having a cost, may serve to identify people who would benefit from early treatment of raised blood pressure.

An alternative management strategy could be to commence treatment with all people with Type 2 diabetes with ACE Inhibitors (or AIIRAs), where their blood pressure is above 135/75 mmHg, without screening to identify those people with microalbuminuria. But this would mean that those people who did not have microalbuminuria (the majority of the group) would face the prospect of an aggressive treatment regime where the evidence does not support that approach (their target threshold is 140/80 mmHg). Moreover, these two classes of drugs are expensive, require caution in their prescription, can have unpleasant side effects and there is no current evidence that these two drug classes are more effective than others in people without microalbuminuria.

For these reasons the Renal care group and the project Recommendations panel reached a strong consensus that all people with Type 2 diabetes should be screened annually for microalbuminuria, and that those people who have persistent microalbuminuria should be treated according to the recommendations in the introduction to Section 7. This will enable targeting of effective treatment on those patients for whom the treatment is of value.

References: choice of urine sample for testing
(with AHCPR evidence grades where appropriate, see page 18)

  Bakker (1999)
  III Collins et al (1993)
  III Hara et al (1994)
  III Osberg et al (1990)
  III Silver et al (1987)
  III Vermes and Spooren (1992)
7. Effective interventions for renal disease in Type 2 diabetes
Interventions

### Definition of higher risk urine albumin excretion

**microalbuminuria** – albumin : creatinine ratio greater than or equal to 2.5 mg/mmol (men)/greater than or equal to 3.5 mg/mmol (women) or albumin concentration greater than or equal to 20 mg/l

**proteinuria** – albumin : creatinine ratio greater than or equal to 30 mg/mmol or albumin concentration greater than or equal to 200 mg/l

---

**For people with lower risk urine albumin excretion**

**Definition of lower risk urine albumin excretion**

Lower risk urine albumin excretion is defined as less than the lower limit of higher risk urine albumin excretion.

---

**Recommendations**

- Maintain good blood pressure control (at or below 140/80 mmHg). (A)
- Measure urinary albumin:creatinine ratio or albumin concentration annually. (C)

**Evidence Statements**

*The lower the haemoglobin A1c, the lower the risk of developing microalbuminuria or proteinuria or renal impairment. (Ib)*

*In the UKPDS, interventions to reduce mean haemoglobin A1c from 7.9 to 7.0% were associated with an absolute risk reduction of developing nephropathy of 11% over 12 years. (Ib)*

*In the UKPDS, interventions to reduce mean blood pressure from 154/87 to 144/82 mmHg were associated with a reduction in absolute risk of developing nephropathy by 8% over 6 years. (Ib)*

*The consensus of the guidelines on the management of blood pressure in people with Type 2 diabetes published by the National Institute for Clinical Excellence (Hutchinson et al 2002) and the British Hypertension Society (Ramsay et al 1999), is that target blood pressure in people without microalbuminuria or proteinuria should be at or below 140/80 mmHg. (III)*
**For people with higher risk urine albumin excretion**

<table>
<thead>
<tr>
<th>Definition of higher risk urine albumin excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>microalbuminuria</strong> – albumin : creatinine ratio greater than or equal to 2.5 mg/mmol (men)/greater than or equal to 3.5 mg/mmol (women)/or albumin concentration greater than or equal to 20 mg/l</td>
</tr>
<tr>
<td><strong>proteinuria</strong> – albumin : creatinine ratio greater than or equal to 30 mg/mmol or albumin concentration greater than or equal to 200 mg/l</td>
</tr>
</tbody>
</table>

**Recommendations**

Maintain blood pressure at or below 135/75 mmHg. (A)

To maximise renal and cardiovascular protection, begin therapy with an appropriately licensed ACE inhibitor. (A)

ACE inhibitors are the drug class of first choice. To achieve target blood pressure, use combination therapy if ACE inhibitors alone are not fully effective. Combination therapy is likely to be necessary for most patients. (A)

If ACE inhibitors are contraindicated or cause side-effects, use Angiotensin II receptor antagonists as an alternative. (B)

Measure urinary albumin:creatinine ratio or albumin concentration and serum creatinine levels at each visit (at least annually). (C)

**Evidence statements**

Cardiovascular risk is increased in people with Type 2 diabetes with microalbuminuria (2 - 4 fold increase) and proteinuria (5 - 8 fold increase), compared to people with normoalbuminuria. (III)

There is evidence from one study that improved glucose control in microalbuminuric people with Type 2 diabetes reduces the numbers progressing to proteinuria. (Ib)

Reduction of blood pressure to less than 135/75 mmHg reduces the rate of progression of renal disease. (Ib)

In microalbuminuric people with Type 2 diabetes, treatment with a variety of ACE inhibitors, β-blockers, non-DHP and long acting DHP calcium channel blockers and diuretics reduces albumin excretion and the risk of progression of microalbuminuria to proteinuria. The lowest achieved blood pressure in these studies was 134/75 mmHg. (Ia)
The reduction in albumin excretion with ACE inhibitors and with Angiotensin II receptor antagonists is generally greater than with other classes of antihypertensive agents, suggesting that these two classes of drugs have antiproteinuric effects independent of blood pressure. (Ia)

In a sub-group analysis of one study, treatment with ACE inhibitors reduced the risk of cardiovascular events by 27% in microalbuminuric people with Type 2 diabetes. The risk of nephropathy was also reduced. (Ib)

No study has been long enough to show prevention of end stage renal disease but several studies suggest that both ACE inhibitor treatment and Angiotensin II receptor antagonist treatment may slow the decline in glomerular filtration rate compared to placebo and to other combinations of drugs. (Ia)

In hypertensive, proteinuric people with Type 2 diabetes, antihypertensive therapy with ACE inhibitors, non-DHP calcium channel blockers and β-blockers reduces protein excretion. Lowest achieved blood pressure was 136/84 mmHg. (Ia)

Evidence suggests that while ACE inhibitors and Angiotensin II receptor antagonists are more effective than other agents at reducing proteinuria, most patients will require combination therapy. (Ia)

The effect of reduction of dietary protein intake on the rate of decline in renal function in Type 2 diabetes remains unclear. (Ib)

Starting ACE inhibitor therapy for patients:

- caution in patients with peripheral vascular disease/renovascular disease
- caution in patients with raised serum creatinine

In all patients, measure serum creatinine and electrolytes one week after:

- initiating ACE inhibitor therapy
- each increase in dose

*Some ACE inhibitors are not licensed for use at the blood pressure levels recommended in this guideline
Introduction

From information presented earlier in relation to incidence, natural history and progression of renal disease, and more importantly the issues concerning increased cardiovascular risks associated with presence of renal disease, it is clear that interventions to reduce both development and progression of diabetic renal disease and associated cardiovascular risk are crucial. The relationship between raised blood pressure and diabetic renal disease is particularly important so the focus of the evidence review of interventions was concerned with interventions with endpoints of reducing hypertension and slowing the progression of renal disease. The evidence suggests that some classes of antihypertensive agent have benefits over and above their antihypertensive effect in renal disease, especially in terms of delaying the progression of renal disease.

The searches conducted to identify the studies for this section took as a starting point the identification of blood pressure outcomes and renal outcomes in studies concerned with interventions used in people with Type 2 diabetes. The study type hierarchy of choice was first, meta-analyses, second systematic reviews, third randomised controlled trials. From these searches the studies identified the following main types of interventions; antihypertensive agents; blood glucose control interventions; lipid regulating agents; multifactorial interventions and dietary interventions. To take account of the rapidly changing evidence on drug interventions, the review was updated in November 2001.

All of the studies available and reviewed are of too short duration to explore whether any impact on end stage renal failure resulted from these interventions.

Summaries of individual reviews and studies

Evidence tables/summaries for each of the drug classes reviewed are published in section 9. In compiling the overall summaries in Section 7 (above), the Working group reviewed the evidence in each evidence table, considered the impact of each drug class individually and them compared the impact of one drug class with another. For individual trials, only those papers with a clinically important (more than 12 month) effect on renal function were considered. For completeness studies with shorter timescales were also reviewed. These evidence tables are available from the authors’ at the project’s website www.shef.ac.uk/guidelines/.

Antihypertensive drugs - summary of effects

All antihypertensive agents appear to have benefits for people with Type 2 diabetes who have renal disease, in that lowering blood pressure appears to lead to beneficial reductions in proteinuria. Reduction in the level of proteinuria may be taken as a proxy for improved renal function, although most studies measure albumin excretion rate rather than directly measuring renal function through glomucular filtration rate.
For people with Type 2 diabetes who have microalbuminuria, the use singly or in combination of ACE inhibitors, Angiotensin II receptor antagonists, β-blockers, non-DHP and long acting DHP calcium channel blockers and diuretics reduces albumin excretion and reduces the risk of progression of microalbuminuria to proteinuria.

**ACE inhibitors and Angiotensin II receptor antagonists**

ACE inhibitors have a beneficial effect on proteinuria even if there is little reduction in blood pressure. For the same reduction in blood pressure they also appear to have a greater impact on proteinuria than other antihypertensives, except for Angiotensin II receptor antagonists. Generally, the reduction in albumin excretion with ACE inhibitors and Angiotensin II receptor antagonists is greater than with other classes of antihypertensive agents, suggesting these two classes of drugs have antiproteinuric effects independent of blood pressure. This appears to apply to both hypertensive and normotensive people with Type 2 diabetes. Evidence from the effectiveness of ACE inhibitors is strong and comes from a number of meta-analyses and systematic reviews of trials (Lovell 2000, Abhijit et al 2000, Weidmann et al 1995, Kasiske et al 1993, Maki et al 1995, Gansvoort et al 1995).

Recent trials (Muirhead et al 1999, Lacouereire et al 2000, Mongensen 2000, Lewis et al 2001, Brenner et al 2001, Parving et al 2001) suggest that Angiotensin II receptor antagonists may be as effective as ACE inhibitors in providing cardiovascular and renal protection. However, although of reasonable quality, the evidence base is still emerging and does not yet justify a recommendation as the first line therapy for people with Type 2 diabetes and albuminuria. Where people with Type 2 diabetes have microalbuminuria and are unable to tolerate ACE inhibitors, Angiotensin II receptor antagonists should be offered as an alternative first line therapy.

It should be noted that not all ACE inhibitors have product licenses for use at blood pressure levels equivalent to the recommended treatment commencement levels. Prescribers should be aware of these limitations and prescribe accordingly. Product information is available for UK licenses from the APBI at www.emu.vhn.net.

**Lipid regulating agents**

The impact of statins on renal function was inconclusive from the studies reviewed and insufficient evidence was available for any other lipid-regulating agents.

**Improved blood glucose control**

Results from the UKPDS (1998a, 1998b, 1998c) indicate that tight blood glucose control (at or below HbA1c 6.5% to 7.5% according to the individual’s target) delays the development of renal disease.

The results from UKPDS appear to be supported in the findings of a study by Ohkubo et al (1995). This found that, over a six year period, a lower haemoglobin A1c delayed the onset and progression of diabetic nephropathy.
Dietary interventions

A review by Kasiske (1993) suggested that people with diabetes could benefit from a reduction in dietary protein intake. However the review included both randomised and non-randomised trials. A trial of protein restriction (Pijls et al 1999) in people with Type 2 diabetes showed some reduction in proteinuria at 6 months (28%, p<0.001) but the reduction was not clinically significant at 12 months (18% reduction, p=0.08). Thus the reliability of this evidence remains in question, especially as far as being able to make clinical practice recommendations based upon the results.

A review that examined the impact of dietary restrictions on people with Type 1 diabetes appears to suggest that a restriction in dietary protein intake may help slow progression of renal failure (Waugh 2000).

There is insufficient evidence about the benefits of a reduced salt diet on renal outcomes in people with Type 2 diabetes to make recommendations in this area.

Multifactorial intervention

Gaede’s (1999) multifactorial intervention study of behaviour change (in smoking, diet and exercise) in parallel with a stepwise introduction of pharmacological therapy showed a reduction in rate of progression of renal disease.
8. Research issues

The renal care working group identified the following areas in the course of the guideline process which they felt were inadequately addressed by the available literature.

♦ Greater understanding of the natural history of renal disease in Type 2 diabetes is needed.

♦ Clarification is needed about the differing proportions of people with Type 1 and Type 2 diabetes in renal replacement therapy.

♦ What are the differences in prevalence of renal disease between different ethnic groups, and the reasons for these differences?

♦ Is it feasible for renal registries to identify people of different ethnic origins?

♦ What are the genetics of diabetic nephropathy in Type 2 diabetes?

♦ What are the impact of serum lipids on renal disease in Type 2 diabetes?

♦ Are Angiotensin II receptor antagonists better than ACE inhibitors or are they best as an additional therapy?

♦ What are the ethnic origin issues in progression of renal disease in Type 2 diabetes?

♦ What are the optimum blood pressure targets to aim for?

♦ What is the role of thiazolidinediones (eg rosiglitazone) in reducing proteinuria?
9. Detailed evidence review of drug and non-drug interventions
Drug interventions
## Antihypertensives:

### ACE inhibitors: systematic reviews/meta-analyses

<table>
<thead>
<tr>
<th>Author</th>
<th>Research question</th>
<th>Review type with meta-analysis</th>
<th>Study design, interventions: follow-up period</th>
<th>Total sample number</th>
<th>Diabetes status and duration</th>
<th>Age (mean/SD/range)</th>
<th>Male/female</th>
<th>Ethnicity</th>
<th>Main outcomes and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovell 2000</td>
<td>Do ACE inhibitors slow progression of early diabetic renal disease, other than through their antihypertensive effect?</td>
<td>Systematic review with meta-analysis MEDLINE plus personal reference lists, and references from retrieved studies</td>
<td>11 randomised controlled trials of ACE inhibitors, captopril (5 studies), enalapril (5) and lisinopril (1), all vs inert placebo (except 1 vs diuretic). Usual diabetic diets, except 1 had salt reduction: Follow-up at least 1 year</td>
<td>ACE 185, placebo 183 (completion rate 88%) Type 1 only (7/11 studies), Type 2 only (3/11), both (1/11), all normotensive with microalbuminuria or proteinuria. No difference in duration of diabetes between treatment and placebo groups (95% CI -0.8, 0.3 years) (duration not given). No difference in ages between treatment and placebo groups (95% CI -1.6, 0.5 years) (ages not given). No difference in sex, treatment group 53% male, placebo 57%</td>
<td>Changes in: Baseline End study Change (95% CI) meta-analysis</td>
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<td>systolic BP (6/11 studies)</td>
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<td>129.7 126.9 sig 119.9 127.7 sig -12.7 (-17.0, -8.3) sig</td>
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<td>mean arterial BP (4/11)</td>
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<td>albumin excretion rate (11/11)</td>
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<td>glomerular filtration rate (ml/min/1.73m²) (4/11)</td>
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<td>ACE can arrest, even reduce, albumin excretion rate in microalbuminuric normotensive diabetics, accompanied by reduction or prevention of increase in systematic blood pressure. No apparent substantial side-effects. Any direct link with postponement of end-stage renal failure not shown.</td>
</tr>
</tbody>
</table>
# Antihypertensives:

## ACE inhibitors: systematic reviews/meta-analyses

<table>
<thead>
<tr>
<th>Author</th>
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<th>Total sample number</th>
<th>Main outcomes and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abhijit et al 2000</td>
<td>Do ACE inhibitors slow progression of renal disease, from any cause, over a broad range of functional renal impairment? Do ACE inhibitors prevent: a) progression of patients with microalbuminuria to proteinuria? b) development of end stage renal disease (ESRD) or doubling of serum creatinine concentration in patients with proteinuria?</td>
<td>Meta-analysis MEDLINE 1970-1999, abstracts of American Society of Nephrology meetings 1992-1999, bibliographies of original articles and reviews, reference lists from contacted pharmaceutical companies. Cumulative incidence of events for each study treatment and placebo group, aggregate relative risk (RR) (95% CI) for microalbuminuric and proteinuric groups. Fixed effects model used. Sensitivity analysis of fixed and random effects models.</td>
<td>20 published, 2 unpublished randomised, placebo-controlled parallel trials, with ≥1 year follow-up, in adults (mean age ≥15 years) with chronic renal disease from any cause. Used 15/20 and 1/2 with data appropriate for analysis.</td>
<td>Microalbuminuric group: Aggregate RR for developing proteinuria 0.35 (95% CI 0.24-0.53) (9 studies) (all patients had diabetic renal disease) Proteinuric group: Aggregate RR for developing ESRD or doubling creatinine serum concentration 0.6 (95% CI 0.49-0.73) (7 studies) (no subset analysis for patients with diabetic renal disease) RR for death 1.05 (95% CI 0.57-1.95) (not significant)</td>
<td>Treatment of chronic renal insufficiency with ACE inhibitors delayed the progression of disease compared with placebo, irrespective of cause of renal insufficiency and spectrum of disease severity examined.</td>
</tr>
</tbody>
</table>
## Antihypertensives:

### ACE inhibitors: systematic reviews/meta-analyses

<table>
<thead>
<tr>
<th>Author</th>
<th>Research question</th>
<th>Review type, Databases used</th>
<th>Study design, interventions: follow-up period</th>
<th>Total sample number</th>
<th>Diabetes status and duration</th>
<th>Main outcomes and results</th>
</tr>
</thead>
</table>
| Weidmann et al 1995 | A comparison of renal therapeutic efficacy of different antihypertensive agents in patients with diabetic nephropathy | Meta-analysis, no information on databases, latest paper 1995 (adds 11 papers to previous meta-analysis of 93 papers) | No information on study designs, 126 treatment groups. ACE (72 treatment groups), diuretics and/or β blockers (24), Ca antagonists (18), nifedipine (12). Follow-up at least 4 weeks | 2151 diabetic patients with microalbuminuria or clinical proteinuria | Type 1-39% of studies, Type 2-40%, both types-14%, unspecified-7%. No significant differences between treatment groups for age, sex, and type of diabetes. Mean age 46 years | Changes in blood pressure associated % change from baseline (95% CI)  
ACE Ca-antagonists nifedipine diuretics &/or β blockers  
proteinuria (126/126)  
albuminuria (126/126)  
glomerular filtration rate (58/126)  
changes in  
proteinuria  
albuminuria  
glomerular filtration rate  
ACE induced changes in albuminuria sig correlated with decreases in BP (p<0.001)  
ACE more effective than other antihypertensive agents in reducing diabetic microalbuminuria or clinical proteinuria. |
# Antihypertensives:

## ACE inhibitors: systematic reviews/meta-analyses

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<tr>
<th>Author</th>
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<th>Total sample number</th>
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</tr>
</thead>
</table>
| Kasiske et al   | To assess relative effect of different antihypertensive agents on proteinuria and renal function in patients with diabetes | Meta regression. MEDLINE and references in recent publications. Time frame not given, papers cover 1976–1991. | 1993            | 100 studies identified, 12 of these were randomised controlled trials. Subanalysis on 11 trials with ACE inhibitors. Follow-up >6 mth for 27% groups (>1 year for 13%). | In total, 2494 patients in 168 study groups (mean±SD number per group 15±10). Type 1 (49% of groups), Type 2 (32%), both (11%), unknown type (9). Mean±SD age (112/168 groups) 48±12 years. Ethnicity not given. Separate details for patients in 11 randomised controlled trials not given. |                  | mean arterial pressure (11/11) treatment effect of ACE –3.05mm Hg (95% CI –4.46, -1.46) p<0.05  
urea albumin excretion (11/11) treatment effect of ACE –2.85mL/min (95% CI –6.55, 0.78), p>0.05  
glomerular filtration rate (11/11) ln treatment effect of ACE –0.59, 95%CI –0.35, -0.82 p<0.05  
ACE caused significant reduction in mean arterial blood pressure and urine albumin excretion but were not significantly different to controls for glomerular filtration rate. |
| Maki et al      | To determine if the effects of antihypertensive agents differ, if the effects are similar in diabetic and non-diabetic patients with renal disease, and if the effects are independent of blood pressure reductions | Meta-analysis MEDLINE and references in recent papers. Time period 1/1980–1/1994. For randomised controlled trials, weighted means were calculated | 1995            | 84 studies identified, 16 were randomised controlled trials. Subanalysis on 14 trials with ACE inhibitors. Follow-up at least 6 months (44% were longer than 12 months). | In total, 156 study groups, Type 1 (23%), Type 2 (30%), type unknown (47%). In trials, 12/14 included diabetes patients. Mean±SD study duration 20±17 months mean±SD age 47±9 years (known in 146 groups). Separate details for patients in 14 randomised controlled trials not given. |                  | mean arterial pressure (11/14) reduction greater in ACE vs controls: mean –4.0mmHg (95% CI –4.9, -3.0)  
glomerular filtration rate (14/14) decline less in ACE vs controls: mean 0.13mL/min/mth (95% CI 0.10, 0.16)  
renal plasma flow (7/14)  
protein excretion (11/14) no differences between ACE and controls: mean 22mL/min (95% CI –25, 69) greater decline with ACE vs controls: mean –0.51 (95% CI –0.68, -0.35) (ln treatment/controls)  
ACE inhibitors have additional beneficial effects on proteinuria independent of blood pressure reductions, long term beneficial effects of antihypertensive agents on proteinuria and glomerular filtration rate are similar in diabetic and non-diabetic patients, these beneficial effects are proportional to blood pressure reductions. |
Antihypertensives:

ACE inhibitors: systematic reviews/meta-analyses

<table>
<thead>
<tr>
<th>Author</th>
<th>Research question</th>
<th>Review type</th>
<th>Study design, interventions: follow-up period</th>
<th>Total sample number</th>
<th>Diabetes status and duration</th>
<th>Main outcomes and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gansvoort et al 1995</td>
<td>To determine whether ACE inhibitors differ from other antihypertensives in their effect to lower proteinuria.</td>
<td>Meta-analysis, MEDLINE, EMBASE, references from recent publications. Time frame not stated, search conducted 2/1994, papers used 1987-1993. Variance of treatment effect and mean weighted differences calculated (35 studies)</td>
<td>41 studies, comprising randomised (34), non-randomised, cross-over, parallel studies of ACE vs another antihypertensive in hypertensive patients (33/41), normotensives (2/41), and mixed (6/41). Follow-up periods not stated.</td>
<td>1124 patients, in 68 study groups. Diabetes patients (type unknown) 315. Duration of diabetes, age and ethnicity not given.</td>
<td>Changes in urinary protein excretion mean arterial blood pressure multivariate analyses, 315 diabetic patients only, mean treatment effect ACE induced response comparator drugs -37.4% (95% CI –41.3, -33.2) -23.7% (95% CI –26.5, -20.8) -12.4% (95% CI –13.9, -11.0) -14.0% (95% CI –14.6, -13.5) Mean antiproteinuric effect significantly greater, but no difference for blood pressure lowering effect, with ACE inhibitors compared with other anti-hypertensive drugs.</td>
<td></td>
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</tbody>
</table>
Antihypertensives:

ACE inhibitors compared with placebo: randomised control trials, ≥ 12 month follow-up

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Setting, location</th>
<th>Numbers randomised</th>
<th>Follow-up Analysis</th>
<th>Patient status (Renal status)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capek et al (1994)</td>
<td><strong>T1</strong>: captopril (37.5mg daily in three doses of 12.5mg)</td>
<td>Not reported, however Austrian authors location</td>
<td>At start <strong>T1</strong>: 10, <strong>T2</strong>: 10, 5 drop outs. At end <strong>T1</strong>: 9, <strong>T2</strong>: 6. <strong>T1</strong>: 64.0±8.2 years (n=9), <strong>T2</strong>: 63.8±1.1 years (n=6). <strong>T1vT2</strong> no significant difference in age, sex, duration of diabetes. Not reported</td>
<td>12 months <strong>Type 2 diabetes with microalbuminuria (AER 30-300mg/24h) and retinopathy. 4 defined as hypertensive, all T1.</strong></td>
<td><strong>No significant changes in SBP or DBP in either T1 or T2 from baseline to 12 months.</strong> <strong>Hypertensive subgroup (n=4 all T1)</strong> <strong>T1</strong>: Significant decrease (p&lt;0.05) in SBP and DBP over 12 months. <strong>Baseline</strong> 154±2/88±1, <strong>12 months</strong> 142±7/78±5</td>
<td><strong>No significant change in T1 vs T2 from baseline to 12 months.</strong> <strong>Hypertensive subgroup (n=4 all T1)</strong> <strong>T1</strong>: significant reduction after 3 months (baseline 74.4 vs. 24mg/24h), and after 6 months (41mg/24h)(p&lt;0.05), but at 12 months initial level reached again. <strong>Glomerular filtration rate</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Urinary albumin</th>
<th>Other parameters assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mean ± SD)</td>
<td>Baseline 139±17, 12 months 138±13</td>
<td><strong>T1 (n=9)</strong></td>
</tr>
<tr>
<td>DBP (mean ± SD)</td>
<td>Hypertensive subgroup (n=4 all T1) <strong>T1</strong>: Significant decrease (p&lt;0.05) in SBP and DBP over 12 months. <strong>Baseline</strong> 154±2/88±1, <strong>12 months</strong> 142±7/78±5</td>
<td><strong>T1 (n=9)</strong></td>
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<td></td>
<td><strong>Hypertensive subgroup (n=4 all T1)</strong> <strong>T1</strong>: significant reduction after 3 months (baseline 74.4 vs. 24mg/24h), and after 6 months (41mg/24h)(p&lt;0.05), but at 12 months initial level reached again.</td>
<td><strong>T1 (n=9)</strong></td>
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</tbody>
</table>
## Antihypertensives:

### ACE inhibitors compared with placebo: randomised control trials, ≥ 12 month follow-up

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Setting, location</th>
<th>Numbers randomised</th>
<th>Follow-up Analysis</th>
<th>Patient status (Renal status)</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Ravid et al (1998b) | **T1**: enalapril (10mg/day)  
**T2**: placebo | Hospital outpatients clinics in the greater Tel-Aviv area, Israel          | **Mean age ±SD (range) (years)**  
**Ethnic group**  
**T1**: 77  
**T2**: 79  
54.9±3.2 (range37-59)  
**T1**: 55.5±3.1 (36-54)  
**T2**: 54.4±2.9 (38.0-59.0)  
Not reported | **6 years**  
Type of analysis not stated.  
Power calculation done. | **Type 2**  
Mean blood pressure (arterial) (mmHg) was significantly lower (p<0.05) in T1 vs T2 in year 5 only.  
(0 98.2±4.3 96.1±3.8  
1 96.0±3.8 98.0±3.1  
2 97.0±4.2 97.0±4.0  
3 97.0±3.4 99.0±4.2  
4 98.0±3.4 101.0±3.8  
5 98.0±3.1 102.0±4.0  
6 100.0±4.7 102.0±4.2)  
*p<0.05.* | **Significant changes in albumin excretion (mg/24hr) from baseline to year 6 in both T1 (p<0.042) and T2 (p=0.001).**  
**Time (years)**  
**T1 (n=77)**  
0 11.6±7.0  
1 10.3±5.0  
2 9.7±4.6  
3 11.2±7.0  
4 12.3±6.0  
5 13.1±7.0  
6 15.8±8.0  
**T2 (n=79)**  
0 10.8±8.0  
1 12.1±6.0  
2 14.4±7.0  
3 17.2±6.0  
4 18.3±7.0  
5 22.3±10.0  
6 26.5±10.0  
**All normoalbuminuric (UAE ≤30mg/24hr) at baseline. Microalbuminuria (>30mg/24hr) developed in 5 of T1 and 15 of T2. Significant differences (p=0.001) in degree of albuminuria T1 vs T2, in years 5 and 6. T1 treatment resulted in an absolute risk reduction of 12.5% (95%CI: 2-23) (p=0.042) for developing microalbuminuria.** |

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Urinary albumin</th>
<th>Other parameters assessed</th>
</tr>
</thead>
</table>
| Significant decrease in creatinine clearance from baseline to year 6 in both T1 (p=0.025) and T2 (p=0.001).  
**Time (years)**  
**T1 (n=77)**  
0 1.78±0.13  
5 1.65±0.1  
6 1.63±0.12  
**T2 (n=79)**  
0 1.83±0.15  
5 1.60±0.12  
6 1.57±0.17  
**Significant difference (p=0.04) in decrease T1 vs T2, in years 5 and 6.** |
## Antihypertensives:

**ACE inhibitors compared with placebo: randomised control trials, ≥ 12 month follow-up**

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<tr>
<th>Author</th>
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<th>Follow-up Analysis</th>
<th>Patient status (Renal status)</th>
<th>Outcome</th>
<th>Other parameters assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmad et al (1997)</td>
<td>T1: enalapril (10mg daily)</td>
<td>Outpatient clinic, India</td>
<td>T1: 60 T2: 60</td>
<td>At start T1: 52 T2: 51</td>
<td>5 years</td>
<td>Type 2 normotensives with microalbuminuria (AER 20-200µg/min)</td>
<td>Rate of progression from microalbuminuria to proteinuria was 7.7% in T1 and 23.5% in T2 producing a 66.7% reduction after 5 years of therapy (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>T2: placebo</td>
<td></td>
<td></td>
<td></td>
<td>4 patients in T1 and T2 had systolic blood pressure≥145mmHg or diastolic blood pressure≥95mmHg. Long acting nifedipine (10-20mg/day) was prescribed.</td>
<td></td>
<td>Rate of progression from microalbuminuria to proteinuria was 7.7% in T1 and 23.5% in T2 producing a 66.7% reduction after 5 years of therapy (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>T1: 49.8±3.0 (43-58)</td>
<td></td>
<td>5 years</td>
<td>No changes in mean systolic and diastolic blood pressure over time in T1 or T2 or T1 vs T2.</td>
<td>Significantly lower AER in T1 vs T2 over 2-5 years (p&lt;0.001) AER (geometric mean) (µg/min)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>T2: 50.3±2.1 (44-55)</td>
<td></td>
<td>4 patients in T1 and T2 had systolic blood pressure≥145mmHg or diastolic blood pressure≥95mmHg. Long acting nifedipine (10-20mg/day) was prescribed.</td>
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</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>Blood pressure</td>
<td>Urinary albumin</td>
<td>Other parameters assessed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SBP</td>
<td>T1(n=52) T2(n=51)</td>
<td>Year 5</td>
</tr>
<tr>
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<td></td>
<td>DBP</td>
<td>T1(n=52) T2(n=51)</td>
<td>Year 5</td>
</tr>
</tbody>
</table>

### Results

- **Blood pressure**
  - **SBP**
    - T1(n=52): 132±6.7
    - T2(n=51): 134±6.7
  - **DBP**
    - T1(n=52): 81±3.8
    - T2(n=51): 83±5.1

- **Urinary albumin**
  - T1(n=52): 55±33
  - T2(n=51): 55±31

- **Other parameters assessed**
  - Glomerular filtration rate
Antihypertensives:

ACE inhibitors compared with placebo: randomised control trials, ≥ 12 month follow-up

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<tr>
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<th>Patient status (Renal status)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ravid et al (1996)</td>
<td>Years 1-5 T1 enalapril maleate (10mg/day) T2 placebo</td>
<td>Not reported, however authors based in Israel</td>
<td>Years 1-5 T1 49 T1a 15* T2 45 T2a 22* T2a 21 * dropouts in these groups 44±4 (range, 34 to 49) Not reported</td>
<td>7 years in total (5 years as blind+2 years further unblinded)</td>
<td>Type 2 with microalbuminuria (30-300mg/24h)</td>
<td>Taking enalapril resulted in an absolute risk reduction of 42% (95%CI 15-69) (p&lt;0.001) over a 7 year period for proteinuria. For AER (mg/24hr), serum creatinine</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>Serum creatinine</td>
</tr>
</tbody>
</table>
### Antihypertensives:

ACE inhibitors compared with placebo: randomised control trials, ≥ 12 month follow-up

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<tr>
<th>Author</th>
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<th>Setting, location</th>
<th>Numbers randomised</th>
<th>Mean age ±SD (range) (years)</th>
<th>Follow-up Analysis</th>
<th>Patient status (Renal status)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Outcomes Prevention Evaluation (HOPE) Study Investigators (2000)</td>
<td>T1: ramipril (10mg) T2: placebo</td>
<td>19 countries: 129 centres in Canada, 27 centres in the USA, 76 centres in 14 European countries, 30 centres in Argentina and Brazil and 5 centres in Mexico</td>
<td>T1: 1808 T2: 1769</td>
<td>T1: 65.3 ± 6.4 T2: 65.6 ± 6.6</td>
<td>Median: 4.5 years, the study was stopped 6 months early by the independent data safety and monitoring board because of a consistent benefit of T1 over T2.</td>
<td>T1: 98% Type 2, 31% microalbuminuric, 58% hypertensive. T2: 97% Type 2, 33% microalbuminuric, 54% hypertensive</td>
<td>Significant reduction in blood pressure from baseline in T1 compared with T2 (p&lt;0.01). T1(n=1808)/T2(n=1769) SBP Baseline 141.7 142.3 change at 1 month -5.3 -1.3 † change at 2 years -2.7 0.6 change at final visit -1.9 0.55 ‡ DBP Baseline 80.0 79.3 change at 1 month -2.6 -0.3 † change at 2 years -2.6 -1.05 † change at final visit -3.3 -2.31 ‡ † p=0.0001, ‡ p=0.0002, † p=0.008, for difference in change from baseline T1 vs. T2. Relative risk reduction 25% (12-36)(p=0.0004) for T1 on primary outcome (combined, MI, stroke, CV death) with or without adjustment for changes in blood pressure.</td>
</tr>
</tbody>
</table>
Antihypertensives:

ACE inhibitors compared with no treatment: randomised control trials, ≥ 12 month follow-up

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Setting, location</th>
<th>Numbers randomised</th>
<th>Follow-up Analysis</th>
<th>Patient status (Renal status)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sano et al (1996)</td>
<td>T1: enalapril (5mg/day) T2: no treatment</td>
<td>Outpatient clinic hospital, Japan</td>
<td>At end T1: 28 T2: 28 after 6 lost to follow-up</td>
<td>Mean age±SEM T1 62.0±4.4 T2 64.3±4.8 No differences in age or duration of diabetes between T1 and T2</td>
<td>Type 2 normotensive, with microalbuminuria (20-300mg/24hr)</td>
<td>There were no differences over the 4 years in either T1 or T2 or T1 vs T2. Blood pressure (mean±SEM) T1(n=30) T2(n=29) Urinary albumin Other parameters assessed</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>4 years Intention to treat analysis. No power calculation</td>
<td></td>
<td>DBP Baseline 73.9±2.6 72.4±2.8 48 Months 70.0 75</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>SBP Baseline 136.4±3.6 134.2±3.9 48 months 132 130</td>
</tr>
</tbody>
</table>
## Antihypertensives:

### ACE inhibitors compared with beta-blockers: randomised control trials, ≥ 12 month follow-up

<table>
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<tr>
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<th>Numbers randomised</th>
<th>Follow-up Analysis</th>
<th>Patient status (Renal status)</th>
<th>Results</th>
<th>Outcome</th>
<th>Other parameters assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schnack et al (1996)</td>
<td>T1: ramipril (2.5mg/day-5mg/day max dose if required) T2: atenolol (50mg/day-100mg/day max dose if required) Additional combination therapy given to both groups as necessary to control diastolic blood pressure. At 12 months: T1: 46% - 2.5mg/day ramipril 30% - 5.0mg/day ramipril 24% - 5.0mg/day ramipril + 5mg felodipine T2: 56% - 50mg/day atenol 20% - 100mg/day atenol 24% - 100mg/day atenol + 25mg hydrochlorothiazide</td>
<td>Outpatient clinic, Austria</td>
<td>At start T1: 46 T2: 45 At end T1: 36 T2: 39 Median (range) T1: 66 (62-72) T2: 68 (61-72) Not reported</td>
<td>1 year Type of analysis not stated. No power calculation</td>
<td>Type 2 with microalbuminuria (24-200mg albumin/g creatinine)</td>
<td>Both treatments show significant reduction (all p&lt;0.001) in SBP, DBP, mean BP from baseline to 12 months. Medians (quartiles, Q25 – Q75) T1 (n=36) T2 (n=39)</td>
<td>No change in albumin creatinine ratio in T1, increase in T2 (p&lt;0.01) from baseline to 12 months; T1 vs T2 (p&lt;0.02). So albumin creatinine ratio higher in T2 vs T1 at 12 months (p&lt;0.02) T1(n=36) T2(n=39)</td>
<td>Creatinine clearance Serum creatinine levels</td>
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<tr>
<td>Blood pressure</td>
<td>Urinary albumin</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>170 (160-190)</td>
<td>180 (163-185)</td>
<td>150 (140-160)</td>
<td>150 (143-160)</td>
<td>100 (95-100)</td>
<td>100 (95-104)</td>
<td>85 (80-90)</td>
<td>80 (80-90)</td>
</tr>
<tr>
<td>12 months</td>
<td>150 (140-160)</td>
<td>150 (143-160)</td>
<td></td>
<td></td>
<td>80 (80-90)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean BP</td>
<td>122 (117-129)</td>
<td>124 (120-130)</td>
<td>107 (103-110)</td>
<td>107 (102-110)</td>
<td></td>
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</tr>
</tbody>
</table>
Antihypertensives:

ACE inhibitors compared with beta-blockers: randomised control trials, ≥ 12 month follow-up

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<tr>
<td>UKPDS 39 (1998c)</td>
<td>T1: captopril (25mg - maximum 100 mg/day) T2: atenolol (50mg - maximum 100 mg/day) T3: treatments excluding ACE or β blockers. Additional medication given if BP controls not met: furosemide, nifedipine, methyldopa, prazosin.</td>
<td>20 hospital based clinics in England, Scotland and Northern Ireland</td>
<td>T1: 400 T2: 358 T3: 390</td>
<td>T1: 56.3±8.1 T2: 56.0±8.2 T1 and T2 ethnicity White: Afro-Caribbean: Asian Indian: Other T1:87%:8%:4%:1% T2:84%:9%:5%:1%</td>
<td>9 years Intention to treat analysis</td>
<td>Type 2 hypertensives T1 and T2 were equally effective in reducing blood pressure with mean±SD of 144±14/83±8 mm Hg and 143±14/81±7 mm Hg respectively. Both groups had 159±20/93±10 mm Hg at baseline. T1 vs. T2 The differences (95% CI) between the groups were 1(-1 to 3)/1(0 to 2) mm Hg. No significant difference for SBP and clinically small difference for DBP (p=0.02). T3 Mean BP 154±16/87±7 mm Hg over 9 years. See UKPDS38 (1998b) for full results. Progression of albuminuria similar in T1 and T2. At nine years, urinary albumin concentration ≥50mg/l, T1 31% (48/153), T2 26% (38/146) (p=0.31); clinical proteinuria ≥300mg/l, T1 5% (7/153), T2 10% (14/146) (p=0.09). Myocardial infarction, stroke Plasma creatinine concentrations</td>
</tr>
</tbody>
</table>
Antihypertensives: ACE inhibitors compared with beta-blockers: randomised control trials, ≥12 month follow-up

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<th>Outcome</th>
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</table>
| Bakris et al (1997)  | T1: verapamil slow release (480mg/day)  
T2: atenolol (100mg/day)  
Additional medication given if BP controls not met: furosemide, other hypertensive agents excluding ACE. |
|                      | Subjects screened from the nephrology clinic of the Alton Ochsner medical clinic, Chicago, USA. | T1: T1: 18  
T2: 16  
5 dropouts but not known which group  
T1: 61±5  
T2: 58±6  
No difference in age, sex, duration of diabetes.  
African Americans |
|                      | At start  
T1:  
T2: 16 |
|                      | Median 54 months (range 28-60) |
|                      | Type of analysis not stated.  
No power calculation. |
|                      | Type 2 with proteinuria (≥1.5g/day), diabetic retinopathy, creatinine clearance<80ml/min, hypertension |
|                      | Baseline (mean±SD)  
T1(n=u/k)  
SBP 163±13  
DBP 101±6  
No difference in mean arterial pressure at follow-up between T1(99±4) and T2(101±3): (p=0.33)  
No difference from baseline in decrease of mean arterial pressure.  
T1 26±6 mm Hg, T2 24±5 (p=0.64). |
|                      | Nielsen et al (1997a)  
T1: lisinopril (10-20mg/day)  
T2: atenolol (50-100mg/day) |
|                      | Diabetes centre, Denmark |
|                      | T1: 17  
T2: 19 |
|                      | T1: 61±8  
T2: 60±8  
No differences by age, sex, duration of diabetes.  
Not reported |
|                      | Median T1 35, T2 37 months (range 12 – 42 months)  
No power calculation.  
Intention to treat analysis. |
|                      | Type 2 with diabetic nephropathy (persistent albuminuria≥300 mg/24h) and hypertension. |
|                      | Mean arterial blood pressure (mean±SD) reduced equally in  
T1 12±2mmHg, T2 10±1mmHg  
Significant differences (all p≤0.01) at follow-up for DBP and SBP; versus baseline for T1 and T2.  
Also significant difference (p≤0.05) at follow-up for SBP, for T1 vs T2.  
DBP  
Baseline 162±5  
42 months 145±4  
SBP  
Baseline 85±2  
42 months 76±2 |
## Antihypertensives:

### ACE inhibitors compared with beta-blockers: randomised control trials, \( \geq 12 \) month follow-up

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<th>Follow-up Analysis</th>
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<th>Outcome</th>
</tr>
</thead>
</table>
| Nielsen et al (1997b) | **T1**: lisinopril (10-20mg/day)  
**T2**: atenolol (50-100mg/day) | Not reported, however authors based at Steno diabetes centre, Gentofte, Denmark | **T1**: 16  
**T2**: 19  
**T1**: 61±7  
**T2**: 60±8  
p=0.635  
Not reported  
No differences between groups for age, sex, duration of diabetes. | 1 year (reported) with further 2.5 years (not reported)  
No power calculation. Type of analysis not stated. | Type 2 with diabetic nephropathy | 24 hour mean arterial blood pressure equally reduced, T1 12±2 mmHg, T2 10±2 mmHg, over 2 months.  
SBP and DBP reductions from baseline similar in T1 and T2 and significant (all \( p \leq 0.01 \)). No differences for T1 vs T2.  
24 hour ambulatory blood pressure (mm Hg) (mean±SEM)  
| T1 | T2 |
| Baseline | 162/85±5/3 | 163/89±4/3 | 144/77±4/2 | 147/82±3/2 | Change during follow-up | -18/-8±3/2 | -16/-7±4/1 |
| Mean differences between changes | \(-2/-1\)  
95% CI \(-12/-7\) (5-3) | \( p \leq 0.01 \) compared with baseline. |

Albuminuria was, on average, reduced by  
**T1** 45% (95% CI, 25-60) (\( p \leq 0.05 \))  
**T2** 10% (-15 - 30) (not significant) mean difference –39% (-52 to –10), (\( p=0.014 \)).  
None |
Antihypertensives:

ACE inhibitors compared with calcium-channel blockers: randomised control trials, ≥ 12 month follow-up

<table>
<thead>
<tr>
<th>Author</th>
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<th>Follow-up Analysis</th>
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<th>Outcome</th>
</tr>
</thead>
</table>
| Chan et al (1992) | **T1**: enalapril (maximum dose 40mg once daily)  
 **T2**: nifedipine (maximum dose 40mg twice daily)  
 Additional treatment with indapamide or frusemide if SBP>140mmHg | Metabolic investigational unit, Hong Kong | At start T1: 50  
 T2: 52  
 At end T1 = 41  
 T2 = 49  
 T1: 60.1±9.2  
 T2: 56.1±9.9  
 All patients were Chinese | 52 weeks  
 Power calculation, Per protocol analysis | Type 2 with normoalbuminuria (<30 mg/day), microalbuminuria (3-<300 mg/day) or macroalbuminuria (>300 mg/day)  
 SBP 150 – 200 mmHg  
 DBP>100 mmHg | Reduction in, and levels achieved for, mean arterial pressures similar in T1 and T2 over 1 year, irrespective of albuminuric status. But blood pressure was significantly higher overall in T1 vs T2 (p<0.001)  
 Mean difference in mean arterial pressure 1 year vs baseline (whole group)  
 **T1**  
 -21.2  
 -17.5  
 **T2**  
 -20.1  
 -17.5 | Proteinuria reduced significantly more in T1 compared with T2 in all patients, microalbuminurics and proteinurics.  
 Data given for whole group; normoalbuminuric; microalbuminuric; and macroalbuminuric. Values are mean relative change expressed as ratios compared with baseline values (95% CI)  
 **T1**  
 whole group: 0.46 (0.32-0.67)  
 normoalbuminuria: 0.88 (0.59-1.34)  
 microalbuminuria: 0.27 (0.15-0.46)  
 macroalbuminuria: 0.29 (0.11-0.77)  
 **T2**  
 whole group: 0.89 (0.66-1.2)  
 normoalbuminuria:0.81 (0.55-1.2)  
 microalbuminuria:0.85 (0.43-0.88)  
 macroalbuminuria: 1.15 (0.85-1.54).  
 **p-values T1 vs T2**  
 whole group: 0.006  
 normoalbuminuric group: 0.751  
 microalbuminuric group: 0.013  
 macroalbuminuric group: 0.006 | Creatinine clearance |
### Antihypertensives:

**ACE inhibitors compared with calcium-channel blockers: randomised control trials, ≥ 12 month follow-up**

<table>
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<tr>
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<th>Follow-up Analysis</th>
<th>Patient status (Renal status)</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Fogari et al (1997a) | T1: enalapril (20 mg once daily) T2: amlodipine (10 mg once daily) | Not reported however authors based at the Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy. | At start T1: 25 T2: 25 At end T1: 23 T2: 22 Mean Age±SEM T1: 53.26±1.08 T2: 54.45±1.22 Not reported | 12 months No power calculation. Type of analysis not stated | Type 2 with microalbuminuria (UAE of ≥ 30 to < 300 mg/24hr) and hypertensive | T1 and T2 significantly reduced SBP and DBP vs baseline after 3 months (p<0.005) with maximum antihypertensive effect at 6 months (p<0.001) and no further reductions. Mean ±SEM T1 (n=23) T2 (n=22) SBP (mm Hg) Baseline 161.0±1.90 159.0±1.77 12 months 144.3±1.81 143.5±2.58 DBP (mm Hg) Baseline 101.1±0.66 100.6±0.70 12 months 91.0±1.13 90.1±1.03 | Both T1 and T2 significantly (p<0.05) decrease urine albumin excretion vs baseline, from 3 months onwards (T1) and 6 months onwards (T2). Mean ± SEM T1 T2 Baseline 99.8±7.08 88.3±6.05 12 months 79.2±7.11 72.2±5.46 | *12 months vs baseline p<0.01

<table>
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<tr>
<th>Blood pressure</th>
<th>Urinary albumin</th>
<th>Other parameters assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>Urea</td>
<td>Creatinine clearance</td>
</tr>
<tr>
<td>Baseline</td>
<td>161.0±1.90</td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>144.3±1.81</td>
<td></td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>Albumin</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>101.1±0.66</td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>91.0±1.13</td>
<td></td>
</tr>
</tbody>
</table>
Antihypertensives:

ACE inhibitors compared with calcium-channel blockers: randomised control trials, ≥ 12 month follow-up

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Setting, location</th>
<th>Numbers randomised</th>
<th>Follow-up Analysis</th>
<th>Patient status (Renal status)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mosconi et al (1996)</td>
<td><strong>T1</strong>: enalapril (5-20mg/day maximum dose if required) <strong>T2</strong>: nitrendipine (10-40mg/day maximum dose if required)</td>
<td>Italy</td>
<td>T1: 6 T2: 7</td>
<td>27 months</td>
<td>Similar results for SBP and DBP in T1 and T2</td>
<td>Significant reduction in UAE rate from baseline to 27 months in T1 and T2</td>
</tr>
<tr>
<td></td>
<td>No differences in age, T1 vs T2 (values not given)</td>
<td></td>
<td>No power calculation. Type of analysis unknown.</td>
<td></td>
<td>SBP (mean±SD)</td>
<td></td>
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<tr>
<td></td>
<td>Still T1: 151.7±14.8 153.3±10.8 15 months 141.9±12.5 15 months 141.9±12.5</td>
<td></td>
<td></td>
<td></td>
<td>T1 T2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DBP (mean±SD)</td>
<td></td>
<td></td>
<td></td>
<td>T1 T2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Still T1: 96.7±2.1 94.8±1.8 3 months 85.0±3.5 3 months 83.6±3.8</td>
<td></td>
<td></td>
<td></td>
<td>T1 T2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 months 90.8±4.3 85.7±6.4 27 months 93.7±7.8 84.9±3.6</td>
<td></td>
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<td>T1 T2</td>
<td></td>
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<tr>
<td></td>
<td>*p&lt;0.05 vs. baseline</td>
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</tbody>
</table>

Glomerular filtration rate.
Antihypertensives:

ACE inhibitors compared with calcium-channel blockers: randomised control trials, ≥ 12 month follow-up

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</tr>
</thead>
<tbody>
<tr>
<td>Ruggenenti et al (1994)</td>
<td>T1: enalapril (5mg/day-10mg/day if sitting DBP&gt;90mm Hg, and to 20mg/day if</td>
<td>Not reported, however authors based in Italy</td>
<td>T1: 8 T2: 8 T1: 55±7 T2: 50±9 No differences in age, sex, or duration of diabetes between T1 and T2 Not reported</td>
<td>Short-term: 98 days Long-term: 1 year Type 2 with microalbuminuria (overnight UAE &gt; 20 µg/min and &lt; 200 µg/min) and hypertension No differences in sitting SBP or DBP between T1 vs T2 at end of either 98 days or 1 year.</td>
<td>Blood pressure</td>
<td>Urinary albumin</td>
</tr>
<tr>
<td></td>
<td>DBP&gt;90mm Hg) T2: nitrendipine (10mg/day-20mg/day if DBP&gt;90mm Hg and to 40mg/day if DBP&gt;90mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No significant differences in changes seen from baseline to 98 days or to one year in overnight urine albumin excretion, in T1 or T2, or T1 vs T2.</td>
</tr>
<tr>
<td></td>
<td>T1 (n=8) T2 (n=8)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Night-time UAE (geometric mean, 95%CI)</th>
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</thead>
<tbody>
<tr>
<td>Baseline † 58.25(30.46-111.4) 47.90(26.53-86.50) At 98 days</td>
</tr>
<tr>
<td>At 1 year</td>
</tr>
<tr>
<td>58.25(22.95-143.06) used elsewhere in text.</td>
</tr>
</tbody>
</table>

* p<0.05, ** p<0.005, *** p<0.001, values compared with baseline.
Antihypertensives:

ACE inhibitors compared with calcium-channel blockers: randomised control trials, ≥ 12 month follow-up

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of intervention Daily dosage</th>
<th>Setting, location</th>
<th>Numbers randomised</th>
<th>Follow up Power calculation</th>
<th>Outcome: BP/Heart rate</th>
<th>Outcome: cardiovascular outcomes and death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estacio et al (2000)</td>
<td>Intensive blood pressure control: T1: nisoldipine (10-60mg) T2: enalapril (5-40mg) Moderate blood pressure control: T3: nisoldipine (10-60ng) T4: enalapril (5-40mg)</td>
<td>not reported, USA</td>
<td>T1: 116 T2: 121 T3: 119 T4: 114</td>
<td>5.3 years Not reported</td>
<td>• dBP ≥ 90mm Hg</td>
<td>Patients randomised to intensive therapy had a lower incidence of all-cause mortality compared to those in moderate therapy (5.5 vs. 10.7%, p=0.037). No statistically significant difference in MI, cerebrovascular events or congestive heart failure.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Mean age ± SD (range) (years) Ethnic group</th>
<th></th>
<th></th>
<th></th>
<th>Baseline</th>
<th>5 years</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>intensive therapy</td>
<td>moderate therapy</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>75.0 ± 4.4</td>
<td>77.5 ± 5.5</td>
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<td></td>
<td></td>
<td></td>
<td>56.9 ± 5.8</td>
<td>52.6 ± 5.8</td>
<td></td>
</tr>
</tbody>
</table>

Only significant difference in intensive vs. moderate control or nisoldipine vs. enalapril with regard to change in creatinine clearance. Patients with overt albuminuria at baseline demonstrated a steady decline in creatinine clearance of 5-6 ml • min⁻¹•1.73m⁻² per year throughout the follow-up period whether or not they were on intensive or moderate therapy.

**Secondary outcomes: UAE (%(p))**

<table>
<thead>
<tr>
<th></th>
<th>Normoalbuminuria to microalbuminuria</th>
<th>Microalbuminuria to overt albuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>intensive therapy</td>
<td>moderate therapy</td>
</tr>
<tr>
<td></td>
<td>25 (0.20)</td>
<td>18 (0.20)</td>
</tr>
</tbody>
</table>

Compared with patients with normo-or microalbuminuria at baseline patients with overt albuminuria (>300mg/day) had significant and continuous decline in creatinine clearance throughout the 5 year period in both moderate and intensive therapy groups. No significant difference between the groups. No difference with regard to patients progressing from normoalbuminuria to microalbuminuria or from microalbuminuria to overt albuminuria between intensive and moderate therapy.

**Blood pressure**

Mean blood pressure: 132/78 mmHg in intensive group and 138/86 mm Hg in moderate group. No statistical difference in intensive group between enalapril and nisoldipine treatments or in moderate group between enalapril and nisoldipine treatments.
### Antihypertensives:

**ACE inhibitors compared with calcium-channel blockers: randomised control trials, ≥ 12 month follow-up**

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
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<th>Numbers randomised</th>
<th>Follow-up Analysis</th>
<th>Patient status (Renal status)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agardh et al (1996)</td>
<td><strong>T1</strong>: lisinopril (2.5mg initially then 10-20mg once daily) <strong>T2</strong>: nifedipine (20mg/day initially then 20-40mg twice daily) Further treatment given of frusemide if blood pressure control not met.</td>
<td>Hospitals in four countries Sweden, Spain, Germany and England</td>
<td>At start</td>
<td>12 months</td>
<td>No power calculation. Type of analysis not stated</td>
<td>No significant differences after 12 months treatment. T1 and T2 equally effective in reducing both sitting systolic and diastolic BP. <strong>T1</strong> reduced sitting BP from 163±17/98±26 mmHg to 147±18/88±10 mmHg <strong>T2</strong> reduced sitting BP from 161±18/97±5 mmHg to 150±18/88±9. Significant reduction in median urine albumin excretion (µg/min) at 12 months for T1 compared with T2. T1 reduced UAE from a median (range) 65.5 (20-297) to 39.0 (2-510). T2 reduced UAE from a median 63.0 (20-289) to 58.0 (9-1192). Between treatment estimated median differences at 6 and 12 months were 20µg/min (95%CI –30 to -10µg/min; p=0.0002) and 20µg/min (95%CI –32 to -9µg/min; p=0.0006) in favour of <strong>T1</strong>. Creatinine clearance Serum creatinine concentrations</td>
</tr>
</tbody>
</table>
Antihypertensives:

**ACE inhibitors compared with calcium-channel blockers: randomised control trials, \(\geq 12\) month follow-up**

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Intervention</th>
<th>Setting, location</th>
<th>Numbers randomised</th>
<th>Follow-up Analysis</th>
<th>Patient status (Renal status)</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Abbott et al (1996) | **T1**: isradipine (5mg twice daily) for 6 months then nifedipine XL (30mg daily) for 6 months  

**T2**: nifedipine XL (30mg daily) for 6 months then isradipine (5mg twice daily) for 6 months. Doses changed to achieve target blood pressures. | Not clear, however study approved by Brooke Army Medical Center, Dallas TX, and the Rush University Hypertension Center, Chicago IL, USA. | **T1**: n=7  
**T2**: n=7  
**T1**: 58±5  
**T2**: 61±4  
Black/white  
**T1**: 3/4  
**T2**: 4/3 | 12 months - 6 month crossover  
No power calculation. Type of analysis not stated. | \(\text{Type 2 with proteinuria (}>500\text{mg albumin in urine})\) and hypertension. | No significant reduction in the level of albuminuria with either T1 or T2 vs baseline. |}

<table>
<thead>
<tr>
<th>Results</th>
<th>Blood pressure</th>
<th>Urinary albumin</th>
<th>Other parameters assessed</th>
</tr>
</thead>
</table>
| Significant reduction in mean arterial pressure, systolic, and diastolic, from baseline with T1 and T2 (\(p<0.05\)). No significant difference in the dose required in T1 and T2 to lower blood pressure. | | Serum creatinine  
Creatinine clearance  
Urinary sodium |
Antihypertensives:

ACE inhibitors compared with calcium-channel blockers: randomised control trials, ≥ 12 month follow-up

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<tr>
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<th>Outcome</th>
</tr>
</thead>
</table>
| Velassi et al (1996) | **T1**: cilazapril (2.5mg/day)  
**T2**: amlodipine (5.0mg/day)  
(doses doubled if blood pressure targets not reached and thiazide or furosemide added) | Outpatient Clinic, University of Padova and Sassari, Italy | Normoalbuminuric:  
**T1**: 13  
**T2**: 13  
Microalbuminuric:  
**T1**: 9  
**T2**: 9  
Normoalbuminuric:  
**T1**: 53±2  
**T2**: 54±3  
Microalbuminuric:  
**T1**: 55±2  
**T2**: 56±4  
Not reported | 3 years  
No power calculation. Type of analysis not stated. | Type 2 either microalbuminuric (AER 20-200µg/min) or normoalbuminuric, all hypertensive | Blood pressure values similar T1 vs T2 at beginning and end of study. Significant (p<0.05) reduction in T1 and T2 at all FU vs baseline.  
**T1(n=13)**  
Normoalbuminuric (means±SE)  
Baseline 169/91±2/1  
1st year 135/73±5/1  
2nd year 133/73±4/2  
3rd year 130/72±3/1  
(n=9)  
Microalbuminuric (means±SE)  
Baseline 183/95±3/1  
1st year 137/75±4/2  
2nd year 136/76±5/1  
3rd year 135/74±4/2  
| Albumin excretion rate reduced by both T1 and T2 in normoalbuminuric (not significant) and microalbuminuric (p<0.05)  
**T1**  
**T2**  
Normoalbuminuric (median and ranges)  
Baseline 9 (2-17)  
3rd year 6 (2-16)  
| Glomerular filtration rate  
Creatinine |
### Antihypertensives:

**ACE inhibitors compared with calcium-channel blockers: randomised control trials, ≥ 12 month follow-up**

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<th>Patient status (Renal status)</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Fogari et al (1999) | **T1**: ramipril (2.5mg once daily to 5.0mg/day after 1 month therapy)  
**T2**: nitrendipine (10mg once daily to 10mg twice daily after 1 month therapy). 
Those not achieving blood pressure targets withdrawn at 3 months. | Hospital, Italy     | At start T1: 54  
T2: 53  
At end T1: 26  
T2: 25 | 2 years Power calculation. Type of analysis not stated. | Type 2 with proteinuria (persistent UAE>300mg/24h) and mild hypertension. | **T1(n=26)** T2(n=25)  
Mean±SD (range)  
SBP (mmHg)  
Baseline 165.7±12  
3 months 147.4±11  
6 months 145.1±10  
12 months 146.2±10  
18 months 146.8±11  
24 months 147.8±10  
Baseline 102.2±8  
3 months 88.3±6  
6 months 86.3±6  
12 months 87.6±6  
18 months 88.1±6  
24 months 88.9±6  
DBP (mmHg)  
Baseline 101.6±8  
3 months 90.2±7  
6 months 88.7±6  
12 months 90.5±6  
18 months 89.1±6  
24 months 91.0±7  
* p<0.05 ** p<0.01 *p<0.05 ** p<0.01, vs baseline | |
Antihypertensives:

**ACE inhibitors compared with calcium-channel blockers: randomised control trials, ≥ 12 month follow-up**

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<th>Patient status (Renal status)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakris et al (1998)</td>
<td>T1: trandolapril (2-8mg/day) T2: verapamil (180mg/day to 180mg twice daily) T3: trandolapril and verapamil in (2/180mg/day to 4/240mg/day)</td>
<td>Four clinical centres (Chicago, Baltimore, California and New Orleans) in the USA</td>
<td>At start</td>
<td>1 year</td>
<td>Power calculation. Type of analysis not stated.</td>
<td>There were no significant differences in mean arterial pressure in T1 vs T2 v T3 at baseline. All treatments reduced diastolic and systolic blood pressure at FU vs baseline (p&lt;0.05).</td>
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<tr>
<td></td>
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<td>T1: 14</td>
<td></td>
<td></td>
<td>Albuminuria reduced in T1, T2 and T3 at FU vs baseline (p&lt;0.05), but T3 produced significantly lower values vs T1 and T2 at FU (p&lt;0.05). Similar results for proteinuria, except non significant change in T2.</td>
</tr>
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<td></td>
<td></td>
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<td>T2: 14</td>
<td></td>
<td></td>
<td>Glomerular filtration rate</td>
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<td>T3: 16</td>
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<td>At end</td>
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<td>T1: 12</td>
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<td>T2: 11</td>
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<td>T3: 14</td>
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<td></td>
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<td></td>
<td>T1: 58±6</td>
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<td>T2: 61±5</td>
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<td>T3: 60±6</td>
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<td>Not reported</td>
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</tbody>
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Antihypertensives:

**ACE inhibitors compared with calcium-channel blockers: randomised control trials, ≥ 12 month follow-up**

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<th>Follow-up Analysis</th>
<th>Patient status (Renal status)</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Bakris et al (1996) | **T1**: lisinopril (mean dose 51±9mg/day)  
**T2**: atenolol (mean dose 86±9mg/day)  
**T3**: one of either verapamil (mean dose 205±16mg/twice a day) slow release or diltiazem SR (mean dose 212±19mg/twice a day) | Study population from the Nephrology and Cardiology clinics of the Alton Ochsner Medical Institutions, USA | Mean age ±SD (range) (years)  
Ethnic group | Median 64 months (range 36-73).  
No power calculation.  
Type of analysis not given. | No significant differences between T1, T2 or T3 at baseline or in the slopes of DBP between T1, T2 and T3 during follow-up. Significant differences in SBP in T2 vs T1 (p = 0.015) and vs T3 (p = 0.007).  
Changes from baseline in proteinuria were significantly different, T2 vs T1 (p = 0.016) and T2 vs T3 (p = 0.0012).  
Mean reduction in albuminuria at 63 months was significantly smaller in T2 compared with T1 and T3 (p<0.01).  
Creatinine clearance. | |

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<th><strong>Blood pressure</strong></th>
<th><strong>Urinary albumin</strong></th>
<th><strong>Other parameters assessed</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Baseline</strong></td>
<td><strong>T1(n=15)</strong></td>
<td><strong>T2(n=11)</strong></td>
<td><strong>T3(n=15)</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>SBP</td>
<td>155±11</td>
<td>161±13</td>
<td>156±11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DBP</td>
<td>97±6</td>
<td>99±7</td>
<td>97±6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MAP</td>
<td>16±6</td>
<td>15±5</td>
<td>18±6</td>
<td></td>
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</tbody>
</table>
Antihypertensives:

ACE inhibitors compared with alpha-blockers: randomised control trials, ≥ 12 month follow-up

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<tr>
<th>Author</th>
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<th>Mean age ±SD (range) (years)</th>
<th>Ethnic group</th>
<th>Follow-up Analysis</th>
<th>Patient status (Renal status)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rachmani et al (1998)</td>
<td>T1: cilazapril (2.5-10mg/day), followed by doxazosin (2-8 mg/day) after 4 months plus hydrochlorothiazide (HcT2), at 8 months. T2: doxazosin (2-8 mg/day), followed by cilazapril (2.5-10mg/day) then at 8 months plus (HcT2) T3: both cilazapril (1.25-5.0mg) and doxazosin (1.0-4.0mg/day) with the later addition of HcT2 after 8 months.</td>
<td>Meir Hospital, Israel</td>
<td>At start</td>
<td>T1: 26 T2: 25 T3: 25</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Blood pressure</th>
<th>Urinary albumin</th>
<th>Other parameters assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP</td>
<td></td>
<td>Creatinine clearance</td>
</tr>
<tr>
<td>T1(n=24)</td>
<td>T2(n=24)</td>
<td>T3(n=24)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>160±7</td>
<td>160±7</td>
<td>159±6</td>
</tr>
<tr>
<td>End of FU</td>
<td>137±5</td>
<td>135±4</td>
<td>132±4</td>
</tr>
<tr>
<td>DBP</td>
<td>82±3</td>
<td>81±3</td>
<td>80±3</td>
</tr>
<tr>
<td>Baseline</td>
<td>101±3</td>
<td>97±4</td>
<td>97±4</td>
</tr>
<tr>
<td>End of FU</td>
<td>82±3</td>
<td>81±3</td>
<td>80±3</td>
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</tbody>
</table>
Antihypertensives:

ACE inhibitors compared with other treatments excluding beta-blockers or ACE: randomised control trials, ≥ 12 month follow-up

<table>
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<tr>
<th>Author</th>
<th>Intervention</th>
<th>Setting, location</th>
<th>Numbers randomised</th>
<th>Follow-up Analysis</th>
<th>Patient status (Renal status)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS 38 (1998b)</td>
<td>T2: treatment excluding ACE or β blockers, (aim BP&lt; 180/105 mmHg)</td>
<td>20 hospital based clinics in England, Scotland and Northern Ireland.</td>
<td>T1: 758</td>
<td>Type 2 hypertensives</td>
<td>Blood pressure in T1 and T2 was similar at baseline, both significantly lower (p&lt;0.0001) at 9 year follow-up. Mean differences between T1 and T2, SBP 10(95% CI 9-12), DBP 5(4-6).</td>
<td>Reduction in risk T1 vs T2: 29% (p=0.009) for urinary albumin concentration ≥50mg/l; 39% (p=0.061) for proteinuria (≥300mg/l). Reductions in risk of diabetes related death (strokes).</td>
</tr>
<tr>
<td></td>
<td>T1: either captopril (25-100 mg/day) or atenolol (50–100 mg/day) (aimBP&lt; 150/85 mmHg)</td>
<td></td>
<td>T2: 390</td>
<td>9 years (median 8.4 years, to death, last record or end of trial)</td>
<td>Intention to treat analysis.</td>
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<td>T1: 56.4±8.1</td>
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<td>T2: 56.5±8.1</td>
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<td>White: Afro-</td>
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<td>Caribbean: Asian:</td>
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<td>Indian: Other</td>
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<td></td>
<td>T1 86%:8%:5%:1%</td>
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<td></td>
<td>T2 88%:6%:4%:1%</td>
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<td>Mean age ±SD (range) (years)</td>
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<td>Follow-up Analysis</td>
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<td>Patient status</td>
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<td>assessed</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Urinary albumin</th>
<th>Other parameters assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP Baseline 159±20 160±18</td>
<td>9 years 144±14 154±16</td>
<td></td>
</tr>
<tr>
<td>DBP Baseline 94±10 94±9</td>
<td>9 years 82±7 87±7</td>
<td></td>
</tr>
</tbody>
</table>

At 9 years follow-up: (a) achieving SBP<150mmHg, DBP<85mg, T1 56%, T2 37%; (b) requiring 3 or more treatments to lower blood pressure to target levels, T1 29% T2 11%
Antihypertensives:

**Angiotensin II receptor antagonists compared with ACE inhibitors: randomised control trials**

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of intervention</th>
<th>Daily dosage</th>
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<th>Numbers randomised</th>
<th>Follow up Power calculation</th>
<th>Outcome: BP/Heart rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacourciere et al (2000)</td>
<td>T1: losartan</td>
<td>(50-100mg)</td>
<td>8 outpatient centres, Canada</td>
<td>T1: 52</td>
<td>52 weeks yes</td>
<td>Blood pressure</td>
</tr>
<tr>
<td></td>
<td>T2: enalapril</td>
<td>(5-20mg)</td>
<td></td>
<td>T2: 51</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>T1: 59.2 ± 9.2</td>
<td></td>
<td>• dBP 90-115 mmHg</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T2: 57.8 ± 10.5</td>
<td></td>
<td>• early nephropathy with UAE rate 20 to 350 µg/min</td>
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<td>Caucasian, oriental, black</td>
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<td></td>
<td>T1: 50, 1, 1</td>
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<td></td>
<td></td>
<td></td>
<td>T2: 49, 2, 0</td>
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</tbody>
</table>

### Blood pressure

Both T1 and T1 administered alone or in combination with other agents significantly decreased (p<0.005) clinic sitting sBP and sitting dBP with no clear difference between the groups.

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of intervention</th>
<th>Daily dosage</th>
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<td>T2: 51</td>
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<td>T1: 50, 1, 1</td>
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<td></td>
<td>T2: 49, 2, 0</td>
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</tbody>
</table>

### Urinary Albumin Excretion (UAE)

Mean decrease in UAE was significant at week 12 (p≤ 0.027) in both T1 and T2 and remained significantly lower (p<0.01) than baseline throughout study period.

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of intervention</th>
<th>Daily dosage</th>
<th>Setting, location</th>
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<td>T1: 50, 1, 1</td>
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<td>T2: 49, 2, 0</td>
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</tbody>
</table>

### Renal Function

Baseline GFR (geometric mean) were nearly identical for T1 (96.7 mL/min) and T2 (95.3 mL/min). A similar decline in GFR was observed in each group starting at week 12. The overall decline of approximately 9% from baseline to week 52 was significant (p≤ 0.001) in both groups.

<table>
<thead>
<tr>
<th>Author</th>
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<th>Daily dosage</th>
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<td>T2: 51</td>
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<td>T1: 59.2 ± 9.2</td>
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<td>T1: 50, 1, 1</td>
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<td>T2: 49, 2, 0</td>
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</tbody>
</table>
## Antihypertensives:

### Angiotensin II receptor antagonists compared with ACE inhibitors: randomised control trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of intervention</th>
<th>Daily dosage</th>
<th>Setting, location</th>
<th>Numbers randomised</th>
<th>Follow up</th>
<th>Patient status</th>
<th>Outcome: BP/Heart rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mogensen et al (2000)</td>
<td>T1: candesartan (16mg)</td>
<td>T2: lisinopril (20mg)</td>
<td>T3: candesartan (16mg) then candesartan (16mg) plus lisinopril (20mg)</td>
<td>T4: lisinopril (20mg) then candesartan (16mg) plus lisinopril (20mg)</td>
<td>T1: 66</td>
<td>T2: 64</td>
<td>T3: 34</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>37 centres: tertiary hospitals and primary care centres in 4 countries (Australia, Denmark, Finland and Israel)</td>
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<td>24 weeks</td>
<td>yes</td>
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<td>- dBP 90-110 mm Hg</td>
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<td>- urinary albumin:creatinine ratio (from baseline to 24 weeks)</td>
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<td><strong>T1</strong></td>
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<td>urinary albumin:creatinine ratio (%)</td>
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<td>(p=0.002)</td>
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<td>Urinary albumin:creatinine ratio (%)</td>
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<td>(p=0.04)</td>
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</tbody>
</table>

*adjusted for centre, treatment, baseline value, weight and change in diastolic blood pressure
Antihypertensives:

Angiotensin II receptor antagonists compared with calcium-channel blocker and placebo: randomised control trials

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Study</th>
<th>Type of intervention</th>
<th>Setting and location</th>
<th>Numbers randomised</th>
<th>Inclusion criteria/Exclusion criteria</th>
<th>Mean age (years) Male/female (M/F) ratio Ethnicity</th>
<th>Mean follow up period</th>
<th>Main outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis et al (2001)</td>
<td>Renoprotective effect of the angiotensin receptor antagonist irbesartan in patients with nephropathy due to Type 2 diabetes [Irbesartan Diabetic Nephropathy Trial]</td>
<td>T1: irbesartan (300mg daily)</td>
<td>210 clinical centres (appears to be worldwide according to locations of collaborating investigators cited)</td>
<td>1715</td>
<td>Included: age range 30-70 years; Type 2 diabetes; hypertension (systolic BP &gt;135mm Hg, diastolic BP &gt;85mm Hg or documented treatment with anti-hypertensive agents); proteinuria (urinary protein excretion of at least 900mg/24 hrs); serum creatinine concentration between 88-265 micromol/litre in women and between 106-265 micromol/litre in men. Excluded: not stated</td>
<td>T1: 59.3 ± 7.1, T2: 59.1 ± 7.9, T3: 58.3 ± 8.2</td>
<td>Mean follow up of 2.6 yrs. Patients monitored quarterly.</td>
<td>Primary: composite of doubling of baseline serum creatinine concentration, onset of end-stage renal disease (indicated by initiation of dialysis, renal transplantation or serum creatinine concentration of ≥6.0 mg/dclititre) or death from any cause. Secondary: composite of death from cardiovascular causes, nonfatal myocardial infarction (MI), heart failure resulting in hospitalisation, permanent neurologic deficit caused by a cerebrovascular event, or lower limb amputation above the ankle.</td>
</tr>
<tr>
<td></td>
<td>T2: amlodipine (10mg daily)</td>
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<td>T3: placebo</td>
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<tr>
<td></td>
<td>T1: irbesartan (300mg daily)</td>
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<td></td>
<td>T3: placebo</td>
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<tr>
<td></td>
<td>T1: irbesartan (300mg daily)</td>
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<td>T3: placebo</td>
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</tbody>
</table>

Results

**Primary outcome (renal):** T1 vs T3: unadjusted RR 0.80 (95% CI 0.66-0.97, P=0.02), adjusted RR 0.81 (95% CI 0.67-0.99, P=0.03). T2 vs T3: unadjusted RR 1.04 (95% CI 0.86-1.25, P=0.69), adjusted RR 1.07 (95% CI 0.89-1.29, P=0.47). T1 vs T2: unadjusted RR 0.77 (95% CI 0.63-0.91, P=0.006), adjusted RR 0.76 (95% CI 0.63-0.92, P=0.005).

**Doubling of serum creatinine concentration:** T1 vs T3: unadjusted RR 0.67 (95% CI 0.52-0.87, P=0.003), adjusted RR 0.71 (95% CI 0.54-0.92, P=0.009). T2 vs T3: unadjusted RR 1.06 (95% CI 0.84-1.35, P=0.60), adjusted RR 1.15 (95% CI 0.91-1.46, P=0.24). T1 vs T2: unadjusted RR 0.63 (95% CI 0.48-0.81, P=0.001), adjusted RR 0.61 (95% CI 0.48-0.79, P=0.001).

Unadjusted RR of end-stage renal disease was 23% lower in T1 patients than in either T2 or T3 (0.77 [95% CI 0.57-1.03, P=0.07] for both comparisons). T2 and T3 patients did not differ significantly in RR of doubling of serum creatinine or end-stage renal disease. No significant differences among the 3 groups in risk of death from any cause. Differences in primary outcome results not explained by differences in BPs achieved. Numbers of patients who completed study without primary outcome (T1: 385 (66.5%), T2: 332 (58.6%), T3: 343 (60.3%).

**Secondary outcome (cardiovascular):** no significant differences among all groups in cardiovascular composite outcome. T1 patients had rate of congestive heart failure needing hospitalisation 23% lower than T3 patients. T2 patients had a rate of nonfatal MI 41% lower than T3 patients. Changes in renal function: serum creatinine concentration increased 24% more slowly in T1 patients than T3 patients (P=0.008) and 21% more slowly than T2 patients (P=0.02).

**Serious adverse events:** Study medication discontinued in one patient due to increase in serum creatinine concentration suggestive of renal-artery stenosis. Also discontinued in 11 patients in T1, 3 in T2, and 2 in T3 (P=0.01 for both comparisons) due to hyperkalemia. 23.7% of all patients stopped study medication before primary end point reached – mostly due to cardiovascular events. Discontinuations evenly spread among groups. T1 had significantly lower rate of adverse events per 1000 days of treatment than T2 and T3 patients (P=0.002).

**Authors’ conclusions:** Irbesartan is effective in protecting against the progression of nephropathy due to Type 2 diabetes, independent of the reduction in blood pressure it causes.
**Antihypertensives:**

**Angiotensin II receptor antagonists compared with placebo: randomised control trials**

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Study</th>
<th>Type of intervention</th>
<th>Setting and location</th>
<th>Numbers randomised</th>
<th>Inclusion criteria/ Exclusion criteria</th>
<th>Mean age (years)</th>
<th>Follow-up period</th>
<th>Main outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parving et al (2001)</td>
<td>The effect of irbesartan on the development of diabetic nephropathy in patients with Type 2 diabetes</td>
<td>T1: irbesartan (150mg once daily)</td>
<td>96 centres worldwide</td>
<td>590</td>
<td>Included: Age range 30-70 years; Type 2 diabetes; persistent microalbuminuria; serum creatinine concentration no more than 133 micromol/litre for men, and no more than 97 micromol/litre for women; hypertension. Excluded: non-diabetic kidney disease; life-threatening disease with death expected within 2 yrs; indication for ACE inhibitors or angiotensin-II-receptor antagonists</td>
<td>T1: 58.4 ±8, T2: 57.3 ±7.9, T3: 58.3 ±8.7</td>
<td>Median of 2 years. Follow up assessments at 3, 6, 12, 18, 22 and 24 months</td>
<td>Primary: time from baseline visit to 1st detection of overt nephropathy (defined by urinary albumin excretion rate &gt;200 microg/min and at least 30% higher than baseline rate on at least 2 consecutive visits). Secondary: changes in level of albuminuria; changes in creatinine clearance; restoration of normoalbuminuria (urinary albumin excretion rate of &lt;20 microg/min) by last visit</td>
</tr>
</tbody>
</table>

| | | T2: irbesartan (300mg once daily) | | | | | | |
| | | T3: placebo (once daily) | | | | | | |
| | | T1:195, T2: 194, T3: 201 | At start: | | | | | |
| | | T1: 168, T2: 174, T3: 171 | At end: | | | | | |

**Results**

**Primary outcome:** Nephropathy developed in 30 patients in T3 (placebo), compared with 19 in T1 and 10 in T2. The difference between the placebo group (T3) and T1 was not significant (P=0.08), but the difference between the placebo group and T2 was significant (P<0.001).

**Secondary outcomes:** Urinary albumin excretion (UAE): For T1 patients, UAE decreased by 24% (95% CI, 19-29%); for T2 patients, UAE decreased by 38% (95% CI, 32-40%) and for T3 patients, UAE decreased by 2% (95% CI, 7-5%). There was a significant decrease in UAE between T3 and both T1 and T2 patients (P<0.001), and a significantly smaller decrease in albuminuria level in T1 patients compared to T2 patients (P<0.001).

Restoration of normoalbuminuria: more frequent in T2 patients (34% (95% CI, 26-40%)) than T1 patients (24% (95% CI, 18-30%) and T3 patients (21% (95% CI, 15-26%)). Significant difference between T2 patients and T3 patients (P=0.006).

Creatinine clearance: no significant difference in decline of creatinine clearance noted between the 3 groups in the initial or sustained (3-24 months) phase.

Blood pressure: average trough BP during study was 143/83mm Hg for T1 patients, 141/83mm Hg for T2 patients and 144/83mm Hg for T3 patients (P=0.004 for comparison of systolic BP between T1/T2 patients combined and T3 patients). Average trough mean arterial BP during study was 103mm Hg for T1 patients, 102mm Hg for T2 patients and 103mm Hg for T3 patients (P=0.005 for comparison between T2 and T3 patients).

Differences between groups in medications taken during study not statistically significant except for antihypertensive agents (P=0.03 T3 patients vs T1 patients and P=0.01 T3 patients vs T2 patients).

Serious adverse events: Serious adverse effects recorded as T3 patients: 22.8% and T1/T2 patients combined: 15.4% (P=0.02). Nonfatal cardiovascular events were more frequent in T3 patients (8.7% vs 4.5% in T2; P=0.11). Study medication discontinued in 18.9% of T3 patients, compared with 14.9% of patients in T1/T2 combined (P=0.21).

**Authors’ conclusions:** irbesartan is renoprotective independently of its blood-pressure-lowering effect in patients with Type 2 diabetes and microalbuminuria.
### Antihypertensives: Angiotensin II receptor antagonists compared with placebo with other therapy: randomised control trials

**Author (s)** | Study | Type of intervention | Setting and location | Numbers randomised | Inclusion criteria/ Exclusion criteria | Mean age (years) | Male/Female (M/F) ratio | Ethnicity | Follow-up period | Main outcome measures |
---|---|---|---|---|---|---|---|---|---|---|
Brenner et al, 2001 | Effects of losartan on renal and cardiovascular outcomes in patients with Type 2 diabetes and nephropathy [RENAAL Study] | **T1**: losartan (50mg once daily) plus antihypertensive therapy (but not including angiotensin-I-converting enzyme inhibitors and angiotensin-II-receptor antagonists) | 250 centres in 28 countries in Asia, Europe, Central America, S America and N America. | 1513 | Included: male/female patients, age range 31-70 yrs, with Type 2 diabetes and nephropathy (nephropathy defined by presence on 2 occasions of ratio of urinary albumin to urinary creatinine of at least 300mg/litre, and serum creatinine values between 115-265 micromol/litre with lower limit of 133 micromol/litre for male patients weighing >60kg). Excluded: patients with Type 1 diabetes or non-diabetic renal disease, including renal artery stenosis. Patients who had had MI or coronary artery bypass grafting within previous month; cerebrovascular accident/ percutaneous transluminal coronary angioplasty within previous 6 months; TIA within previous year; any history of heart failure. | T1: 60 ±7, T2: 60 ±7 | Males: T1: 61.5% T2: 64.8% | Females: T1: 38.5% T2: 35.2% | Mean follow up of 3.4 years (range 2.3-4.6 yrs). Patients monitored at least every 3 months.* | Primary: composite end point of doubling of serum creatinine concentration, end-stage renal disease, or death. Doubling of serum creatinine concentration defined as 1 st serum creatinine value that was twice baseline value as confirmed by 2 nd serum creatinine value obtained at least 4 wks after initial doubling. End-stage renal disease defined by need for long-term dialysis or renal transplantation. Secondary: composite of MI, stroke, 1 st hospitalisation for heart failure or unstable angina, coronary or peripheral revascularisation, or death from cardiovascular causes. Also progression of renal disease and changes in level of proteinuria. |

**Results**

**Primary outcomes:** primary composite outcome reached in 327 T1 patients (43.5%) vs 359 T2 patients (47.1%) giving risk reduction of 16% in T1 patients compared to T2 patients (P=0.02 [P=0.03 after adjustment for BP]). Also, T1 patients had risk reduction of 25% vs T2 patients for doubling of serum creatinine concentration (P=0.006); 28% for end-stage renal disease (P=0.002); and 20% for end-stage renal disease or death (P=0.01). No significant difference in mortality between the 2 groups (P=0.88).

**Secondary outcomes:** composite outcome of morbidity/mortality from cardiovascular causes showed no significant differences between the 2 groups. No significant differences in most cardiovascular outcomes, except 1 st hospitalisation with heart failure (11.9% of T1 patients vs 16.7% of T2 patients, giving a risk reduction of 32% [P=0.005]). T1 patients also had an average reduction in level of proteinuria of 35% whereas in T2 patients, urinary albumin-to-creatinine ratio tended to increase (P<0.001 for overall treatment effect). T1 patients had reduced rate of decline in renal failure by 18% compared with T2 patients (P=0.01). T1 patients had 15.2% reduction in estimated decline in glomerular filtration rate compared with T2 patients (P=0.01).

**Blood pressure:** No significant differences in mean arterial and pulse pressure between the 2 groups at baseline (P=0.38 and P=0.13, respectively), at 2 years (P=0.38 and P=0.37, respectively) or at the end of study (P=0.59 and P=0.77, respectively). However, significant difference at one year, with mean arterial pressure 100.9mm Hg and 103.1mm Hg, respectively [P<0.001] and pulse pressure 67.8mm Hg and 69.8mm Hg, respectively [P=0.05]. Authors state, however, that statistical analysis corrected for these differences still bear out benefits of T1.

**Serious adverse events:** Study medication discontinued in 17.2% of T1 patients and 21.7% of T2 patients due to adverse clinical events. Also discontinued due to increased serum concentrations of creatinine or potassium in 1.5% and 1.1% of T1 patients vs 1.2% and 0.5% of T2 patients, respectively.

**Authors’ conclusions:** Losartan gave significant renal benefits in patients with Type 2 diabetes and nephropathy, and it was generally well tolerated.
### Antihypertensives:

**Dihydropyridine compared with non-dihydropyridine calcium-channel blockers: randomised control trials, ≥ 12 month follow-up**

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Setting, location</th>
<th>Numbers randomised</th>
<th>Follow-up Analysis</th>
<th>Patient status (Renal status)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al (1998)</td>
<td><strong>T1</strong>: nifedipine (max dose 90mg/day)</td>
<td>Rush – Presbyterian-St.Luke’s Medical Centre, USA</td>
<td>At start</td>
<td>21 months</td>
<td>Type 2 with proteinuria (&gt;300mg/day) and hypertensive.</td>
<td>Significant reduction (p&lt;0.05) in T1 and T2 versus baseline values. No differences between T1 and T2 anytime.</td>
</tr>
<tr>
<td></td>
<td><strong>T2</strong>: diltiazem (max dose 480mg/day)</td>
<td></td>
<td>T1: 14</td>
<td>Power calculation.</td>
<td></td>
<td><strong>T1 (n=10)</strong> T2 (n=11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T2: 14</td>
<td></td>
<td></td>
<td>Significant reduction in amount of proteinuria change from baseline in T2 vs T1 (p&lt;0.001).</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>At end</td>
<td></td>
<td></td>
<td><strong>T1 (n=10)  T2 (n=11)</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T1: 10</td>
<td></td>
<td></td>
<td>Difference from baseline 4±10% -57±18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T2: 11</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>T1: 57±4</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>T2: 59±8</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Caucasian %</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>T1: 100</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>T2: 93</td>
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</tbody>
</table>

- **Blood pressure**
  - SBP (mm Hg)
    - Baseline: 172±11, 162±12
    - 21 months: 136±9, 138±9
- **Urinary albumin**
  - **T1 (n=10)**  T2 (n=11)
  - Difference from baseline 4±10% -57±18%

- **Other parameters assessed**
  - Glomerular filtration rate.
  - Renal plasma flow.
### Sulphonylureas:

**Sulphonylureas compared with placebo, other sulphonylureas: randomised control trials, ≥ 12 month follow-up**

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Setting, location</th>
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<th>Follow-up Analysis</th>
<th>Patient status (Renal status)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giustina et al (1998)</td>
<td><strong>T1</strong>: picotamide (300mg) <strong>T2</strong>: placebo</td>
<td>Outpatient clinic, Italy</td>
<td><strong>T1</strong>: 15 <strong>T2</strong>: 15 after 3 dropouts</td>
<td>1 year</td>
<td>Type 2 with microalbuminuria (UAE between 20-200µg/min) normotensives</td>
<td>Systolic and diastolic BP at rest, after exercise, or over time, did not change significantly in T1 or T2. Decrease in UAE in T1 after 6 months vs baseline sustained at 12 months (p&lt;0.05), and vs T2 also sustained at 12 months (p&lt;0.005). None</td>
</tr>
<tr>
<td><strong>UKPDS 33 (1998a)</strong></td>
<td><strong>T1</strong>: Intensive treatment with sulphonylureas or insulin. <strong>T1a</strong> chlorpropamide <strong>T1b</strong> glibenclamide <strong>T1c</strong> insulin <strong>T2</strong> conventional treatment with diet.</td>
<td>23 participating UKPDShospitals, UK</td>
<td><strong>T1a</strong>: 619 <strong>T1b</strong>: 615 <strong>T1c</strong>: 911 <strong>T2</strong>: 896 / 3041 loss to FU 122</td>
<td>11.1 years (IQR 90-130)</td>
<td>Type 2 (HbA1c status: At baseline (mean (SD))) <strong>T1a</strong>: 6.3 (1.4) <strong>T1b</strong>: 6.3 (1.3) <strong>T1c</strong>: 6.1 (1.1) <strong>T2</strong>: 6.2 (1.2) At 10 years (median) <strong>T1a</strong>: 6.7 <strong>T1b</strong>: 7.2 <strong>T1c</strong>: 7.1 <strong>T2</strong>: 7.9</td>
<td>Blood pressure (mm Hg) not reported Reduced risk of microalbuminuria after 9 years in T1 vs T2 (p&lt;0.03). Reduced risk of proteinuria at 9 and 12 years only in T1 vs T2 (p&lt;0.03) Death from renal disease Renal failure Plasma creatinine</td>
</tr>
</tbody>
</table>
### Sulphonylureas:

**Sulphonylureas compared with placebo, other sulphonylureas: randomised control trials, ≥ 12 month follow-up**

<table>
<thead>
<tr>
<th>Author</th>
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<th>Follow-up Analysis</th>
<th>Patient status (Renal status)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jerums et al (1987)</td>
<td>T1: gliclazide (average daily dose was between 2 and 2.5 tablets, range 0.5 – 3) T2: glibenclamide (average daily dose was between 2 and 2.5 tablets, range 0.5 – 3) dosages adjusted according to level of blood sugar control</td>
<td>Clinic, Australia</td>
<td>At start T1: 10 T2: 9 at end T1: 9 T2: 8 T1: 60 ±2 T2: 59 ±2 No difference in age and sex, but duration of diabetes 122 months±23 in T1 and 76±22 in T2 (p&lt;0.05) Not reported</td>
<td>2 years No power calculation. Type of analysis not stated.</td>
<td>Type 2 (a group of Type 1 also in study but their results not reported). (HbA1c status: At baseline (mean ± SEM) T1: 9.0 ± 0.5 T2: 10.1 ± 1.0 At 2 years (mean ± SEM) T1: 9.5 ± 0.7 T2: 9.5 ± 0.7 Baseline vs 2 years T1: 1.19 T2: 0.81</td>
<td>No significant differences at baseline or over duration of study for T1 and T2. SBP/DBP (mean±SEM) T1 (n=9) T2 (n=8) -12 to 0 months 144±6/88±3 150±7/91±2 3 to 24 months 142±4/84±1 150±6/88±2 No significant differences within or between T1 and T2. No significant differences at baseline or over duration of study for T1 and T2. Total proteinuria (mg/24h) (mean 95% CI) months T1 (n=9) T2 (n=8) 0 504 (243-765) 349(146-512) 12 439 (269-609) 471 (317-625) 24 426 (338-514) 492 (358-626) Creatinine clearance</td>
</tr>
</tbody>
</table>
## Insulin therapies:

**Randomised control trial, ≥12 month follow-up**

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Setting, location</th>
<th>Numbers randomised</th>
<th>Mean age ±SD (range) (years)</th>
<th>Ethnic group</th>
<th>Follow-up Analysis</th>
<th>Patient status (Renal status)</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Ohkubo et al (1995) | **Primary Prevention Cohort** (UAE <30mg/24hr, no retinopathy) | Outpatient clinic, Japan | T1: 25  
T2: 26  
T3: 25  
T4: 26  
T1: 49 ±14  
T2: 47 ±9  
T3: 52 ±15  
T4: 49 ±13  
All Japanese | T1: 49 ±14  
T2: 47 ±9  
T3: 52 ±15  
T4: 49 ±13 | 6 years | No power calculation. Intention to treat analysis. | Type 2 with microalbuminuria (urine albumin excretion <30mg/24hr)  
(HbA1c status:  
At baseline  
T1: 8.9 ± 1.8  
T2: 9.2 ± 1.8  
T3: 9.0 ± 1.9  
T4: 9.4 ± 1.8  
At 6 years  
HbA1c not given) | Baseline values only, final values, not reported. | Primary prevention cohort  
After 6 years, the cumulative percentage of patients who developed nephropathy was significantly lower in T2 than in T1 (7.7% vs. 29%, p = 0.032).  
5 patients in T1 and 2 patients in T2 developed microalbuminuria.  
2 patients in T1 developed proteinuria.  
Secondary prevention cohort  
After 6 years, the cumulative percentage of patients with progression of nephropathy was significantly lower in T4 than in T3 (11.5 vs. 32%, p = 0.044)  
6 patients in T1 and 3 patients in T2 developed microalbuminuria.  
2 patients in T1 developed proteinuria.  
Combined cohort  
After 6 years, the cumulative number of patients with worsening nephropathy was significantly lower in the combined T2, T4 groups than in the combined T1, T3 groups (9.6 vs. 30.0%, p = 0.005).  
No worsening of nephropathy in patients with HbA1c below 6.5%. | None |
Lipid regulating drugs:

Randomised control trials, ≥12 month follow-up

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Setting, location</th>
<th>Numbers randomised</th>
<th>Follow-up Analysis</th>
<th>Patient status (Renal status)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lam et al (1995)</td>
<td><strong>T1</strong>: lovastatin (20-60 mg/day)</td>
<td>Outpatient clinic, Hong Kong</td>
<td><strong>T1</strong>: 16</td>
<td>24 months</td>
<td>No significant change in mean arterial pressure in T1 or T2 over time.</td>
<td>24hr urinary protein increased significantly over 24 months compared with baseline in T1 (p&lt;0.05) and T2 (p&lt;0.05)</td>
</tr>
<tr>
<td></td>
<td><strong>T2</strong>: placebo</td>
<td></td>
<td><strong>T2</strong>: 18</td>
<td></td>
<td>No power calculation. Type of analysis not stated.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean age ± SEM</td>
<td></td>
<td>T1: 58.9±2.3</td>
<td></td>
<td>Type 2 with proteinuria (&gt;0.15g/day), and hypercholesterolemia.</td>
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<tr>
<td></td>
<td>T2: 53.9±2.5</td>
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</tr>
<tr>
<td></td>
<td>No differences between T1 and T2 for age or sex. All Chinese</td>
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<td></td>
<td>Follow-up</td>
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<td></td>
<td>Analysis</td>
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<tr>
<td></td>
<td>Blood pressure</td>
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<tr>
<td></td>
<td>Urinary albumin</td>
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<tr>
<td></td>
<td>Other parameters assessed</td>
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</table>

Values are mean±SEM, mmHg

<table>
<thead>
<tr>
<th></th>
<th>T1(n=16)</th>
<th>T2(n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>6.6 ± 0.1</td>
<td>6.3 ± 0.1</td>
</tr>
<tr>
<td>12 months</td>
<td>4.9 ± 0.2</td>
<td>6.6 ± 0.2</td>
</tr>
<tr>
<td>24 months</td>
<td>4.9 ± 0.1</td>
<td>6.4 ± 0.2</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>1.10 ± 0.05</td>
<td>1.10 ± 0.07</td>
</tr>
<tr>
<td>12 months</td>
<td>1.07 ± 0.04</td>
<td>0.97 ± 0.06</td>
</tr>
<tr>
<td>24 months</td>
<td>1.09 ± 0.06</td>
<td>0.99 ± 0.07</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.3 ± 0.3</td>
<td>4.1 ± 0.2</td>
</tr>
<tr>
<td>12 months</td>
<td>3.0 ± 0.2</td>
<td>4.0 ± 0.2</td>
</tr>
<tr>
<td>24 months</td>
<td>3.0 ± 0.2</td>
<td>3.8 ± 0.2</td>
</tr>
</tbody>
</table>
**Lipid regulating drugs:**

**Randomised control trials, ≥12 month follow-up**

<table>
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<tr>
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<th>Numbers randomised Mean age ±SD (range) (years)</th>
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<th>Follow-up Analysis</th>
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</tr>
</thead>
</table>
| Tonolo et al (1997) | **T1**: simvastatin (20mg/day) for 12 months then placebo for a further 12 months. **T2**: placebo for 12 months then simvastatin (20mg/day) for a further 12 months | University laboratory, Italy | T1: 10 T2: 9 Not reported Not reported | 2 years No power calculation. Per protocol analysis | Type 2 with micro-albuminuria, and hypercholesterolemia | No significant changes in SBP or DBP in either T1 or T2 | **Blood pressure**

<table>
<thead>
<tr>
<th>Time</th>
<th>T1(n=10)</th>
<th>T2(n=9)</th>
<th>SBP (mean±SD)</th>
<th>DBP (mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>129±2</td>
<td>128±3</td>
<td>78±1</td>
<td>76±3</td>
</tr>
<tr>
<td>3 months</td>
<td>122±3</td>
<td>124±4</td>
<td>75±1</td>
<td>74±2</td>
</tr>
<tr>
<td>6 months</td>
<td>124±3</td>
<td>125±4</td>
<td>75±2</td>
<td>77±3</td>
</tr>
<tr>
<td>12 months</td>
<td>126±3</td>
<td>124±4</td>
<td>76±2</td>
<td>75±3</td>
</tr>
<tr>
<td>15 months</td>
<td>128±5</td>
<td>129±5</td>
<td>78±4</td>
<td>77±3</td>
</tr>
<tr>
<td>18 months</td>
<td>127±4</td>
<td>125±5</td>
<td>78±3</td>
<td>76±4</td>
</tr>
<tr>
<td>24 months</td>
<td>128±5</td>
<td>126±3</td>
<td>77±3</td>
<td>75±1</td>
</tr>
</tbody>
</table>

(In T1, overall there were no changes in total cholesterol and HDL cholesterol over 24 months, although both decreased in just 12 months (p<0.01), but increased during second 12 months. In T2, no changes in first 12 months for total cholesterol and HDL cholesterol, followed by reduction in second 12 months (p<0.02))

**Total cholesterol (mean±SD)**

<table>
<thead>
<tr>
<th>Time</th>
<th>T1(n=10)</th>
<th>T2(n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>6.4 ± 0.4</td>
<td>6.7 ± 0.3</td>
</tr>
<tr>
<td>12 months</td>
<td>5.2 ± 0.3</td>
<td>6.9 ± 0.4</td>
</tr>
<tr>
<td>24 months</td>
<td>6.7 ± 0.5</td>
<td>5.3 ± 0.3</td>
</tr>
</tbody>
</table>

**HDL cholesterol (mean±SD)**

<table>
<thead>
<tr>
<th>Time</th>
<th>T1(n=10)</th>
<th>T2(n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1.3 ± 0.1</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>12 months</td>
<td>1.3 ± 0.1</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>24 months</td>
<td>1.4 ± 0.2</td>
<td>1.3 ± 0.3</td>
</tr>
</tbody>
</table>

**LDL cholesterol (mean±SD)**

<table>
<thead>
<tr>
<th>Time</th>
<th>T1(n=10)</th>
<th>T2(n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>4.7 ± 0.4</td>
<td>4.9 ± 0.3</td>
</tr>
<tr>
<td>12 months</td>
<td>3.3 ± 0.3</td>
<td>4.9 ± 0.4</td>
</tr>
<tr>
<td>24 months</td>
<td>4.8 ± 0.3</td>
<td>3.2 ± 0.3</td>
</tr>
</tbody>
</table>

**Blood pressure**

<table>
<thead>
<tr>
<th>Time</th>
<th>T1(n=10)</th>
<th>T2(n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>129±2</td>
<td>128±3</td>
</tr>
<tr>
<td>3 months</td>
<td>122±3</td>
<td>124±4</td>
</tr>
<tr>
<td>6 months</td>
<td>124±3</td>
<td>125±4</td>
</tr>
<tr>
<td>12 months</td>
<td>126±3</td>
<td>124±4</td>
</tr>
<tr>
<td>15 months</td>
<td>128±5</td>
<td>129±5</td>
</tr>
<tr>
<td>18 months</td>
<td>127±4</td>
<td>125±5</td>
</tr>
<tr>
<td>24 months</td>
<td>128±5</td>
<td>126±3</td>
</tr>
</tbody>
</table>

**Urinary albumin**

<table>
<thead>
<tr>
<th>Time</th>
<th>T1(n=10)</th>
<th>T2(n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>73</td>
<td>70</td>
</tr>
<tr>
<td>3 months</td>
<td>42*</td>
<td>70</td>
</tr>
<tr>
<td>6 months</td>
<td>32†</td>
<td>78</td>
</tr>
<tr>
<td>12 months</td>
<td>48*</td>
<td>81†</td>
</tr>
<tr>
<td>15 months</td>
<td>41</td>
<td>70</td>
</tr>
<tr>
<td>18 months</td>
<td>55</td>
<td>49*</td>
</tr>
<tr>
<td>24 months</td>
<td>60</td>
<td>46*</td>
</tr>
</tbody>
</table>

* p<0.05 vs. time 0, † p<0.01 vs. time 0; ‡ p<0.05 for T1 vs. T2;
### Lipid regulating drugs:

#### Randomised control trials, ≥12 month follow-up

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Setting, location</th>
<th>Numbers randomised</th>
<th>Follow-up Analysis</th>
<th>Patient status (Renal status)</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Shimizu et al (1995) | **T1**: oral eicosapentaenoic acid ethyl (EPA-E: 900mg/day)  
**T2**: control group (non-EPA-E treated) | Department of Internal Medicine, Gunma University, Japan | T1: 29  
T2: 16  
T1: 66.3±2.5  
T2: 58.6±1.8  
Not reported | 12 months  
No power calculation. Type of analysis not stated. | Type 2 | During the 12 months of the study neither SBP nor DBP levels were changed in either T1 or T2.  
**T1(n=29)**  
**T2(n=16)**  
*SBP (mean±SEM)*  
Baseline 136.1±3.5  
12 months 136.9±3.9  
*DBP (mean±SEM)*  
Baseline 76.2±2.0  
12 months 76.4±2.7  
*Total cholesterol (mg/dl) (mean±SEM)*  
Baseline 204.8 ± 6.8  
12 months 203.4 ± 4.7  
*HDL cholesterol (mg/dl) (mean±SEM)*  
Baseline 49.5 ± 3.7  
12 months 55.8 ± 2.9  |
|                 | **T1**: Significant decrease in urine albumin excretion level/urine creatinine excretion level in T1 at 3 months (p<0.01) sustained at 12 months (p<0.01)  
**T1(n=29)**  
**T2(n=16)**  
*Urine albumin*  
3 months 57.8± 6.7%  
12 months 59.2± 11.3%  
*Other parameters assessed*  
None |
### Lipid regulating drugs:

**Randomised control trials, ≥12 month follow-up**

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Setting, location</th>
<th>Numbers randomised</th>
<th>Follow-up</th>
<th>Patient status (Renal status)</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Smulders et al (1997) | **T1**: gemfibrozil (600 mg twice daily)  
**T2**: placebo | Not reported       | T1: 7, T2: 8       | 12 months | Type 2 with microalbuminuria (albumin to creatinine ratio (ACR) 3-30mg mmol⁻¹) | Blood pressure remained stable during follow-up in all patients. Final BP values not reported. There were no changes in cholesterol in either T1 or T2 over 12 months (p=0.11) but the change in HDL cholesterol was significant between T1 and T2 (p=0.03) |
|                     |                                   |                   | Mean age T1: 64, T2: 49 |           |                              | No significant difference (p>0.1) in progression of microalbuminuria in T1(36%) vs T2(65%). Final values for albumin to creatinine ratio/24 hour urine, T1 8.9, T2 14.2. |

|                  |                      |                   |                   |           |                              | Serum creatinine Lipid changes |
|                  |                      |                   |                   |           |                              |                           |
|                  |                      |                   |                   |           |                              |                           |
|                  |                      |                   |                   |           |                              |                           |

**Outcome**

**Blood pressure**

- **Cholesterol**
  - **Baseline**
  - **T1**: 6.0
  - **T2**: 6.6
  - **Change in 12 months**
    - **T1**: -16%
    - **T2**: +4%

- **HDL Cholesterol**
  - **Baseline**
  - **T1**: 0.9
  - **T2**: 0.9
  - **Change in 12 months**
    - **T1**: +2.7%
    - **T2**: -12%
Multi-factorial intervention:

Randomised control trial, ≥12 month follow-up

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Setting, location</th>
<th>Numbers randomised</th>
<th>Follow-up Analysis</th>
<th>Patient status (Renal status)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaede et al (1999)</td>
<td>T1: Standard treatment by GP’s in accordance to 1988 recommendations of the Danish Medical Association. T2: Intensive multi-factorial intervention with behaviour modification (diet, exercise, smoking) and stepwise introduction of pharmacological therapy.</td>
<td>Steno Diabetes Centre, Denmark</td>
<td>At start T1: 80 T2: 80 At end T1: 76 T2: 73</td>
<td>Mean±SD 3.8 ±0.3 years Power calculation. Intention to treat analysis</td>
<td>Type 2 with microalbuminuria (30-300mg/24h)</td>
<td>Significantly greater reduction in systolic blood pressure values in T2 versus T1 (p&lt;0.01). No differences in diastolic. SBP (mean, SD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DBP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DBP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DBP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Serum creatinine</td>
</tr>
</tbody>
</table>

- **Blood pressure**
  - SBP (mean, SD)
  - DBP

- **Urinary albumin**
  - T1(n=76) 149(19) 142(20)
  - T2(n=73) 142(20) 142(20)

- **Other parameters assessed**
  - Glomerular filtration rate
  - Serum creatinine
Non-drug interventions
Dietary interventions:

Salt reduction diet: systematic reviews/meta analyses

<table>
<thead>
<tr>
<th>Author</th>
<th>Research question</th>
<th>Review type</th>
<th>Study design, interventions: follow-up period</th>
<th>Total sample number</th>
<th>Main outcomes and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graundal et al 1998</td>
<td>Does a reduction in sodium intake decrease blood pressure?</td>
<td>Meta-analyses of hypertensive and normotensive studies.</td>
<td>Randomised studies (double-blind, single-blind, open, with parallel or cross-over design) of low sodium and high sodium diets.</td>
<td>For 58 hypertensive studies; median of mean ages 49 years (range 23-73), median duration 28 days (4-365); number of people 2161. For 56 normotensive studies: median of mean ages 27 years (range 15-67), median duration 8 days (4-1100); number of people 2581. No information on diabetes status, and status not a requirement for inclusion. Known, 2883 males, 1411 females, 354 blacks but information incomplete.</td>
<td>Weighted meta-analyses. Hypertensive persons (weighted sodium reduction 118 mmol/24 hours) 3.9 mm Hg (95% CI 3.0 – 4.8) (p&lt;0.001) Systolic BP Diastolic BP 1.9 mm Hg (95% CI 1.3 – 2.5) (p&lt;0.001) Normotensive persons (weighted sodium reduction 160mmol/24 hours) 1.2 mm Hg (95% CI 0.6 – 1.8) (p&lt;0.001) Systolic BP Diastolic BP 0.26 mm Hg (95% CI -0.3 – 0.9) (p=0.12) Stability of result of effect size since 1985. Results of meta analyses do not support a recommendation for sodium reduction.</td>
</tr>
<tr>
<td>Alam and Johnson 1999</td>
<td>What is the effect of sodium chloride ingestion on blood pressure in the elderly?</td>
<td>Meta analysis MEDLINE (1966-1998), EMBASE (1988-1998), Current Contents (part 1997 and 1998), AMI (1966-1998), API (1970-1998), Cochrane Library, bibliographies of review and primary articles searched. Pooled estimates of SD, variance of difference, pooled mean effect, SE and 95% CI all calculated.</td>
<td>11 randomised controlled trials of low versus high NaCl diets in healthy elderly aged around 60 years of age or over. (33 trials matched inclusion criteria but 21 excluded because of inadequate or insufficient information, 1 excluded as a duplicate) 8 trials were cross-over, 3 parallel design; 9 involved essential hypertensives, 2 were in normotensives; 485 subjects, trial completion rate 93%. Mean size of trial 44 patients. Mean duration 25.4 weeks, minimum 9 weeks. Treatment period 9-104 weeks. 91% of trials carried out in English-speaking countries.</td>
<td>Effect due to increased NaCl consumption (low to high NaCl diet) Weighted pooled mean increase 5.58 mm Hg (95% CI 4.31 – 6.85) Erect mean SBP Erect mean DBP Weighted pooled mean increase 3.5 mm Hg (95% CI 2.62 – 4.38) Greater effect of salt on SBP than DBP (standardised weighted mean increase was 1.10 times more for SBP than DBP) Significant association (p=0.05), Na intake accounted for 37% of variability in participants Significant association (p=0.05), Na intake accounted for 37% of variability in participants Difference for DBP, 2.69 (1.44-3.94) vs 2.63 (3.56-7.36). Little difference for DBP. 2.69 (1.44-3.94) vs 2.63 (3.56-7.36). There is a positive association with SBP, high NaCl intake and ageing. Level of SBP (less so for DBP) in elderly individuals with essential hypertension is positively and strongly influenced by salt consumption.</td>
<td>Non-significant (p=0.76) association Significant association (p=0.05), Na intake accounted for 37% of variability in participants Significant association (p=0.05), Na intake accounted for 37% of variability in participants</td>
</tr>
</tbody>
</table>
### Dietary interventions:

**Protein restriction diet: systematic reviews/meta analyses**

<table>
<thead>
<tr>
<th>Author</th>
<th>Research question</th>
<th>Review type</th>
<th>Study design, interventions: follow-up period</th>
<th>Total sample number</th>
<th>Main outcomes and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kasiske et al 1998</td>
<td>What effect does dietary protein have on rate of decline of renal function?</td>
<td>Meta analysis</td>
<td>Randomised or prospective studies of adults on dietary protein restriction</td>
<td>23 studies (13 randomised controlled trials) 2248 patients. RCTs: 1,919 subjects (range 14-840 per study) Mean study follow-up 21.8 months (range 6-36 months) 4 studies included diabetes patients only (102 patients with 15 - 35 per study). Other studies included up to 14% diabetes patients.</td>
<td>Renal function – glomerular filtration rate of decline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Databases used</td>
<td>Study design, interventions: follow-up period</td>
<td></td>
<td>With protein restriction reduced rate of decline by 0.53 ml/min/yr (95% CI 0.08 – 0.98) (exclusion of 1 large study: 0.66 ml/min/yr (95% CI 0.18 – 1.14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time period covered</td>
<td>Study design, interventions: follow-up period</td>
<td></td>
<td>Reduced dietary protein intake reduces rate of decline in GFR among patients with renal disease but magnitude of the effect is small.</td>
</tr>
<tr>
<td>Waugh and Robinson 2000</td>
<td>Does protein restriction slow or prevent progression of diabetic nephropathy towards renal failure?</td>
<td>Systematic review. MEDLINE 1976-1996, EMBASE 1974-1996, plus hand searching of journals and reference lists.</td>
<td>Trials of reduced or modified protein diets (0.3-0.8 g/kg of protein) for 4 months or longer.</td>
<td>5 studies (4 RCTs) 7-20 patients, Type 1, with follow-up from 4 – 12 months.</td>
<td>Change in glomerular filtration rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Data analysis</td>
<td>Study design, interventions: follow-up period</td>
<td></td>
<td>Mean change between usual protein diet and low protein diet –0.3 (range -0.03 - -1.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Study design, interventions: follow-up period</td>
<td></td>
<td>Lower protein intake does slow progression of diabetic nephropathy towards renal failure but does not establish what level of protein restriction is most effective to achieve this.</td>
</tr>
</tbody>
</table>
## Dietary Supplement intervention:

### Homocysteine concentration reduction: systematic review/meta analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Research question</th>
<th>Review type</th>
<th>Study design, interventions: follow-up period</th>
<th>Total sample number</th>
<th>Diabetes status and duration</th>
<th>Age (mean/SD/range)</th>
<th>Male/female</th>
<th>Ethnicity</th>
<th>Main outcomes and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocysteine Lowering Trialists' Collaboration</td>
<td>What level of reduction in homocysteine concentrations can be achieved with dietary supplementation with folic acid and vitamins B12 or B6?</td>
<td>Meta analysis MEDLINE (no dates given), reference lists and personal contact. Analysis of co-variance</td>
<td>Randomised controlled trials</td>
<td>14 RCTs (2 unpublished and not available) 10 parallel group, 2 cross-over (used data from first period only). 1114 patients No information on diabetes status and status not a requirement for inclusion. Mean age 52 years (range 23-75), mean duration of treatment 6 weeks (range 3-12 weeks).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Homocysteine lowering effect of folic acid Vitamin B12 plus folic acid Vitamin B6 plus folic acid</td>
</tr>
</tbody>
</table>
10. References


III Poulsen PL, Hansen B, Amby T, Terkelsen T, Mogensen CE (1992) Evaluation of a dipstick test for microalbuminuria in three different clinical settings, including the correlation with urinary albumin excretion rate *Diabete & Metabolisme; 18*: 395-400


III UK Prospective Diabetes Study (UKPDS) 10 (1993) Urinary albumin excretion over 3 years in diet treated Type 2 (non-insulin-dependent) diabetic patients and association with hypertension, hyperglycaemia and hypertryglyceridaemia. Diabetologia; 36: 1021-1029.

III UK Prospective Diabetes Study (UKPDS) 22 (1997). Effect of age at diagnosis on diabetic tissue damage during the first 6 years of NIDDM. Diabetes Care; 20: 1435-1441.


11. Appendices
Appendix 1:

The economics of renal disease prevention in Type 2 diabetes
Epidemiological and trial data presented in this guideline demonstrate that patients with diabetes may progress through microalbuminuria and proteinuria to end stage renal failure. In addition to renal disease, patients are at raised risk of other microvascular morbidity (retinopathy and neuropathy) and macrovascular morbidity (myocardial infarction, angina, heart failure, peripheral vascular disease, stroke). Preventative treatments recommended in the guideline have a varying impact upon these diseases: consequently the value of preventing or managing renal disease cannot be examined in isolation. Consistent with the guideline this commentary examines the value of treatments in lower risk normoalbuiminuric patients and subsequently in higher risk microalbuminuric or proteinuric patients. In this context the value of screening for microalbuminuria is explored. This commentary explores the bounds of costs and consequences but should not be considered a systematic or rigorous treatise, as might a guideline report: the necessary resources and process have not been afforded it.

Raised blood sugar and blood pressure are two important risk markers that have been targeted in trials to achieve reductions in morbidity across the spectrum of microvascular and macrovascular disease. This is reflected in the design of the UK Prospective Diabetes Study (UKPDS) which included 21 single clinical endpoints as well as a number of combined endpoints. UKPDS involved 4,209 newly diagnosed adult-onset patients with diabetes, who demonstrated persistent sequential raised fasting plasma glucose (6.1 to 15 mmol/L) after a run in 3 month period of diet therapy. Of these patients, 3,867 were randomised in equal number to a sulphonylurea, insulin therapy, or diet therapy alone. A subgroup of 753 overweight patients (≥120% of ideal bodyweight) was enrolled in a semi-nested study, which included an additional treatment arm for metformin. Additionally a further nested study randomised 1,148 hypertensive patients (systolic/diastolic ≥160/≥90 mm Hg) into two tight control groups (target <150/85 mm Hg; with an angiotensin converting enzyme (ACE) inhibitor or beta blocker), or to a less tight control group (<180/105 mm Hg). At enrolment into UKPDS approximately 12% of patients had microalbuminuria and 2% had proteinuria. The UKPDS thus provides data on a largely low risk population of diabetic patients.

UKPDS 33 reported intensive blood glucose control by either sulphonylurea or insulin therapy compared with diet alone. The median glycated haemoglobin, HbA1c during follow-up was 7.0% in the intervention groups and 7.9% in the control group (p<0.0001). Intensive therapy achieved a relative risk reduction in any diabetes-related endpoint of 12% (95% CI: 1% to 11%) after a median 10 years of follow-up. In absolute terms this was a reduction in of 5.1 per 1000 patients-years of treatment (95% CI: 0.2 to 10), or a number needed to treat of 196 per year to prevent one diabetes related event. This reduction was due primarily to lower rates of retinal photocoagulation (p=0.0031) and cataract extraction (p=0.046), followed by myocardial infarction (p=0.052). Renal failure was very rare during the trial (25 events in total) and no difference could be attributed to treatment. However, intensive therapy reduced the absolute risk of progression of microalbuminuria by 6.2% (p=0.00062) and proteinuria by 2.1% (p=0.036) after 9 years.

UKPDS 34 reported intensive glucose control by metformin in overweight patients, compared to diet alone, over a median 10.7 years follow-up. The median glycated haemoglobin, HbA1c during follow-up was 7.4% in the intervention group and 8.0% in the control group. Metformin achieved an absolute reduction in all cause mortality of 7.1 per 1000 patients-years of treatment (95% CI: 1.3 to 12.9), or a number needed to treat of 141 per year to prevent one death. This reduction was primarily due to lower cardiovascular death, particularly myocardial infarction. Diabetes related events fell by 13.5 per 1000 patients-years of treatment (95% CI: 4.5 to 22.5). Renal failure occurred in 4 patients and no difference could be attributed to treatment. Progression of microalbuminuria and proteinuria was not reported. Compared with overweight patients treated intensively with sulphonylurea or
insulin therapy, patients on metformin achieved statistically significantly better outcomes for all-cause mortality and diabetes-related events.

UKPDS 38 reported tight blood pressure control with either an ACE inhibitor or beta blocker compared with less tight control group (no drug treatment), over a median follow-up of 8.4 years. Significant reduction in blood pressure was achieved by intervention (mean values over 9 years: 144/82 mm Hg vs. 154/87 mm Hg; p<0.0001). In absolute terms there was a reduction in diabetes related events of 16.5 per 1000 patients-years of treatment (95% CI: 5.2 to 27.8), or a number needed to treat of 61 per year to prevent one diabetes related event. The reduction was achieved primarily by reductions in cardiovascular and ocular disease although no single clinical endpoint reached statistical significance except heart failure. There were no differences between treatments in occurrence of renal failure, but a reduction in the progression of microalbuminuria (≥50mg/L;) of 8.2% (p=0.0085) and proteinuria of 2.3% (p=0.061) after 6 years. Ravid et al (1998) reported a randomised placebo controlled trial in 156 normoalbuminuric adult onset patients with diabetes. Similarly to UKPDS 38, ACE inhibition demonstrated (in protocol completers) a 12.5% absolute risk reduction (95%CI: 2% to 23%) in progression to microalbuminuria after 6 years.

UKPDS 39 reported a comparison of the ACE inhibitor and beta-blocker employed to achieve tight blood pressure control, but found no statistically significant difference in any single or aggregate endpoint. ACE inhibition and beta blockade demonstrated similar rates of progression to microalbuminuria (≥50mg/L; 31% vs. 26%, p=0.31) and proteinuria (≥300mg/L; 5% vs. 10%, p=0.09).

The UKPDS presents a complex study design, and it the interpretation of its major findings has been disputed (McCormack et al, 2000). Stepwise addition of further glycaemic and hypertensive agents was permitted when targets were not met on allocated treatments, either initially or over the duration of the trials (Nathan, 1998). There was some overlap of glycaemic treatment between groups and the possibility of dilution of treatment effects. The UKPDS featured scheduled 3-month follow-up visits unlikely to be replicated in routine care and it is unclear what impact less frequent contact might have on compliance and outcomes. Additionally, each treatment has its own side-effect profile and such issues need presenting to inform patient decision-making. The apparent benefits of metformin in obese diabetic patients are striking, while the benefits of other intensive blood glucose control agents and hypertensive therapy are more modest. Economic analyses of intensive glucose control with sulphonylurea or insulin therapy (UKPDS 41) and intensive blood pressure control with a beta blocker or ACE inhibitor (UKPDS 40) have suggested that savings from reduced morbidity may largely or wholly offset the costs of intensive treatment in the long run.

Consideration of the evidence of the modest net costs and consequences reported by the UKPDS supports the conclusion of the guideline that intensive blood pressure and blood glucose control should be discussed with, and offered to, lower risk patients. Current evidence supports the UKPDS investigators assertion that metformin may be the first choice therapeutic in overweight diabetic patients. More than half of participants (52%) in UKPDS were overweight at enrolment (≥120% of ideal bodyweight).

The HOPE trial provides important evidence for the value of an ACE inhibitor in higher risk diabetic patients. The trial featured a randomised placebo controlled two-by-two factorial design, with an ACE inhibitor and vitamin E as active treatments. The full trial included 9,541 patients with or without diabetes, aged 55 years or more, who had a history of cardiovascular disease, or diabetes and at least one cardiovascular risk factor (which could be microalbuminuria). The trial was stopped 6 months prematurely because of consistent benefit for intervention. The diabetic sub-study provided data for 3,577 patients and featured a median 4.5 years of follow-up. The mean duration of diabetes in these patients was 11½ years, approximately one third had microalbuminuria and two-thirds had
some form of existing cardiovascular disease. Randomisation to an ACE inhibitor featured relative risk reductions in the primary outcome (myocardial infarction, stroke or cardiovascular death) of 25% (95%CI: 12% to 36%) and some secondary endpoints: notably overall mortality 24% (95%CI: 8% to 37%) and proteinuria 24% (95%CI: 3% to 40%). In absolute terms there was a reduction in of 7.1 deaths per 1000 patients-years of treatment (95% CI: 0.2 to 12.2), or a number needed to treat of 141 per year, to prevent one death. Eighteen patients began dialysis during the study with no difference attributable to treatment. Estimation of the progression to proteinuria depended upon the diagnostic criteria used. The headline 24% relative reduction derives from the least stringent definition and corresponds at absolute reduction in the incidence of proteinuria of 2% (p=0.03) over 4.5 years.

The relative reductions in risk achieved in HOPE are (statistically) similar across most microvascular and macrovascular endpoints. Although sub-group analyses should be interpreted with caution, the absolute benefits are suggested to vary dramatically within subgroups. In patients with microalbuminuria at enrolment, the approximate reduction due to ACE inhibition in the primary outcome was 19 per 1000 patient-years of treatment (95%CI: 6% to 32%) compared to 7 per 1000 patient-years (95%CI: 0% to 14%) in normoalbuminuric patients. Although this might suggest considerable benefit from ACE inhibition for patients with microalbuminuria, the finding could have been confounded by other important differences between the strata such as the level of pre-existing cardiovascular disease. This can be seen by the primary outcome reduction of approximately 12 per 1000 patient-years of treatment (95%CI: 4% to 20%) enrolled with cardiovascular disease compared to 4 per 1000 patient-years (95%CI: -5% to 17%) in those without. Multivariate analysis by the HOPE investigators might provide the best evidence of the independent impact of microalbuminuria on health outcomes.

Despite a therapeutic target dose, the change in blood pressure achieved by ACE inhibition in HOPE was modest (-2.47/-1.00 mm Hg) leading to speculation that benefits were not mediated by blood pressure reduction alone, and that ACE inhibition may have an additional independent protective effect. A similar finding was obtained by Lewis et al (1993) for 207 proteinuric patients randomised to ACE inhibitor or placebo with a median follow-up of three years. Despite small average differences to blood pressure during the study (<2/<4 mm Hg), ACE inhibition was associated with an (adjusted) relative risk reduction of 46% (95%CI: 10% to 68%) compared to placebo for the combined end point of death, dialysis or transplantation. In absolute terms this was a reduction of 32.3 events per 1000 years of treatment (95%CI: 6.5 to 58), or a number needed to treat of 31 per year, to prevent one such event.

HOPE provides evidence in diabetic patients at risk of cardiovascular disease. In this broad group of higher risk patients the value of ACE inhibition is substantial.

Should we screen for microalbuminuria?

UKPDS describes the benefits of intensive glucose and blood control in patients with type 2 diabetes. On clinical and economic grounds these interventions should be explained and offered to all patients regardless of underlying risk of cardiovascular disease. The value of ACE inhibition has been demonstrated to increase as microvascular and macrovascular disease progress. On balance, it would seem justifiable that ACE inhibition should be offered at initial diagnosis and then re-offered periodically to patients declining treatment. Consequently, under routine care patients should be directed to available beneficial treatments; the additional value of knowing microalbuminuric status in terms of modifying clinical care may be modest. However screening for microalbuminuria, as part of a patient’s annual diabetic review, is inexpensive at approximately £10-20 per patient per year for laboratory testing, assuming two repeat tests following an initial positive result.
Different viewpoints are possible about screening for microalbuminuria. Reviewing the guideline, there appears no convincing evidence of the value of a test result to improve patient care, and microalbuminuria and proteinuria are asymptomatic - not directly affect patient quality of life. However, patients may feel that information about their condition is in itself valuable, while clinicians may argue that a positive test result provides an important opportunity to assess and discuss disease progression and review or tighten therapeutic control decisions with patients. The rationale for screening might lie in providing patients with information and improved compliance with uptake of available treatments, but this is itself a research question. In proteinuria the impact of ACE inhibition is considerable, and detection of proteinuria should prompt a review of preventative therapy.

References:


Appendix 2: Renal care clinical path

This clinical pathway was developed at the start of the project in order to develop priority areas of care to be covered by the evidence review.

Person with Newly Diagnosed Type 2 Diabetes

Definitions and epidemiology

- What is the definition of renal disease due to diabetes in patients with Type 2 diabetes?
- What proportion of patients have a normal GFR at time of initial presentation/diagnosis of Type 2 diabetes?
  - what does epidemiological data have to say about this?
  - what does demographical data have to say about this?
- If there is loss of albumin in the urine,
  - is it due to kidney disease?
- Are there any abnormalities of the kidney we need to know about?
- What is the ‘normal’ range of albuminuria
  - for the general population?
  - for those with diabetes?
  - for those with Type 2 diabetes?
- For people with Type 2 diabetes with ‘abnormal’ levels of microalbuminuria,
  - how is ‘progression’ of the disease defined?
  - is microalbuminuria \( \rightarrow \) macroalbuminuria progression?
- What is the gold standard for diagnosis of renal disease due to diabetes in patients with Type 2 diabetes?
  - for kidney disease in people with Type 2 diabetes with no other obvious cause?
- Does renal disease in people with Type 2 diabetes differ from that in people without Type 2 diabetes, and if so how?
- Is proteinuria a good enough indicator for nephropathy?
- What is the best way to identify nephropathy in Type 2 diabetes?
- How do we define progression of renal disease due to Type 2 diabetes?
Identification/screening

- Is urine testing the best method to identify problems?
  - If so
    - what urine should be tested?
    - who should be screened?
    - how should the sample be taken?
    - what methods provide the best sensitivities and specificities?
    - how often should urine be tested?
    - how cost-effective are the various approaches to urine testing?

- How do we know that it is diabetic kidney disease rather than other types of kidney disease, how are other conditions excluded?

- How to screen: what are the best methods (including sensitivities and specificities) eg
  - biopsy
  - urine testing
  - proteins
    - albumin
    - other proteins
  - other substances, eg
    - blood
    - nitrites
    - leucocytes
  - serum creatinine
  - GFR
  - genetics
  - blood pressure
    - how to do correctly  →  hypertension group
  - retinopathy
  - other methods

The impact of screening on prognosis / management

- Does screening have any impact on:
  - future action?
  - delay progress disease?
  - affecting other aspects of Type 2 diabetes, eg cardiovascular disease, interactions between eg lipids smoking?

- Should we screen?
Risk and risk factors and confounders

- Who are at risk of developing renal disease?
- Who are not at risk of developing renal disease?
- Can we break down different levels of risk?
  - can we grade different levels of risk?
    - for renal disease?
    - other disease?
      - eg cardiovascular disease
      - eye disease
  - what influences degree of risk?
    - ethnicity?
    - are different screening mechanisms therefore required for screening of different ethnic groups?
- Is there any way of identifying those at risk?
- Are there different risks for renal disease
  - in those with diabetes?
    - are there other risk factors for developing renal disease?
    - is there a sub-group of patients with higher risk factors
      - eg blood glucose levels?
      - is it possible to identify those at risk before development of disease?
- What is the evidence that there are confounders for microalbuminuria, eg fever, urinary tract infection, heart failure?
Interventions and progress of disease

Predisease (primary prevention) and post disease

- For each of the following interventions,
  - when should the intervention be undertaken?
  - what levels should be aimed for?
  - what method/agent (if >1) is the preferred method/agent?
    - glucose control
    - blood pressure
    - lipids
    - low protein diet
    - smoking
    - salt reduction
    - aldose reductase inhibitors
    - ACE inhibitors
    - interventions for progression
    - others

- How do we monitor
  - progression?
  - clinical outcomes?

- Are there any interventions of primary prevention
  - can we stop people (who have ‘normal’ albumin levels) developing renal disease?

- Is there anything we can do that alters the natural progression of the disease?
  - at different stages?
  - should we stratify it?
    - is there evidence to support stratification?
    - does it have an impact on?
      - management?
      - progression of the disease?

- Is there anything we can do to affect sequelae of microalbuminuria?
  - does intervention on the
    - kidney?
    - cardiovascular system?
    - cardiovascular outcomes
    - urinary protein
    - GFR
    - creatinine
    - blood pressure - ambulatory; clinic
    - lipids
    - other

impact upon the
kidney?
cardiovascular system?
Management of care

- Someone has abnormality
  - how do we care for them?
    - diabetic kidney disease?

- Once Type 2 diabetes is diagnosed
  - do you need to do anything more than screening?
  - does it matter if it is hypertensive renal disease in someone with diabetes?
  - do we need to know if its
    - ureter?
    - bladder?

- Are there clinical examinations or labs that need to be done, looking for eg
  - peripheral vascular disease?
  - lupus
  - renal athersclerosis
  - renal angiogram?
  - do we need to know?
  - does intervention help?

- Does knowing about abnormal albuminuria affect future management of the patient?

- Level of risk
  - which ‘in trouble’ patient needs hospital diabetic clinic?
  - with abnormal reading without abnormal reading
    - how often should you check / re-check levels
    - what to do

Delivery of Care

- Who should provide care? Where should care be provided? When does nephrologist become involved?

- Recording of data, how, what systems etc
  - IT systems; Decision support

- General organisational issues

- Shared care; joint diabetics and renal clinic?

Outcomes

- Death

- Renal replacement
### Appendix 3: Recommendations panel: membership

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
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<tbody>
<tr>
<td>Professor Richard Baker</td>
<td>Director, Clinical Governance Research &amp; Development Unit, University of Leicester</td>
</tr>
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<td>Professor Colin Bradshaw</td>
<td>General Practitioner, Marsden Road Health Centre, Tyne and Wear (until May 2000)</td>
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<tr>
<td>Ruth Davis</td>
<td>Senior Lecturer, School of Nursing &amp; Midwifery, University of Glamorgan</td>
</tr>
<tr>
<td>Dr Anne Dawson</td>
<td>Senior Medical Officer, Department of Health</td>
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<tr>
<td>Professor Martin Eccles</td>
<td>Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle</td>
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<td>Professor Gene Feder</td>
<td>Professor of Primary Care Research and Development, Queen Mary and Westfield College, London</td>
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<td>Department of Ophthalmology, University of Aberdeen</td>
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<td>Dr Gary Frost</td>
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<td>Dr Chris Griffiths</td>
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<tr>
<td>Dr Margaret Guy</td>
<td>NHS Executive, London Regional Office</td>
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<tr>
<td>Professor Philip Home</td>
<td>Professor of Diabetes Medicine, Department of Medicine, Medical School, University of Newcastle</td>
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<tr>
<td>Professor Allen Hutchinson</td>
<td>Director, RCGP Effective Clinical Practice Programme, Professor of Clinical Public Health, Section of Public Health, ScHARR, University of Sheffield</td>
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<tr>
<td>Suzanne Lucas</td>
<td>Director of Care, Diabetes UK</td>
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<tr>
<td>Dr Sally Marshall</td>
<td>Reader in Diabetes, Department of Medicine, Medical School, University of Newcastle</td>
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<tr>
<td>Paula-Jayne McDowell</td>
<td>Guidelines Initiative Officer, Royal College of General Practitioners</td>
</tr>
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</table>
Aileen McIntosh  Senior Research Fellow, ScHARR and
Programme Manager, RCGP Effective Clinical Practice Programme,
University of Sheffield

Professor James Mason  Professor of Health Economics,
Centre for Health Services Research, University of Newcastle

Professor Rhys Williams  Professor of Epidemiology & Public Health,
Nuffield Institute for Health, Leeds

Dr Robert Young  Consultant Diabetologist,
Salford Royal Hospital Trust, Hope Hospital, Manchester
Appendix 4: Renal care working group: membership

The Renal care working group consisted of relevant health care professionals and specialist resources (including reviewers and guideline methodologists).

Membership of the renal care working group comprised:

<table>
<thead>
<tr>
<th>Name</th>
<th>Position and Affiliation</th>
</tr>
</thead>
<tbody>
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<td>Dr Dennis Barnes</td>
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<tr>
<td>Dr James Walker</td>
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</tr>
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The Renal care group met 6 times between February 1999 and May 2000.